# Assessment of Periodontal Disease Indices in Breast Cancer Patients: A Case-Control Study

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**ABSTRACT**

**Background/Aim:** Breast cancer is the most prevalent malignant tumor and the leading cause of cancer in females in Europe. The purpose of the current research was to assess the potent discrepancies concerning the periodontal health status between females suffering from invasive ductal and lobular carcinoma, confirmed by histopathological examinations, and healthy ones. **Materials and Methods:** Data from an oral and dental clinical examination of 130 females suffering from breast cancer and 290 matching healthy controls were collected through a modified standardized questionnaire and analyzed using a univariate and multivariate regression model. Periodontal status concerned the following indices, Gingival Index (GI), Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), and Bleeding on Probing (BOP). Odds ratios (OR's) and 95% Confidence Intervals (CI's) were also recorded after adjustment for potential con-founders. **Results:** Female breast cancer patients showed worst CAL compared with healthy females (p=0.040, OR=1.787, 95% CI=1.208-2.651) after controlling for smoking and socio-economic level. **Conclusion:** CAL was statistically significantly different between females who were suffered from breast cancer and healthy ones.

**Keywords:** Breast Cancer, Periodontal disease, Risk factors, Females

## INTRODUCTION

Breast Cancer (BCa) is the most prevalent malignant tumor and the leading cause of cancer in females, in Europe, as it has been assessed that more than one in 10 females are affected and represents approximately 28.8% cancers in females [1]. It is also responsible for 25% of all cancer cases and 15% of all cancer-related deaths among females [2]. In addition,



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20-30% of newly diagnosed BCa cases may be associated with diverse risk factors that are involved in initiation or modification of breast cells malignant transformation [3]. BCa risk factors include age over 40 years old, BCa history in first-degree relatives, mammary gland diseases history, early age of menarche and childbearing advanced age (after 35 years), menopause advanced age, genetic susceptibility [4], alcohol consumption [5], ionizing radiation therapy [6], Caucasian race [7], obesity as expressed by body mass index (BMI), physical inactivity, and treatment with hormones and oral contraceptives [8]. However, in 75-80% of BCa cases no risk factor has been detected [7]. Periodontal disease (PD), is divided into two main types, gingivitis and periodontitis and is a chronic inflammatory disease caused by bacterial infection which invades gingiva and periodontal supporting tissues [9]. Periodontal bacteria [10] and viruses [11] are responsible for a host immuno-inflammatory response in periodontal tissues that results in periodontal pocket formation, attachment loss, bleeding and bone loss, whereas its prevalence and severity increases with age [12] and in case of aggressive and severe PD leads to tooth loss [13]. Chronic PD risk factors are smoking, diabetes mellitus, and obesity [12].

Periodontal infection has systemic implications [14] as PD patients show an increased risk of diverse diseases and disorders such as ischemic heart disease [15], stroke [16], diabetes mellitus type 2 [14], respiratory diseases [17], rheumatoid arthritis [18], osteoporosis [14], and several types of cancers [19]. A significant total cancer risk [20,21] and certain location-specific types of cancer [22-24] have been associated with poor oral hygiene, PD development, and tooth loss, independent of age, smoking, and alcohol consumption. The possible causative role of PD in cancer pathogenesis has been investigated by several researches in diverse organs such as oral cavity, oesophagus, stomach, lungs, pancreas [21,25-28] with conflicting results, even after adjustment for possible confounders such as smoking habits, socio-economic status, etc.

Accumulating evidence supposed an important role of immune-inflammatory mechanisms that may be common to PD and cancer [29,30]. Periodontal bacteria may directly affect breast carcinogenesis, stating evidence for oral bacterial species appearance in breast tissues [31], whereas it has also been proposed that PD may affect and/or reflect systemic inflammatory procedures that contribute to breast carcinogenesis [32]. However, the exact mechanisms for the potential relationship between PD and risk for cancer development still remain unknown.

Previous and recent researches have recorded an elevated BCa risk among females with PD [29,30, 33-36], however, remarkable limitations of those studies concerned inadequate sample sizes and inadequate control for possible confounding factors. Moreover, conflicting observations regarding the relationship between PD and BCa risk have been carried out as previous studies, have revealed no association between both diseases [26,37-40].

In contrast to the mentioned investigations, few researches have investigated oral health conditions or periodontal health in females BCa patients and they have focused on patients undergoing adjuvant therapy, such as chemotherapy, radiotherapy, hormone therapy and anti-body treatment [41-46].

