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Examination of the association between periodontal disease indices and risk of breast cancer in Greek females: A case - control study

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Abstract

Objective: To assess the possible association between Periodontal Disease indices and risk of developing breast cancer in Greek females.

Materials and Methods: The study sample consisted of 156 cases diagnosed with the main histological types of breast carcinoma, invasive ductal and invasive lobular carcinoma, and 314 age and socio-economic status matched controls. Data on periodontal health was obtained through dental examination and questionnaire including aspects of their medical and dental history, and concerned Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), Bleeding on Probing and the known risk factors for breast cancer development. Odds ratios (OR's) and 95% Confidence Intervals (CI's) were assessed using univariate and logistic regression models adjusted for possible confounders.

Results: The multivariate regression analysis model application showed that family history (p= 0.010, OR= 1.733, 95% CI=1.138-2.640), increased Body Mass Index (BMI) (p= 0.036 OR= 1.767, 95% CI= 1.178-2.651), genetic predisposition (p= 0.047, OR= 1.514, 95% CI= 0.988-2.319) and deep periodontal pockets (p= 0.022, OR= 2.182, 95% CI=1.447-3.291) were statistically significantly associated with risk for breast cancer development.

Conclusion: Individuals with a positive breast cancer family history, genetic predisposition, increased body mass index and those with deep periodontal pockets were at significantly higher risk for developing breast cancer.

Introduction

Periodontal Disease (PD), is a chronic inflammatory disease and a public health problem, is partially responsible cause for tooth loss with dental caries, is characterized by altered oral microbiota and a pro-inflammatory environment [1].

Previous and recent epidemiological studies have inked PD to many systemic diseases and disorders, such as cardiovascular disease [2], preterm birth [3], osteoporosis [4], and diabetes mellitus [5], all of which may be attributed to systemic infection and inflammation [6].

In recent years, there is increased interests in exploring the possible association between PD and cancer risk, particularly for cancers in the head and neck, upper gastrointestinal system, lung, and pancreas [7-19], as there is evidence that individuals with PD are at increased risk of oral, eso-phageal, head and neck, pancreatic, and lung cancers [11-13]. Moreover, accumulating evidence suggests an hypothesized role of immune-inflammatory mechanisms that may be common to both PD and cancer [14,15]. Investigators have suggested that periodontal pathogens may directly influence breast carcino-genesis, citing evidence for the presence of oral bacterial species in breast tissues [16], whereas others have suggested that PD may influence and/or reflect systemic inflammatory processes that promote breast carcinogenesis [17].

The most important risk factors for Breast Cancer (BC) are age over 40, history of mammary gland diseases, history of cancer in first-degree relatives, early menarche and late childbearing (after 35 years of age), age at menopause, Caucasian race [18], genetic susceptibility [19] ionizing radiation therapy [20], alcohol consumption [21], body mass index (BMI), physical activity, hormone therapy and receiving oral contraceptives [22]. Despite the identification of many factors increasing the risk of BC existence, in 75-80% of females no risk factor is found [18].

Previous and recent reports have observed an increased risk of BC among females with PD [14,15, 23-26], however, notable limitations of those included inadequate sample sizes and inade-quate adjustment for potential confounders. In those studies, the sample sizes ranged from 151 [15] to 80,280 individuals [14], with the Women's Health Initiative Observational Study (WHI OS) [23] including the most BC cases (N=2,124), and all other studies each having fewer than 550 BC cases.

A Swedish study (n=3,273) revealed that more BC cases were recorded among females who had PD accompanied by missing molars (5.5%) compared with those with PD and not missing molars [24]. However, almost half of the participants (n=1,597) did not receive any clinical oral examination. A similar study in Brazil, composed of 87 BC cases and 134 controls, utilized four different case definitions

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for periodontitis and found that the odds of having BC in all instances varied from 2- to 3-fold based on the case definition applied [27].

However, similar studies have reported inconsistent findings on the association between PD and risk of BC**.** To be more specific, previous reports, have recorded no association between PD and BC risk [28-32]. In another study PD status was assessed based on radiographic analyses of alveolar crestal height showed that the risk of BC was not associated with either mild/moderate or severe PD after adjusting for age and smoking [30]. In terms of BC mortality, a National Health and Nutrition Examination Survey study of 11,328 individuals reported an increased but statistically insignificant risk of BC mortality among those with periodontitis [29]. There are no previous prospective or retrospective studies estimating the possible association between PD and risk of BC in Greece. The aim of the current retrospective case-control study was to assess the possible association between PD indices and risk of BC in a sample of adult females in Greece.

Materials and methods

Study design and study population sample

A retrospective case - control study was conducted between March 2019 and June 2021. The study size was estimated considering the BC prevalence [33], determined by Hyman et al. [34], with 95% Confidence Interval and relative precision 25.0%, whereas the age group was based on the World Health Organization (WHO) recommendations [35,36] for assessing PD prevalence.

This procedure led to a study sample of 470 females [34]. The current investigation was carried out on 156 females with BC - cases and 314 healthy females - controls, aged 45 to 77.

Cases and controls selection criteria

Participants who had less than 20 natural teeth, those who were undergone a conservative or surgical PD treatment within the previous six months and those who had received a systemic-antibiotics or anti-inflammatory or other systemic drugs, such as glucocorticoids the previous six weeks were not included in the study protocol as those conditions could influence [37] the oral tissues condition, and could lead to biased secondary associations.

Patients with advanced BC under medical treatment, patients with breast metastases of a primary focus at a different location, and those diagnosed in other focuses in the region of head-neck-thorax (carcinogenesis field theory [38]), were excluded from the study protocol. Hospital patients were also not included.

The case group included individuals whose the primary diagnosis of BC was based on patients' files and included Mammography findings, but definitive diagnosis was based on histopathological examination of the intraoperatively removed tumor or its parts, using traditional histological, cytologic and histochemical methods [39]. Fine needle aspiration (FNA) biopsy was performed [40] in a low rate of BC patients (13 or 8.44%).

The control group selection was based on the friendly and collegial environment of cases group in an effort to control potential confounders such as age, smoking, socio-economic level.

Research questionnaire

Cases and controls filled in a modified Minnesota Dental School Medical Questionnaire [41], that included epidemiological indices such as age, gender, smoking status, alcohol intake, socio-economic and educational status, BMI, BC family history, early menarche, late age at first pre-gnancy, later menopause, physical inactivity, genetic predisposition for BC, current diseases and disorders, and past medical/dental history.

Individuals' age was classified as 45-50, 51-60, 61-70, 71+; socio-economic status as ≤ 1,000 and >1,000 €/month; educational status as elementary level and graduated from University/College; smoking status as never smokers and former/current smokers.

For establishment of the intraexaminer variance a randomly chosen sample of 32 (20%) individuals were re-examined clinically by the same dentist after three weeks, and no differences were recorded between the 1st and the 2nd clinical assessment *(Cohen's Kappa = 0.94*). During this time period no oral hygiene instructions were given to the participants.

Periodontal status examination

Periodontal status indices were estimated at six sites in all teeth (mid-buccal, disto-buccal,mesio-buccal, mesio-lingual disto-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, the worst values of PPD and CAL on six sites per tooth and the presence/ absence of BOP were recorded and coded as dichotomous variables.

Probing Pocket Depth (PPD) index was classified as 0-3.00 mm (absence of disease/mild disease) and ≥ 4.0 mm (moderate and severe disease) for mean PPD [42], attachment loss (CAL) severity was classified as mild, 1-2.0 mm of attachment loss and moderate/severe, ≥3.0 mm of attachment loss [43], and 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 reviewed and approved by authorized committees (Ministry of Health, etc.), as in Greece only experimental studies must be approved by those Authorities. An informed consent form was obtained by the individuals who agreed to participate in the current study.