In Greece similar prospective or retrospective studies that examined the possible differences in periodontal status between female BCa patients and healthy ones have not been carried out.

The current report was performed to estimate the potential differences in periodontal health status between females who suffered from BCa, confirmed by histopathological examinations, and healthy ones.

## MATERIALS AND METHODS

### Study population sample and study design

The current retrospective case-control research was carried out between November 2021 and July 2022. Sample size estimation was based on BCa prevalence [47] and the EPITOOLS guidelines (https://epitools.ausvet.com.au) determined with 95% Confidence Interval (CI) and desired power 0.8. The World Health Organization (WHO) recommendations for evaluating periodontal status incidence were used for assessing age group [48]. In the study sample included 420 females, 130 who suffered from BCa cases and 290 healthy females - control, aged 45 to 78 and were derived from three private practices, one dental and two medicals. The patients group consisted of females whose BCa primary diagnosis was based on patients' Mammography findings, however, the definitive diagnosis was confirmed by histopathological examination of the intraoperatively removed tumor or its components, using traditional cytologic, histological, and histochemical methods[49]. The diagnostic method of fine needle aspiration (FNA) biopsy was done [50] in a low rate of BCa patients (21 or 16.15%).

**Eligibility criteria**

To be eligible, the participants, patients and healthy individuals, should not have been treated by a conservative or a surgical procedure in their oral cavity during the last 6 months, or prescribed for systemic antibiotic or immunosuppression agents or glucocorticoids within the previous 6 months. Moreover, they should have more than 15 teeth and periodontitis from stage I to IV [51]. Exclusion criteria concerned females with diabetes mellitus, cardiovascular diseases or any other type of cancer, and hospital patients for controlling possible confounders such as age, smoking habits, and socio-economic level. Females with advanced BCa under medical treatment, those with breast metastases caused by a primary focus at a different region, and those diagnosed in other locations in head-neck-thorax region (carcinogenesis field theory [52]), were also excluded from the study protocol. The friendly and collegial environment of cases determined the control group selection as were inhabitants of the same city with cases, and were visited the mentioned practices for their routine health follow-up. Moreover, patients and healthy individuals were matched for age and gender. The mentioned conditions could affect oral and periodontal tissues and lead to biased secondary associations.

The present research was not approved by authorized Greek committees as was a non-experimental one. Patients and healthy individuals were informed about the aims/methods and significance of the importance of the present research, and gave their written consent to enroll in the study protocol.

**Research questionnaire**

Participants answered to a modified Minnesota Dental School Medical questionnaire [53], that contained epidemiological variables such as age, smoking status, educational and socio-economic level, BMI, current diseases and disorders, and past medical/dental history.

For assessing the intra-examiner variance, a sample of 84(20%) participants was chosen randomly and 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 = 0.96*), whereas no oral hygiene instructions were given to the participants during the mentioned period.

**Periodontal Disease indices assessment**

All interproximal sites, mesial and distal, were measured regarding the following indices, Gingival Index (GI), Probing Pocket Depth (PPD), Clinical Attachment Loss (CAL), and Bleeding on Probing (BOP) in the whole of the quadrants except remaining roots and third molars, the worst values were calculated to the nearest 1.0 mm and coded as dichotomous variables for each participant, using a Williams probe with a controlled force of 0.2 N (DB764R, Aesculap AG & Co. KG, Tuttlingen, Germany), GI categorized as score 0, which corresponds to Löe [54] classification 0 and 1, and-score 1, which corresponds to Löe classification as score 2 and 3. PPD was dichotomously calculated as score 0: stage I [maximum PPD ≤ 4.0 mm] and score 1: stage II-IV [PPD ≤ 4.0-≥ 6.0 mm], and CAL severity was calculated as score 0: stage I [CAL: 1.0-2.0 mm], and score 1: stage II-IV [CAL: 3.00-≥ 5.0 mm] [55]. BOP was categorized as score 0: absence, and score 1: BOP presence and regarded as positive if it displayed within 15 seconds of probing.

**Assessment of covariates**

Socio-demographic variables and potential variables were included as covariates in the univariate and multivariable analyses. Cases and controls' age was categorized as 45-50, 51-60, and 61+; education level was classified as elementary and higher education (University/College) level. Socio-economic status was categorized as ≤1,000 and >1,000 €/month. Cigarette smoking was categorized as never (females who smoked less than 100 cigarettes during their lifetime), and former (females who smoked at least 100 cigarettes in their lifetime and reported that they now smoke "not at all") / present smokers (females who smoked at least 100 cigarettes in their lifetime and reported they now smoke "every day" or "some days"). BMI is an obesity index and was classified as normal (<30 Kg/m$^2$) and high (≥30 Kg/m$^2$) [8].

**Statistical analysis**

For each case and control, the worst values of PPD and CAL on six sites per tooth and the BOP presence/absence were calculated and categorized as dichotomous variables, as already mentioned. Univariate analysis model was performed to assess the possible relationship between cases/controls and the independent variables examined. Logistic regression model was applied to assess the mentioned associations using the Enter and Wald methods. Adjusted OR's and 95% CI were also recorded. The SPSS ver.19.0 package was used, and a p-value of less than 5% ($p< 0.05$) was regarded significant for all statistical tests done. Moreover, the statistical model of Cohran's and Mantel-Haenszel's was applied order to control the possible confounders, in an attempt to avoid biased secondary associations.

## RESULTS

Cases and controls showed a mean age of 62.4 (± 2.32) years.

Invasive ductal (64.2%) and lobular cancer (35.8%) were the dominant histopathological types, as the infrequent histological types of BCa were excluded.

After performance of the univariate analysis cases showed significantly higher values in CAL, compared with controls (p=0.002, 95% CI=0.489-0.774), whereas no one other PD index was found to be statistically significantly different between BCa patients and healthy females (Table 1). No statistically significant differences were recorded between BCa patients and healthy females concerning epidemiological parameters such as age (p= 0.387), educational status (p=0.222, 95% CI=0.510-1.170), socio-economic status (p=0.184, 95% CI=0.472-1.156), BMI (p=0.545-1.274), whereas cases showed significantly higher values concerning smoking com-pared with healthy females (p=0.020, 95% CI=0.389-0.924).

**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 | 23 (17.7) | 58 (20.0) | | |
| 51-60 | 42 (32.3) | 81 (27.9) | | |
| 61-70 | 48 (36.9) | 96 (33.1) | 0.387 | |
| 71+ | 17 (13.1) | 55 (19.0) | | |
| Educational level | | | | |
| Low | 67 (51.5) | 168 (57.9) | 0.222 | 0.772 (0.510-1.170) |
| High | 63 (48.5) | 122 (42.1) | | |
| S/economic level | | | | |
| Low | 38 (29.2) | 104 (35.9) | 0.184 | 0.739 (0.472-1.156) |
| High | 92 (70.8) | 186 (64.1) | | |
| Smoking status | | | | |
| Never | 43 (33.1) | 131 (45.2) | **0.020*** | 0.600 (0.389-0.924) |
| Previous/Current | 87 (66.9) | 159 (54.8) | | |
| Body Mass Index | | | | |
| <30 kg/m$^2$ | 49 (37.7) | 122 (42.1) | 0.399 | 0.833 (0.545-1.274) |
| ≥30 kg/m$^2$ | 81 (62.3) | 168 (57.9) | | |
| Gingival Index | | | | |
| Absence/Mild | 40 (30.8) | 102 (35.2) | 0.378 | 0.819 (0.526-1.277) |
| Moderate/Severe | 90 (69.2) | 188 (64.8) | | |
| Probing pocket depth | | | | |
| ≤ 4.0 mm | 29 (22.3) | 78 (26.9) | 0.318 | 0.780 (0.479-1.271) |
| ≤ 4.0-≥ 6.0 mm | 101 (77.7) | 212 (73.1) | | |
| Clinical Attachment Loss | | | | |
| 1.00-2.00 mm | 33 (25.4) | 119 (41.0) | **0.002*** | 0.489 (0.309-0.774) |
| 3.0-≥ 5.0 mm | 97 (74.6) | 171 (59.0) | | |
| Bleeding on Probing | | | | |
| Absence | 38 (29.2) | 99 (34.1) | 0.321 | 0.797 (0.509-1.249) |
| Presence | 92 (70.8) | 191 (65.9) | | |

*p-value statistically significant.