Statistical analysis

For each individual, the worst values of PPD and CAL on six sites per tooth and the presence/ absence of BOP were recorded and coded as dichotomous variables. Never smokers, individuals with a low socio-economic (income/monthly ≥ 1,000 €) and educational (graduated from Uni-versity/College) level and individuals that reported a physical inactivity were coded as 0. Age groups distribution was coded as 0,1,2 and 3 for ages 45-50, 51-60, 61-70 and 71+ respectively.

Univariate analysis model was applied to examine the relationship between the independent variables examined and BC risk, separately, by using chi-square test. Multivariate regression model was carried out to test the associations between the dependent variable, BC, and in-dependent ones that were determined by the enter method. Adjusted Odds Ratios (OR's) and 95% CI were also assessed. Finally, the independent variables were included to stepwise method in order to estimate gradually the indices that showed significant associations with the dependent ones. Statistical analysis was carried out using the SPSS ver.19.0 package. A p-value of less than 5% ($p< 0.05$) was considered significant for all statistical test conducted.

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 51-60 61-70 71+	 27 (17.3) 68 (43.6) 42 (26.9) 19 (12.2)	 60 (19.1) 132 (42.0) 88 (28.0) 34 (10.9)	 **0.030*** 	 ———
Educational level Low High	 97 (62.2) 59 (37.8)	 182 (58.0) 132 (42.0)	 0.381	 1.192 (0.804-1.768)
S/economic level Low High	 87 (55.8) 69 (44.2)	 151 (48.1) 163 (51.9)	 0.117	 1.361 (0.925-2.002)
Smoking status No Yes	 55 (35.3) 101 (64.7)	 123 (39.2) 191 (60.8)	 0.410	 0.846 (0.567-01.260)
BC family history No Yes	 51 (32.7) 105 (67.3)	 223 (71.0) 91 (29.0)	 **0.000***	 0.198 (0.131-0.300)
Early menarche No Yes	 62 (39.7) 94 (60.3)	 192 (61.1) 122 (38.9)	 **0.000***	 0.419 (0.283-0.621)
Later Menopause No Yes	 67 (42.9) 89 (57.1)	 163 (51.9) 151 (48.1)	 0.067	 0.697 (0.474-1.027)
Late age at 1st pregnancy No Yes	 61 (39.1) 95 (60.9)	 193 (61.5) 121 (38.5)	 **0.000***	 0.403 (0.272-0.597)
BRCA gen. predisposition No Yes	 48 (30.8) 108 (69.2)	 259 (82.5) 55 (17.5)	 **0.000***	 0.094 (0.060-0.148)
Body Mass Index <25 kg/m^2 >25 kg/m^2	 58 (37.2) 88 (62.8)	 148 (47.1) 166 (52.9)	 0.664	 0.041 (0.448-0.983)
Alcohol consumption <45 grams/day >45 grams/day	 75 (48.1) 81 (51.9)	 138 (43.9) 176 (56.1)	 0.397	 1.181 (0.803-1.736)
Physical inactivity No Yes	 70 (44.9) 86 (55.1)	 141 (44.9) 166 (55.1)	 0.999	 0.995 (0.679-1.469)
Probing pocket depth 0-3.00 mm ≥ 4.0 mm	 51 (32.7) 105 (67.3)	 160 (51.0) 154 (49.0)	 **0.000***	 0.468 (0.313-0.688)
Clin. Attachment Loss 1.00-2.00 mm ≥ 3.0 mm	 75 (48.1) 81 (51.9)	 176 (56.1) 138 (43.9)	 0.103	 0.726 (0.494-1.067)
Bleeding on Probing Absence Presence	 62 (39.7) 94 (60.3)	 155 (49.4) 159 (50.6)	 **0.049***	 0.677 (0.458-0.999)

* p-value statistically significant

Results

The mean age of the sample was 58.4 ± 3.2 years. The main histological types were invasive ductal (72.6%) and lobular cancer (27.4%), as in the study protocol were not included the infrequent histological types of BC.

The epidemiological indices of BC patients and healthy individuals after carrying out the univariate analysis are shown in Table 1.

Age (p= 0.03), BC family history (p= 0.000), early menarche (p= 0.000), later menopause (p= 0.067), late age at 1st pregnancy (p= 0.000), BC genetic predisposition (p=0.000), increased BMI (p= 0.041), deep periodontal pockets (p= 0.000) and BOP (p= 0.049) were statistically signifi-cantly associated with risk for BC development. Table 1 also shows Unadjusted Odds Ratio and 95% Confidence Interval (CI) for each variable examined.

After performance of the first method (step 1a) of the regression model it was found that BC family history (p= 0.014), increased BMI (p= 0.043), and deep periodontal pockets (p= 0.031) were significantly associated with BC risk (Table 2). Table 2 also shows Unadjusted Odds Ratio and 95% CI for each parameter examined. The final step of multivariate regression analysis model (Wald method) is presented in Table 2, in which also shown that BC family history (p= 0.010), increased BMI (p= 0.036), BC genetic predisposition (p= 0.047) and deep periodontal pockets (p= 0.022) were statistically significantly associated with risk for developing BC.

Discussion

The association between PD indices and increased cancer risk has been investigated for more than 50 years, however, findings to date have little practical value as prevention indices. Recently, exists an increasing interest in exploring the possible relationship between PD and cancer

Table 2. Presentation of association between potentially risk factors and BC according to Enter (first step-1a) and Wald (last step 12a) 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	,032	,120	,073	1	,788	1,033	,817	1,306
	education.level	-,209	,218	,921	1	,337	,811	,529	1,243
	socioecon.level	-,222	,221	1,014	1	,314	1,249	,810	1,926
	smok.status	,098	,226	,188	1	,664	1,103	,708	1,717
	famil.history	,540	,220	6,046	1	**,014***	1,716	1,116	2,640
	early.menarch	,189	,222	,726	1	,394	1,208	,782	1,865
	late.age.1st.preg	,074	,214	,119	1	,730	,929	,610	1,414
	later.menopause	,207	,218	,898	1	,343	1,230	,802	1,885
	alcohol.consumpt	,389	,218	3,199	1	,074	,678	,442	1,038
	physical.inactiv	-,114	,230	,245	1	,620	1,121	,714	1,759
	body. mass. index	,677	,229	5,738	1	**,043***	1,968	1,256	3,082
	genet.predisposition	,380	,228	2,777	1	,056	1,462	,935	2,284
	bleed.prob	,267	,220	1,469	1	,225	1,306	,848	2,012
	clin.attach.loss	,069	,224	,095	1	,758	1,071	,691	1,663
	prob.pock.dept	,652	,219	6,831	1	**,031***	2,121	1,382	3,256
	Constant	2,455	,448	30,096	1	,000	,086		
Step 12[a]	famil.history	,550	,215	6,566	1	**,010***	1,733	1,138	2,640
	body.mass.index	,570	,207	5,581	1	**,036***	1,767	1,178	2,651
	genet.predisposition	,415	,218	3,635	1	**,047***	1,514	,988	2,319
	prob.pock.dept	,780	,210	6,860	1	**,022***	2,182	1,447	3,291
	Constant	2,067	,279	55,063	1	,000	,127		
a. Variable(s) entered on step 1: age, education.level, socioecon.level, smok.status, famil.history, early.menarch, late.age.1st.preg, later.menopause, alcohol.consumpt, physical.inactiv, body.mass.index, genet.predisposition, bleed.prob, clin.attach.loss, prob.pock.dept.									

* p-value statistically significant

risk, especially for cancers in the head and neck location, upper gastrointestinal system, pancreas and lung [7-10], as there is evidence that PD patients were at increased risk of those types of cancers [11-13].

BC is the most common cancer and the main cause of female cancer in Europe, as is estimated that affect more than one in 10 females and accounts for 28.8% of female cancers[44]. Moreover, it is responsible for 25% of all cancer cases and 15% of all cancer-related deaths among females [45]. Kamińska et al. [46] found that 20-30% of newly diagnosed BC cases may be associated with the occurrence of several risk factors that are implicated in initiation or modification of the process of neoplastic transformation of breast cells.

The outcomes of the current study showed that BC family history, increased BMI, BC genetic predisposition, and deep periodontal pockets were statistically significantly associated with risk for developing BC.

Previous studies stated that BC is a disease of older females and its incidence increases with age, and it is rare below the age of 20 years [47,48]. In the current study no association between age and risk of BC was observed.

Individuals of higher Socioeconomic Status (SES) have been linked to a higher risk for developing BC [49,50], whereas well educated individuals have a higher probability of receiving BC screening [51], observation that could lead to a reduced risk of BC. The outcomes of the current study showed no associations between SES/Educational Status and risk of BC.

Smoking is a known carcinogenesis risk factor and can affect BC risk [52]. However, previous studies generally found conclusive evidence for a causal association between smoking and BC risk [21,52]. More recent epidemiological reports recorded modest raised risks with former or current [53-56] female smokers, but it remains unclear whether this association is a consequence of confounders such as alcohol consumption, whether the mentioned risk is increased in case that smoking starts in adolescence or before first childbirth, and whether risk is modified by family history of the disease [57].

Cogliano et al. [58] suggested that smoking could be a factor with limited evidence of causing BC, as the number of females included in the study was too small to draw conclusions. Similarly, the current research showed no association between smoking and BC risk. It is obvious that further research is required to clarify the possible impact of smoking on BC.

Obesity and generally increased BMI have been consistently associated with an increased risk of BC although a difference exists between pre-and postmenopausal status and Estrogen Receptor/ Progesterone receptor (ER/PR) tumor status [59,60].

The World Cancer Research Fund/American Institute Cancer Research (WCRF) suggested that exists convincing evidence showing that greater body fatness is responsible for post-menopausal BC [61].

Suzuki et al. [60], in a meta-analysis of 31 reports, 22 case-control and 9 cohort, found that each 5-kg/m^2 increase in BMI was associated with a 33% increase in ER-positive and PR-positive breast tumors, whereas was protective against the incidence of ER/PR-positive breast tumors in pre-menopausal females. However, no associations were found between increased BMI and ER/PR-negative breast tumors or ER-positive/PR negative tumors in either post- or pre-menopausal females. In another similar meta-analysis of 31 prospective studies Renehal et al. [62] found that a 5-kg/m^2 increase in BMI increased the risk of postmenopausal BC by 12%, whereas Arnold et al. [63] assessed the possible association in postmenopausal BC cases occurring worldwide in 2012, and found that 10% could be attributed to high BMI (≥ 25 kg/m^2), findings that were in accordance with the outcomes of the current research.

Genome-wide association studies carried out worldwide and showed that susceptibility genes and genomic sequences were responsible for less than one third of all inherited BC cases [64].

Germ-line mutations in *BRCA1* and *BRCA2* genes are the main part of genetic and hereditary factors that are responsible for breast and ovarian cancers [65,66]. *BRCA1* and *BRCA2* genes are the

strongest susceptibility genes for BC [67]. Mutations in those genes are so effective in the increased risk for developing early-onset BC and familial ovarian cancer, however mutations in those two genes are not only responsible for 90% of hereditary BC cases but also for the majority of hereditary ovarian cancer [68-71]. *BRCA1*-related cancers are frequently triple negative, whereas *BRCA2*-related cancers are often hormone-dependent but highly proliferative [72]. The results of the current research confirmed the mentioned findings.

Females with any relative, a first-degree relative, a sister or a mother with BC have about twice the risk of developing BC. The risk is appreciably higher among females who have a mother and a sister with BC and among younger females, for females less than 50 years of age who have relatives with BC diagnosed before the age of 50 years [28]. The current study and previous studies confirmed the role of BC family history in BC etiology [73-76].

The associations between menarche age and the hormonal patterns of adolescent menstrual cycles have been investigated to obtain information regarding the possible role of early menarche as an important risk factor for BC [77-79]. However, inconsistent results have been found regarding age at menarche and BC risk. It has been found that younger age at menarche increases BC risk only in pre-menopausal females, whereas other researchers found increased risk only for post-menopausal females. In those studies, age at menarche was found to be associated with both pre-and post-menopausal BC whereas it was also recorded no association with either pre- or post-menopausal BC [48, 80]. No association was observed in the current study between menarche age and BC risk.

Late menopause increases the risk of BC, however menopause does not cause cancer, but the risk of developing cancer increases as a female ages. A female who undergoes menopause after age 55 has an increased risk of breast, ovarian, and uterine cancers. The risk is greater if a female also began menstruating before age 12. A longer exposure to estrogen increases a female's risk of BC. Consequently, females who have been through natural menopause are more possible to develop cancer around as twice as high because of hormonal influences [81]. Moreover, post-menopausal females have a lower risk of BC than pre-menopausal females of the same age and childbearing pattern [82,83].

In another study, in which majority of the females reached menopause after the age of 45 years, was observed that the risk of developing BC increased in both pre-and post-menopausal females who had early onset of menarche and late menopause possibly due to the increase in the duration of hormonal exposure [84]. The present report found no association between late menopause and BC risk.

Another risk factor for BC development is the late age at first pregnancy. Early age at first full-term pregnancy is inversely related to BC risk [84]. This association maybe reflects either a pregnancy induced maturation of breast cells, and thus making them less susceptible to carcinogenic trans-formation or a long-lasting hormonal alteration or both. Late age at last full-term pregnancy has also been found to be associated with a higher risk of BC, but not in all studies [48,85]. More studies must be carried out to investigate the association between age at any full-term pregnancy and BC risk. The outcomes of the current report did not confirm that association.

Alcohol consumption is associated with a modest increase in BC risk. This association has been consistently found in case-control and cohort studies, reducing the probability that it could be attributed to selection or information biases [86]. Extensive epidemiological studies have found such an association [87-90]. The overall estimated association showed a rate of 30-50% increase in BC risk from 15-30 grams/day of alcohol consumption (about 1-2 drinks/day) [91,92].

A meta-analysis of 53 studies reported that compared with females who did not consumed alco-hol , the risk of BC increased by 32% for those with consumption of 35-44 grams/day (approxi-mately 3-4 drinks per day), and by 46% for ≥45 grams/day of alcohol use (approximately more than 4 drinks per day) [93]. Overall, the risk of BC is increased by 7% for each additional 10 grams of alcohol consumed per day [21].

According to IARC consumption of alcoholic beverages is a carcinogenic factor for the female breast[58] and a dose-response association has been suggested between alcohol consumption and the risk of BC [61]. The Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) stated that females who consumed 35-44 grams or 45 grams or more of alcohol per day showed a 32% or 46% higher risk of developing BC than non-drinkers and the risk increased by 7.1% for each additional drink (10 grams) of alcohol per day regardless of smoking status.

Although the majority of the studies to date do not support increased BC risk with higher alcohol consumption in females, as the current report, prospective studies are needed to count out possible biases.