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Similarly, the Enter and the Wald step of multivariate regression model confirmed the previous finding regarding CAL, (p=0.048, 95% CI=1.291-2.883, and p= 0.040, 95% CI=1.208-2.651, respectively) (Table 2). The first step of the model also showed no statistically significant differences concerning age (p=0.788, 95% CI=0.817-1.306), educational level (p=0.337, 95% CI=0.529-1,243), socio-economic status (p=0.314, 95% CI=0.810-1.926), smoking status (p=0.064, 95% CI=0.708-1.717), gingival inflammation (p=0.056,95% CI=0.935-1.984), bleeding on probing (p=0.225, 95% CI=0.848-1.812), and deep periodontal pockets (p=0.131, 95% CI=1.022-1.456), between cases and controls, except a marginal statistically significant difference concerning BMI (p=0.053, 95% CI=1.056-2.082).

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

| **Variables in the Equation** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | B | S.E. | Wald | df | Sig. | Exp (B) | 95% CI. 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 | ,064 | 1,103 | ,708 | 1,717 |
| | body.mass ind | ,677 | ,229 | 5,738 | 1 | **,053*** | 1,968 | 1,056 | 2,082 |
| | gingival index | ,380 | ,228 | 2,777 | 1 | ,056 | 1,462 | ,935 | 1,984 |
| | bleed.prob | ,267 | ,220 | 1,469 | 1 | ,225 | 1,306 | ,848 | 1,812 |
| | clin.attach.loss | ,069 | ,224 | ,095 | 1 | **,048*** | 1,471 | 1,291 | 2,883 |
| | prob.pock.dept | ,652 | ,219 | 6,831 | 1 | ,131 | 1,121 | 1,022 | 1,456 |
| | Constant | 2,455 | ,448 | 30,096 | 1 | ,000 | ,086 | | |
| Step 2[a] | body.mass.ind | ,550 | ,215 | 6,566 | 1 | **,048*** | 1,733 | 1,138 | 2,340 |
| | clin.attach.loss | ,570 | ,207 | 5,581 | 1 | **,040*** | 1,787 | 1,208 | 2,651 |
| | Constant | 2,067 | ,279 | 55,063 | 1 | ,000 | ,127 | | |

a. Variable(s) entered on step 1: age, education.level, socioecon.level, smok.status, body.mass.index, ging.

index, bleed. prob, clin.attach.loss, prob.pock.dept.

*p-value statistically significant.

After using Cohran's and Mantel-Haenszel's method for adjusting known confounders such as smoking and socioeconomic status the same associations were recorded (Table 3).

**Table 3:** Cohran's and Mantel-Haenszel's statistical model for controlling possible confounders.

| Variables | Exp (B) | 95% Confidence Interval |
|---|---|---|
| Clinical Attachment Loss | | |
| Non-smokers | 1.733 | 1.135-2.624 |
| Previous/Current smokers | 3.422 | 1.543-5.843 |
| Clinical Attachment Loss | | |
| Low socio-economic status | 1.688 | 1.058-2.447 |
| High socio-economic status | 2.727 | 1.182-3.119 |



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## DISCUSSION

The outcomes of the present study recorded statistically significant differences between BCa patients and healthy females examined, regarding BMI and CAL. Moreover, the results did not reveal any statistically significant difference between cases and controls, regarding epidemiological variables such as age, socio-economic level, however, OR's values for age, socio-economic and smoking status, GI, PPD and BOP were to some degree higher in cases compared with controls.

PD has been associated with cancer risk over the years [19,21], whereas it has been stated the role of PD therapy in decreasing the risk of different cancer types [56].

The initiation and development of PD and cancer is associated with chronic inflammatory response and possible abnormalities in the cellular signaling pathways. Therefore, any type of PD treatment, conservative or surgery could eliminate the levels of biomarkers and mediators that are implicated and promote a disturbed chronic inflammatory reaction, giving importance to the application of a strict oral care program and preventive dentistry of BCa patients [57].

Smoking is a main causative factor for PD pathogenesis and various cancer types [58,59] and often acts as a confounder in articles investigating that association. However, smoking is not considered as a BCa risk factor [3]. The results of the present survey revealed that smoking was not statistically significant difference between BCa patients and healthy females.

Obesity and mainly raised BMI have been constantly associated with an increased risk of BCa [60]. The results recorded that BCa patients had significantly higher values of BMI compared with controls, finding that cannot be confirmed by previous reports as similar reports have not been carried out.