Previous reports have found a link between physical activity and BC risk. Epidemiological data that was based on73 studies carried out around the world showed a 25% average risk reduction amongst physically active females as compared to the least active ones. The associations were significant for entertaining activity, for activity maintained over the life-time or after menopause, and for activity that is of moderate to strong intensity and performed regularly [93]. Some evi-dence was also recorded for a stronger effect of physical activity amongst postmenopausal females, those who were normal weight, and those that had no family history of BC [94].

Moreover, in females with a family history of BC, physical activity was associated with reduced post-menopausal, but not pre-menopausal, BC risk and was not modified by extent of family history [95].

It is possible that physical activity is associated with decreased BC risk due to multiple inter-related biologic pathways that may implicate sex hormones, insulin resistance, insulin growth factors, changes in free radical generation, factors affecting body fat distribution, chronicinflammation and direct effects on cancer [93,94,96-99]. Physical exercise may act as an immune modulator that induces alterations in the activity of macrophages, natural killer cells, lymphokine activated killer cells, neutrophils, and regulating cytokines [96]. The effects of physical activity on age at menarche, menstrual cycle function, and level of endogenous sex steroid hormone levels in girls and young females are often mentioned as potential mechanisms for reduced BC risk [100]. Wu et al. [101] in a recent meta-analysis of 31 prospective studies, found that physical activity was protective against BC, however, the inverse association between physical activity and the risk of BC was stronger for females with a BMI of less than 25 kg/m^2,for premenopausal females and for ER/PR-negative tumors.

Similar observations were revealed in another age-matched case-control study by Llerenas et al. [102], whereas the current study recorded no association between the indices examined. Inversely, in a meta-analysis of 75 studies, Lee et al. [103] observed that physical inactivity, in-sufficient physical activity to meet current recommendations, increased the risk of BC by 33%.

In a case-control study in low-income females in Brazil, females who had a sedentary lifestyle showed a 2.39 times higher risk of developing malignant breast diseases than controls. The strength of the association remained the same after further adjustment for hormone-related factors, a family history of BC, and the percentage of body fat [104]. PD is a chronic infectious diseases [105], and its association with cancer risk has been investiga-ted over the years [11,106]. Moreover, useful aspects have been provided on the role of PD treatment in reducing the risk of different types of cancers [107].

PD among females was associated with conditions such as puberty, menstruation, pregnancy, and menopause [108,109], whereas it has also been observed that PD was positively associated with autoimmune diseases, disorders infertility, adverse pregnancy, low birth weight, preterm birth, and BC [110,111]. Consequently, it has been suggested that oral health amongst females should be a cause for concern regarding the mentioned conditions.

Freudenhelm et al. [23] in a prospective analysis showed that the presence of PD was associated with 14% increased BC risk among post-menopausal females, and that highest risk was observed among former smokers, especially for those who quit in the past 20 years. Similarly, two meta-analyses showed [25,26], modest positive associations between PD and BC risk, and a case-control study revealed that after adjusting for important covariates, females diagnosed with periodontitis had two to three times higher odds of BC than those without periodontitis, whereas cases showed significantly greater CAL than controls (P=0.04) [36]. Similar reports confirmed the mentioned association [112,113].

Eight studies, involved 168,111 females, also found that PD did increase susceptibility to BC (RR = 1.18, I^2 = 17.6%), with robust results confirmed by sensitivity analysis [114]. Other investigators suggested that PD might be a risk factor for female-specific BC, however a number of confounders might be influencing the results of the overall analysis, including study design, follow-up period, and history of periodontal therapy [14,15,24,26], whereas in a similar prospective study the association was found to be weaker [115].

Hujoel et al. [29] observed that clinical measurement of periodontitis was associated with a 32% increase in BC risk. However, the study included only 19 BC cases and the increase was not statistically significant.

On the other hand, different findings have been recorded regarding the association examined. A non-significant increase in BC risk of 12% was recorded in a prospective study in which the measure of PD was of tooth mobility, a measure with good specificity but poor sensitivity [32], and in a large, prospective cohort study [116]. In another prospective study where PD status was assessed based on radiographic analyses of alveolar crestal bone height no association was detected between PD and invasive BC risk [30]. Michaud et al. [28] found that BC risk was not associated with varying clinical measures of severe periodontitis, and when limited to never-smokers. Similar studies have confirmed the mentioned outcomes [117,118].

Differences in individuals of the mentioned study samples (both pre- and post-menopausal or postmenopausal females only), methods of exposure register (self-reported with or without clinical dental measurements), severity of PD (not specified, mild, moderate or severe), as well as adjustment factors (differences in potential confounding factors) may explain part of the discrepancies observed across those observational studies. Similarly, as with any exposure estimation, measurement and classification of PD may be defective, even when based on a clinical dental examination carried out as part of the cohort protocol. Given that the examination performed after the diagnosis of cancer, it is possible that any mis-measurement of PD would produce an overestimate of the association.

Several potential mechanisms have been proposed to explain the observed association of PD with BC. It is possible that periodontal pathogens directly implicated in carcinogenesis. Perio-dontal bacteria from the oral cavity enter the blood circulation following activities including tooth brushing, flossing and chewing, particularly among individuals with PD [119]. Despite the fact that circulating oral bacteria are rapidly cleared, a considerable cumulative exposure to tissues has been revealed [120]. Moreover, breast ducts are not sterile, breast ductal tissues are exposed to bacteria and viruses during lactation and human milk contains a complex and variable variety of bacteria [121,122]. There is also evidence that bacteria are present in breast tissues [16,123] including in breast tumors [123]. The source of those bacteria in breast tissues and tumors are still unknown, however the oral cavity and intestine might contribute to the mentioned colonization [122]. Some of the bacteria species revealed in breast tissues [16] have also been found in the mouth although it is unknown whether there are the same species.

Although not consistent [124,125], there is some evidence [126,127], that an increase in BC risk has been associated with antibiotic use, as particular antibiotics might or might not alter the oral microbiome.

Another potential mechanism is inflammation that could be attributed to the PD influencing systemic processes including breast carcinogenesis [128]. PD triggers a chronic systemic inflammation that is characterized by increased levels of C-reactive protein (CRP) [129], cytokines, chemokines and other biomarkers in blood circulation [130] with a potential impact on carcino-genesis [131]. In addition, bacterial metabolites produced in oral cavity including nitrosamines and acetaldehyde could have a systemic impact on carcinogenesis [132].

It is possible that common risk factors such as smoking, physical activity or diet, inflammation, oxidative stress or shared genetic factors may contribute to host susceptibility to both BC and PD [133-135]. To be more specific, the cytokine receptor activator of Nuclear Factor-κB (RANK) and its ligand (RANKL) may be implicated in breast carcinogenesis and metastasis [136-138], as blood and salivary RANKL are increased in, especially among smokers [139,140].

It has been found that BC risk associated with PD was limited to smokers, particularly former smokers who had quit in the previous 20 years [23]. Smoking is a major risk factor for PD [141], and the bacterial microbiota in PD patients differs between smokers and non-smokers [142,143].

Smokers' microbiomes have less diversity, higher prevalence of species that associated with periodontal pathogenesis and lower prevalence of those associated with health [142,144].

Moreover, lower humoral immune response in both current and former smokers compared to never smokers has been recorded [145].

Study strengths and limitations should be taken into account in interpretation of the recorded findings. Strengths of the study 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 BC 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 in a previous report compared with never smokers, former smokers were more likely to undergo mammographic screening, whereas current smokers were less likely to receive screening [146].

This study was limited to post-menopausal females, thus findings can only be generalized with confidence to the mentioned group, and further reports could explore the association between various severity of PD and different subtypes of breast cancer.

Conclusion

Individuals with a positive breast cancer family history, genetic predisposition, increased body mass index and those with deep periodontal pockets were at significantly higher risk for developing breast cancer.

Conflicts of interest and source of funding statement

The author declares that he has no conflicts of interest.

References

1. Linden GJ, Herzberg MC, on behalf of working group 4 of the joint EFP/AAP workshop (2013). Periodontitis and systemic diseases: a record of discussions of working group 4 of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol* 84:S20-S23.
2. Leng WD, Zeng XT, Kwong JS, Hua XP (2015). Periodontal disease and risk of coronary heart disease: an updated meta-analysis of prospective cohort studies. *Int J Cardiol* 201:469-72.
3. Chambrone L, Guglielmetti MR, Pannuti CM, Chambrone LA (2011). Evidence grade asso-ciating periodontitis to preterm birth and/or low birth weight: I. A systematic review of pro-spective cohort studies. *J Clin Periodontol* 38:795-808.
4. Penoni DC, Fidalgo TK, Torres SR, Varela VM, Masterson D, Leao AT, et al (2017). Bone density and clinical periodontal attachment in postmenopausal women: a systematic review and meta-analysis. *J Dent Res* 96:261-269.
5. Artese HP, Foz AM, Rabelo Mde S, Gomes GH, Orlandi M, Suvan J, et al (2015). Periodontal therapy and systemic inflammation in type 2 diabetes mellitus: a meta-analysis. *PLoS ONE* 10:e0128344.
6. Mawardi HH, Elbadawi LS, Sonis ST (2015). Current understanding of the relationship between periodontal and systemic diseases. *Saudi Med J* 36:150-158.
7. Zeng XT, Deng AP, Li C, Xia LY, Niu YM, Leng WD (2013). Periodontal disease and risk of head and neck cancer: a meta-analysis of observational studies. *PLoS ONE* 8:e79017.
8. Yin XH, Wang YD, Luo H, Zhao K, Huang GL, Luo SY, et al (2016). Association between tooth loss and gastric cancer: a meta-analysis of observational studies. *PLoS ONE* 11:e 0149653.
9. Zeng XT, Xia LY, Zhang YG, Li S, Leng WD, Kwong JS (2016). Periodontal disease and in-cident lung cancer risk: a meta-analysis of cohort studies. *J Periodontol* 87:1158-1164.
10. Maisonneuve P, Amar S, Lowenfels AB (2017). Periodontal disease, edentulism, and pan-creatic cancer: a meta-analysis. *Ann Oncol*. (2017) 28:985-995.
11. Fitzpatrick SG, Katz J (2010). The association between periodontal disease and cancer: A review of the literature. *J Dentistry* 2010; 38:83-95.
12. Ahn J, Segers S, Hayes RB (2012). Periodontal disease, Porphyromonas gingivalis serum antibody levels and orodigestive cancer mortality. *Carcinogenesis* 2012; 33:1055-1058.
13. Linden GJ, Lyons A, Scannapieco FA (2013). Periodontal systemic associations: review of the evidence. *J Clin Periodontol* 84:S8-19.
14. Chung SD, Tsai MC, Huang CC, Kao LT, Chen CH (2016). A population-based study on the associations between chronic periodontitis and the risk of cancer. *Int J Clin Oncol* 21(2): 219-223.
15. Dizdar O, Hayran M, Guven DC, Yilmaz TB, Taheri S, et al (2017). Increased cancer risk in patients with periodontitis. *Curr Med Res Opin* 33(12), 2195-2200
16. Urbaniak C, Cummins J, Brackstone M, Macklaim JM, Gloor GB, et al (2014). Microbiota of Human Breast Tissue. Applied and Environmental Microbiology 80(10):3007-3014.
17. Jiang X, Shapiro DJ. The immune system and inflammation in breast cancer (2014). *Mol Cell Endocrino*l 382(1):673-682.
18. Bucholc M, Łepecka-Klusek C, Pilewska A, et al (2001). Ryzyko zachorowania na raka piersi w opinii kobiet. *Ginekol Pol* 72: 1460-1456.
19. Shulman L (2013). Genetic and genomic factors in breast cancer. In: Hansen NM, editor. Management of the patient at high risk for breast cancer. New York: Springer; p. 29-47.
20. Clemons M, Loijens L, Goss P (2000). Breast cancer risk following irradiation for Hodgkin's disease. *Cancer Treat Rev* 26(4):291-302.
21. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW Jr, et al.; Collaborative Group on Hormonal Factors in Breast Cancer (2002). Alcohol, tobacco and breast cancer-collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br J Cancer* 87(11):1234-1245.
22. American Cancer Society. Breast Cancer. 2015. Available at: www.cancer.org.
23. Freudenheim JL, Genco RJ, LaMonte MJ, Millen AE, Hovey KM, Mai X, et al (2016). Periodontal Disease and Breast Cancer: Prospective Cohort Study of Postmenopausal Women. *Cancer Epidemiol Biomarkers Prev* 25(1):43-50.
24. Soder B, Yakob M, Meurman JH, Andersson LC, Klinge B, Soder PO (2011). Periodontal disease may associate with breast cancer. *Breast Cancer Res Treat* 127(2):497-502.
25. Shi T, Min M, Sun C, Zhang Y, Liang M, Sun Y (2018). Periodontal disease and susceptibi-lity to breast cancer: A meta-analysis of observational studies. *J Clin Periodontol* 45(9)1025-1033
26. Shao J, Wu L, Leng WD, Fang C, Zhu YJ, et al (2018). Periodontal Disease and Breast Cancer: A Meta-Analysis of 173,162 Participants. *Front Oncol* 2018;8:601.
27. Sfreddo CS, Maier J, De David SC, Susin C, Moreira CHC (2017). Periodontitis and breast cancer: a case-control study. *Commun Dent Oral Epidemiol* 45(6):545-551.
28. Michaud DS, Lu J, Peacock-Villada AY, Barber JR, Joshu CE, Prizment AE, et al (2018). Periodontal Disease Assessed Using Clinical Dental Measurements and Cancer Risk in the ARIC Study. *J Natl Cancer Inst* 110(8):843-854.
29. Hujoel PP, Drangsholt M, Spiekerman C, Weiss NS (2003). An Exploration of the Periodon-titis-Cancer Association. *Ann Epidemiol* 13(5):312-316.
30. Mai X, LaMonte MJ, Hovey KM, Freudenheim JL, Andrews CA, et al (2016). Periodontal disease severity and cancer risk in postmenopausal women: the Buffalo OsteoPerio Study *Cancer Causes Control* 27(2):217-228.
31. Han MA (2018). Oral health status and behavior among cancer survivors in Korea using nationwide survey. *Int J Environ Res Public Health* 15:14.
32. Arora M, Weuve J, Fall K, Pedersen NL, Mucci LA (2010). An exploration of shared genetic risk factors between periodontal disease and cancers: a prospective co-twin study. *Am J Epi-demiol* 171(2):253-259.
33. WHO International Agency for Research in Cancer, WHO: Globocan, 2020
34. Hyman JJ, Reid BC (2003). Epidemiologic risk factors for periodontal attachment loss among adults in the United States. *J Clin Periodontol* 30(3):230-237.
35. World Health Organization. Oral health surveys: basic methods. Geneva: World Health Organization; 1997. https://apps.who.int/iris/bitstream/handle/10665/41905/9241544937. pdf? sequence=1&isAllowed=y
36. Lwanga SK, Lemeshow S, World Health Organization. Sample size determination in health studies: a practical manual. World Health Organization; 1991.
37. Machuca G, Segura-Egea JJ, Jimenez-Beato G, Lacalle JR, Bullón P (2012). Clinical indica-tors of periodontal disease in patients with coronary heart disease: A 10 years longitudinal study. *Med Oral Patol Oral Cir Bucal* 17:e569-574.
38. Rubin H (2011). Fields and field cancerization: the preneoplastic origins of cancer asympto-matic hyperplastic fields are precursors of neoplasia, and their progression to tumors can be tracked by saturation density in culture. *Bio Essays* 33: 224-231.
39. Webster LR, Bilous AM, Willis L, Byth K, Burgemeister FC, et al (2005). Histopathologic indicators of breast cancer biology: insights from population mammographic screening. *Br J Cancer* 92(8): 1366-1371.