GI indicates the severity of gingival inflammation; however, the usage of that index is restricted in epidemiological investigations despite the fact that counts the gingival tissue inflammatory load whereas, Hujoel et al. suggested a special role for gingival inflammation as a risk factor for diverse types of cancer appearance [26].

Amodio et al. observed that cases with BCa compared to controls showed significantly higher scores for sites with detectable plaque [41]. Previous articles also confirmed the mentioned finding showing that plaque index was worse in cases with BCa compared to controls with significantly higher scores [42-45]. Those articles are not fully comparable as different indices were used regarding dental plaque accumulation and concerned female BCa patients undergoing adjuvant treatment, as similar articles have not been conducted up to now.

PPD is used for assessing PD severity [61], and the outcomes showed that PPD was not statistically significant different between female BCa patients and healthy ones. In the literature a limited number of articles have been performed concerning the oral or periodontal health status in patients who suffered from BCa and concerned female BCa patients undergoing adjuvant treatment as already mentioned.

Previous research that investigated the periodontal health status in BCa postmenopausal females showed no significant difference for sites with a depth ≥4.0 mm, between BCa patients and healthy females [41]. In another recent similar study which investigated periodontal health status in BCa females in adjuvant treatment the main outcomes were those BCa females undergoing Tamoxifen or Aromatase Inhibitor (AI) treatment showed a very high prevalence of mild/moderate periodontitis [46]. Similar outcomes confirmed in an article by Eagle et al. in which female BCa patients showed significantly deeper probing depths, as compared to controls at the 6-, 12-, and 18-month study visits ($p<0.05$) [42].

BOP is a crucial indicator of periodontal examination and diagnosis, and the most valid PD activity indicator [62] and reflects the host's vascular response with reference to hyperemia, the capillaries' dilation and elevated blood flow in the inflammation location. PD and CAL refer to the long-term stages of chronic inflammation including destructive processes signs of a chronic inflammatory reaction [63]. BOP is a widely used criterion to diagnose gingival inflammation, however deep periodontal pockets, ≥ 5.0 mm, showed a significantly higher incidence of BOP [62].

No statistically significant difference was observed concerning BOP between cases and controls, finding that was not in agreement with the higher gingival inflammation scores observed in the BCa group after adjusting for possible confounders smoking habits, and socio-economic status. In a previous article in postmenopausal female BCa patients was observed that the median full-mouth gingival BOP score was 16.05 for the cases and 0 for the controls ($p=0.04$) [41]. Similar longitudinal research recorded significant differences in BOP between the groups from baseline to 18-month visits with a greater increase found in the control group than the AI group

[42]. Similar findings reported in a study by Krishnan et al. [43].

CAL is an indicator of cumulative tissue destruction, including past PD, whereas PPD is an indicator of current disease status inflammation [64].

The only periodontal index that was worse in cases with BCa compared to controls with significantly higher scores concerned CAL, finding that was in line with that of previous reports [41-45].

The higher risk of PD in cancer patients has been proposed to be an effect of psychological burden rather than disturbances in patients' nutrition or alterations in the oral cavity concerning the quality/quantity of saliva, or disturbances in the balance of microbiological and immunological agents in the oral cavity that could be influenced because of the chemotherapy or radiotherapy [65,66]. It is also potential that female BCa patients are more susceptible to the progression and destruction of periodontal tissue than the healthy individuals, suggestion that could be attributed to the poor prognosis of BCa in cases of metastatic invasive histological types [67].

The purpose of the current research was to compare female BCa patients and epidemiologically matched healthy females concerning diverse PD indices and not to explore a potential association between PD indices, as etiological or risk factors, and BCa development. Therefore, the current research has certain limitations. Retrospective case-control studies do not have the reliability of the prospective ones, whereas selection random, recall, biases and the effect of possible confounders could lead to biased secondary associations concerning the parameters examined. Moreover, those studies are based on questionnaires and the participants either could not respond or could state no reliable responses or over- or underestimate their potential medical health status.

The strengths of present research are the fullness of follow-up, the well-characterized cohort that it was possible to consider confounding and interaction by known risk factors.

Another aspect is the PD status determination by oral and dental clinical examination and not by self-report questionnaires, consequently, no possible misclassification of exposure to PD exists. Such misclassification may result in the miscalculation of the relationship between PD and risk of developing BCa.

PD expressed by CAL was found statistically different in BCa female patients compared with healthy individuals.

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