40. Mišković J, Zorić A, Radić Mišković H, Šoljić V (2016). Diagnostic Value of Fine Needle Aspiration Cytology for Breast Tumors. *Acta Clin Croat* 55(4):625-628.

41. Molloy J, Wolff LF, Lopez-Guzman A, Hodges JS (2004). The association of periodontal disease parameters with systemic medical conditions and tobacco use. *J Clin Periodontol* 31:625-632.

42. Cutress TW, Ainamo J, Sardo-Infrri J (1987). The community periodontal index of treatment needs (CPITN) procedure for population groups and individuals. *Int Dent J* 37(4):222-233.

43. Wiebe CB, Putnins EE (2000). The periodontal disease classification system of the American academy of periodontology an update. *J Can Dent Assoc* 66:594-597.

44. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, et al (2013). Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 49:1374-1403.

45. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, et al (2015). Global cancer stati-stics, 2012. *CA Cancer J Clin* 65:87-108.

46. Kamińska M, Ciszewski T, Łopacka-Szatan K, Miotła P, Starosławska E (2015). Breast cancer risk factors. *Prz Menopauzalny* 14(3): 196-202.

47. Pathy NB, Yip CH, Taib NA, Hartman M, Saxena N, et al (2011). Breast cancer in a multi-ethnic Asian setting: Results from the Singapore-Malaysia hospital-based breast cancer registry. *Breast* 20 (Suppl 2):S75-80.

48. Butt Z, Haider SF, Arif S, Khan MR, Ashfaq U, et al (2012). Breast cancer risk factors: A comparison between pre-menopausal and post-menopausal women. *J Pak Med Assoc* 62:120-124.

49. Quaglia A, Lillini R, Mamo C, Ivaldi E, Vercelli M, et al (2013). Socio-economic inequa-lities: a review of methodological issues and the relationships with cancer survival. *Crit Rev Oncol Hematol* 85:266-277.

50. Akinyemiju TF, Genkinger JM, Farhat M, Wilson A, Gary-Webb TL, et al (2015). Residen-tial environment and breast cancer incidence and mortality: a systematic review and meta-analysis. *BMC Cancer* 15:191.

51. Barry J, Breen N (2005). The importance of place of residence in predicting late-stage dia-gnosis of breast or cervical cancer. *Health Place* 11:15-29.

52. Terry PD, Rohan TE (2002). Cigarette smoking and the risk of breast cancer in women: a review of the literature. *Cancer Epidemiol Biomarkers Prev* 11(10 Pt 1):953-971.

53. Gaudet MM, Carter BD, Brinton LA, Falk RT, Gram IT, Luo J, Milne RL, et al (2017). Pooled analysis of active cigarette smoking and invasive breast cancer risk in 14 cohort stu-dies. *Int J Epidemiol* 46(3):881-893.

54. Macacu A, Autier P, Boniol M, Boyle P (2015). Active and passive smoking and risk of breast cancer: a meta-analysis. *Breast Cancer Res Treat* 154(2):213-224.

55. Gaudet MM, Gapstur SM, Sun J, Diver WR, Hannan LM, Thun MJ (2013). Active smoking and breast cancer risk: original cohort data and meta-analysis. *J Natl Cancer Inst* 105(8):515-525.

56. Jones ME, Schoemaker MJ, Wright LB, Ashworth A, Swerdlow AJ (2017). Smoking and risk of breast cancer in the Generations Study cohort. *Breast Cancer Res*19:118:1-14.

57. National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, US Department of Health and Human Services. The health consequences of smoking-50 years of progress: a report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention; 2014.

58. Cogliano VJ, Baan R, Straif K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. (2011). Preventable exposures associated with human cancers. *J Natl Cancer Inst* 103(24):1827-1839.

59. Ceschi M, Gutzwiller F, Moch H, Eichholzer M, Probst-Hensch NM (2007). Epidemiology and pathophysiology of obesity as cause of cancer. *Swiss Med Wkly* 137(3-4):50-56.

60. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A (2009). Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status–a meta-analysis. *Int J Cancer* 124(3):698-712.

61. WCRF/AICR (2007). Food, nutrition, physical activity, and the prevention of cancer: a global perspective. World Cancer Research Fund/American Institute for Cancer Research. Available from: http://www.dietandcancerreport.org/cancer_resource_center/downloads/Second_Expert_Report_full.pdf

62. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational stu-dies. *Lancet* 371(9612):569-578.

63. Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. (2015). Global burden of cancer attributable to high body-mass index in 2012: a population-based study. *Lancet Oncol* 16(1):36-46.

64. Shulman L (2013). Genetic and genomic factors in breast cancer. In: Hansen NM, editor. Management of the patient at high risk for breast cancer. New York: Springer; p. 29-47.

65. Kwong A, Ng EK, Tang EY, Wong CL, Law FB, Leung CP, et al (2011). A novel de novo BRCA1 mutation in a Chinese woman with early onset breast cancer. *Familial Cancer* 2011;10(2):233-237.

66. Narod SA, Salmena L (2011). BRCA1 and BRCA2 mutations and breast cancer. *Discov Med.* 12(66):445-453.

67. Seong MW, Cho S, Noh DY, Han W, Kim SW, Park CM. et al (2009). Comprehensive mutational analysis of BRCA1/BRCA2 for Korean breast cancer patients: evidence of a founder mutation. *Clinical Genetics* 76(2):152-160.

68. Chen W, Pan K, Ouyang T, Li J, Wang T, Fan Z. et al (2009). BRCA1 germline mutations and tumor characteristics in Chinese women with familial or early-onset breast cancer. Breast *Cancer Res Treat* 117(1):55-60.

69. Malone KE, Daling JR, Doody DR, Hsu L, Bernstein L, Coates RJ. et al (2006). Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. *Cancer Res* 66(16):8297-8308.

70. Nanda R, Schumm LP, Cummings S, Fackenthal JD, Sveen L, Ademuyiwa F. et al (2005). Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. *JAMA* 294(15):1925-1933.

71. Jancarkova N, Zikan M, Pohlreich P, Freitag P, Matous B, Zivny J (2003). Detection and occurrence of BRCA 1 gene mutation in patients with carcinoma of the breast and ovary. *Ceska gynekologie/Ceska lekarska spolecnost J Ev Purkyne* 68(1):11-16.

72. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, et al, EMBRACE (2013). Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst* 105(11):812-822.

73. Brewer HR, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ (2017). Family history and risk of breast cancer: an analysis accounting for family structure. *Breast Cancer Res Treat* 165(1): 193-200.

74. Colditz G, Rosner B, Speizer F (1996). Risk factors for breast cancer according to family history of breast cancer. *J Natl Cancer Inst* 88:65-71.

75. Parazzini F, La Vecchia C, Negri E, Franceschi S, Bocciolone L (1992). Menstrual and re-productive factors and breast cancer in women with family history of the disease. *Int J Cancer* 51:677-681.

76. Figueiredo J, Ennis M, Knight J, McLaughlin J, Hood N, O'Malley F, et al (2007). Influence of young age at diagnosis and family history of breast or ovarian cancer on breast cancer outcomes in a population-based study. *Breast Cancer Res Treat* 105:69-80.

77. Luján IJE, García RF, Figueroa PG, Hernández MI, Ayala AR. Early menarche as a risk factor of breast cancer. *Ginecol Obstet Mex* 74(11):568-572.

78. Kara Britt (2012). Menarche, menopause, and breast cancer risk. Lancet Oncol 13(11): 1071-1072

79. Khalis M , Charbotel B, Chajès V, Rinaldi S, Moskal A, Biessy C, et al (2018). Menstrual and reproductive factors and risk of breast cancer: A case-control study in the Fez region, Morocco *PLoS ONE* 13(1): e0191333.

80. Kwan ML, Kushi LH, Weltzien E, Maring B, Kutner SE, Fulton RS, et al (2009). Epidemio-logy of breast cancer subtypes in two prospective cohort studies of breast cancer survivors. *Breast Cancer Res* 11:R31.

81. Cooper K. Springhouse: Springhouse Corp (1998). Pathophysiology Made Incredibly Easy. Sandhu DS, Sandhu S, Karwasra RK, Marwah S (2010). Profile of breast cancer patients at a tertiary care hospital in North India. *Indian J Cancer* 47:16-22.

82. McCormack VA, dos Santos Silva I (2006). Breast density and parenchymal patterns as markers of breast cancer risk: A meta-analysis. *Cancer Epidemiol Biomarkers Prev* 15:1159-1169.

83. Aruna Surakasula, Govardhana Chary Nagarjunapu, KV Raghavaiah (2014). A comparative study of pre- and post-menopausal breast cancer: Risk factors, presentation, characteristics and management. *J Res Pharm Pract* 3(1): 12-18.

84. Henderson IC (1993). Risk factors for breast cancer development. *Cancer* 71 (6 Suppl): 2127-2140.

85. McDonald JA, Goyal A, Beth Terry M (2013). Alcohol Intake and Breast Cancer Risk: Weighing the Overall Evidence. *Curr Breast Cancer Rep* 5(3): 10.1007/s12609-013-0114-z.

86. Seitz HK, Pelucchi C, Bagnardi V, La Vecchia C (2012). Epidemiology and pathophysiology of alcohol and breast cancer: Update 2012. *Alcohol Alcoholism* 47(3):204-212.

87. Dumitrescu RG, Shields PG (2005). The etiology of alcohol-induced breast cancer. *Alco-hol* 35(3):213-225.

88. Oyesanmi O, Snyder D, Sullivan N, Reston J, Treadwell J, Schoelles KM, et al (2010).

89. Alcohol consumption and cancer risk: understanding possible causal mechanisms for breast and colorectal cancers. Evid Rep/Techn Assess (197):1-151.

90. Fernandez SV (2011). Estrogen, alcohol consumption, and breast cancer. *Alcohol Clin Exp Res* 35(3):389-391.

91. Terry MB, Zhang FF, Kabat G, Britton JA, Teitelbaum SL, Neugut AI, et al (2006). Life-time alcohol intake and breast cancer risk. *Ann Epidemiol* 16(3):230-240.

92. Chen WY, Rosner B, Hankinson SE, Colditz GA, Willett WD (2011). Moderate alcohol consumption during adult life, drinking patterns, and breast cancer risk. *JAMA* 306(17): 1884-1890.

93. Lynch BN , Neilson HK, Friedenreich CN (2011). Physical activity and breast cancer pre-vention. *Recent Results Cancer Res* 186:13-42.

94. Suleeporn Sangrajrang , Arkom Chaiwerawattana, Pattama Ploysawang, Kanjamad Nook-lang, Paphawin Jamsri, Sopittra Somharnwong (2013). Obesity, diet and physical inactivity and risk of breast cancer in Thai women. *Asian Pac J Cancer Prev* 14(11):7023-7027.

95. Niehoff NM, Nichols HB, Zhao S, White AJ, Sandler DP (2019). Adult Physical Activity and Breast Cancer Risk in Women with a Family History of Breast Cancer. *Cancer Epide-miol Biomarkers Prev* 28(1):51-58.

96. Shephard RJ, Shek PN (1995). Cancer, immune function, and physical activity. *Can J Appl Physiol* 20, 1-25.

97. Inoue M, Yamamoto S, Kurahashi N, Iwasaki M, Sasazuki S, Tsugane S,et al (2008). Daily total physical activity level and total cancer risk in men and women: results from a large-scale population-based cohort study in Japan. *Am J Epidemiol* 168; 391-403.

98. van Gils CH, Peeters PH, Schoenmakers MC, Nijmeijer RM, Onland-Moret NC, van der Schouw YT, et al (2009). Physical activity and endogenous sex hormone levels in post-meno-pausal women: a cross-sectional study in the Prospect-EPIC Cohort. *Cancer Epide-miol Biomarkers Prev* 18, 377-383.

99. Velthuis MJ, Schuit AJ, Peeters PH, Monninkhof EM (2009). Exercise program affects body composition but not weight in postmenopausal women. *Menopause* 16, 777-784.

100. Bernstein L, Henderston BE, Hanisch R, Sullivan-Halley J, Ross RK (1994). Physical exer-cise and reduced risk of breast cancer in young women. *J Natl Cancer Inst* 86, 1403-1408.

101. Wu Y, Zhang D, Kang S (2013). Physical activity and risk of breast cancer: a meta-analysis of prospective studies. *Breast Cancer Res Treat* 137(3):869-882.

102. Angeles-Llerenas A, Ortega-Olvera C, Pérez-Rodríguez E, Esparza-Cano JP, Lazcano-Ponce E, Romieu I, et al. (2010). Moderate physical activity and breast cancer risk: the effect of menopausal status. *Cancer Causes Control* 21(4):577-586.

103. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Lancet Physical Activi-ty Series Working Group (2012). Effect of physical inactivity on major non- communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 380(9838):219-229.

104. Pena GG, Maia YC, Mendes MC, Furtado WR, Machado-Coelho GL, Freitas RN (2014). Physical activity is associated with malignant and benign breast diseases in low-income Brazilian women. *Nutr Cancer* 66(4):707-715.

105. Sledziewski TK, Glinska K (2015). Pro-inflammatory cytokines in periodontal diseases and certain systemic disorders. *Przegl Lek*. 72:354-357.

106. Michaud DS, Liu Y, Meyer M, Giovannucci E, Joshipura K (2008). Periodontal disease, tooth loss, and cancer risk in male health professionals: a prospective cohort study. *Lancet Oncol* 9:550-558.

107. Hwang IM, Sun LM, Lin CL, Lee CF, Kao CH (2014). Periodontal disease with treatment reduces subsequent cancer risks. *QJM* 107:805-812.

108. Meurman JH, Tarkkila L, Tiitinen A (2009). The menopause and oral health. *Maturitas* 63:56-62.

109. Armitage GC (2013). Bi-directional relationship between pregnancy and periodontal disease. *Periodontol* 2000:160-176.

110. Lamonte MJ, Hovey KM, Millen AE, Genco RJ, Wactawski-Wende J (2014). Accuracy of self- reported periodontal disease in the women's health initiative observational study. *J Periodontol* 85:1006-1018.

111. Martelli ML, Brandi ML, Martelli M, Nobili P, Medico E, Martelli F (2017). Periodontal disease and women's health. *Curr Med Res Opin* (2017) 33:1005-1015.

112. Guven DC, Dizdar O, Akman AC, Berker E, Yekeduz E, Ceylan F, et al (2019). Evaluation of cancer risk in patients with periodontal diseases. *Turk J Med Sci* 49: 826-831.

113. Corbella S, Veronesi P, Galimberti V, Weinstein R, Del Fabbro M, Francetti L (2018). Is periodontitis a risk indicator for cancer? A metaanalysis. *PLoS ONE* 13(4): e0195683.

114. Tingting Shi , Min Min , Chenyu Sun, Yun Zhang , Mingming Liang, Yehuan Sun (2018). Periodontal disease and susceptibility to breast cancer: A meta-analysis of observational studies *J Clin Periodontol* 45(9):1025-1033.

115. Luo J, Margolis KL, Wactawski-Wende J, Horn K, Messina C, Stefanick ML, et al (2011). Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study. *Brit Med J* 342:d1016.

116. Jia M, Wu Z, Vogtmann E, O'Brien KM, Weinberg CR, Sandler DP, Gierach GL (2020). The association between periodontal disease and breast cancer in a prospective cohort study. *Cancer Prev Res (Phila)* 13(12): 1007-1016.

117. Nwizu NN, Marshall JR, Moysich K, Genco RJ, Hovey KM, Xai X, et al (2017). Periodon-tal disease and incident cancer risk among postmenopausal women: Results from the Women's Health Initiative observational cohort. *Cancer Epidemiol Biomarkers Prev* 26(8): 1255-1265.

118. Farhat Z, Cadeau C, Eliassen AH, Freudenheim Jo L (2021).. Periodontal Disease and Breast Cancer Risk: Results from the Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev* 10.1158/1055-9965.EPI-21-0257.

119. Van Dyke TE, van Winkelhoff AJ (2013). Infection and inflammatory mechanisms. *JPerio-dontol* 84:S1–S7.

120. Tomas I, Diz P, Tobias A, Scully C, Donos N (2012). Periodontal health status and bacte-raemis from daily oral activities: systematic review/meta-analysis. *J Clin Periodontol* 39: 213028.

121. Ward TL, Hosid S, Ioshikhes I, Altosaar I (2013). Human milk metagneome: a functional capacity analysis. *BMC Microbiol* 13:116.

122. Fernandez L, Langa S, Martin V, Mardonado A, Jimenez E, Martin R, Rodriguez JM (2013). The human milk microbiota: origin and potential roles in health and disease. *Pharma-col Res* 69:1-10.

123. Xuan C, Shamonki JM, Chung A, Dinome ML, Chung M, Sieling PA, et al (2014). Micro-bial dysbiosis is associated with human breast cancer. *PLoS One* 9:e83744.

124. Sorenson HT, Skriver MV, Friis S, McLaughlin JK, Blot WJ, Baron JA (2005). Use of anti-biotics and risk of breast cancer: a population-based case control study. *Br J Cancer* 92:594-596.

125. Rodriguez LAG, Gonzalez-Perez A (2005). Use of antibiotics and risk of beast cancer. *Am J Epidemiol* 161:616-619.

126. Velicer CM, Heckbert SR, Lampe JW, Potter JD, Robertson CA, Taplin SH (2004). Anti-biotic use in relation to the risk of breast cancer. *JAMA* 291:827-835.

127. Friedman GD, Oestreicher N, Chan J, Quesenberry CP, Udaltsova N, Habel LA (2006). Antibiotics and risk of breast cancer: up to 9 years of follow-up of 2.1 million women. *Ca Epidemiol Biomarkers Prev* 15:2102-2106.

128. Chan DS, Bandera EV, Greenwood DC, Norat T (2015). Circulating c-reactive protein and breast cancer risk-systematic literature review and meta-analysis of prospective cohort stu-dies. *Ca Epidemiol Biomarkers Prev* (10):1439-1449.

129. Noack B, Genco RJ, Trevisan M, Gross S, Zambon JJ, De Nardin E (2001). Periodontal in-fections contribute to elevated systemic C-reactive protein level. *J Periodontol* 72:1221-1227.

130. Hayashi C, Gudino CV, Gibson FC, Genco CA (2010). Pathogen-induced inflammation at sites distant from oral infection: bacterial persistence and induction of cell-specific innate immune inflammatory pathways. *Mol Oral Microbiol* 25:305-316.

131. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA (2013). Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. *Nat Rev Cancer* 13:759-771.

132. Schwabe RF, Jobin C (2013). The microbiome and cancer. *Nat Rev Cancer* 13:800-812.

133. Soory M (2010). Oxidative stress induced mechanisms in the progression of periodontal di-sease and cancer: a common approach to redox homeostasis? *Cancers* 2:670-692.

134. Miricescu D, Greabu M, Totan A, Mohora M, Didilescu A, Mitrea N, et al (2011). Oxida-tive stress-a possible link between systemic and oral diseases. *Farmacia* 59:329-337.

135. Bartold PM, Van Dyke TE (2013). Periodontitis: a host-mediated disruption of microbial homeostasis.Unlearning learned concepts. *Periodontol 2000* 62:203-218.

136. Gonzalez-Suarez E, Jacob AP, Jones J, Miller R, Roudier-Meyer MP, Erwert R, et al (2010). Rank ligand mediates progestin-induced mammary epithelial proliferation and carci-nogenesis. *Nature* 468:103-107.

137. Schramek D, Leibbrandt A, Sigl V, Kenner L, Pospislik JA, Lee HJ, et al (2010). Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer. *Nature* 468:98-102.

138. Sigl V, Penninger JM (2014). RANKL/RANK-From bone physiology to breast cancer. Cy-tokine. *Growth Factor Rev* 25:205-214.

139. Belibasakis GN, Bostanci N (2012). The RANKL-OPG system in clinical periodontology. *J Clin Periodontol* 39:239-248.

140. Tobon-Arroyave SI, Isaza-Guzman DM, Restrepo-Cadavid EM, Zapata-Molina SM, Marti-nez Pabon MC (2012). Association of salivary levels of the bone remodeling regulators sRANKL and OPG with periodontal clinical status. *J Clin Periodontol* 39:1132-1140.

141. US Department of Health and Human Services. A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004. The Health Consequences of Smoking.

142. Bizzarro S, Loos BG, Laine ML, Crielaard W, Zaura E (2013). Subgingival microbiome in smokers and non-smokers in periodontitis: an exploratory study using traditional targeted techniques and a next-generation sequencing. *J Clin Periodontol* 40:483-492.

143. van Winkelhoff AJ, Bosch-Tijhof CJ, Winkel EG, can der Reijden WA (2001). Smoking affects the subgingival microflora in periodontitis. *J Peridontol* 72:666-671.

144. Shchipkova AY, Nagaraja HN, Kumar PS (2010). Subgingival microbial profiles of smo-kers with periodontitis. *J Dent Res* 89:1246-1253.

145. Michaud D, Izard J, Rubin Z, Johansson I, Weiderpass E, Tjonneland A, et al (2013). Life-style, dietary factors and antibody levels to oral bacteria in cancer-free participants in a European cohort study. *Cancer Causes Control* 24:1901-1909.

146. Sanford NN, Sher DJ, Butler S, Xu X, Ahn C, D'Amico AV, et al (2019). Cancer Screening Patterns Among Current, Former, and Never Smokers in the United States, 2010–2015. *JAMA* 2(5):e193759