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Subgingival microbial profile of women with breast cancer: a cross-sectional study

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Abstract

Background: Some prospective studies have observed associations between periodontal disease and breast cancer. Therefore, the aim of the present study was to investigate the composition of the subgingival biofilm of women diagnosed with breast cancer, who also presented with chronic periodontitis.

Methods: All subjects underwent clinical and microbiological assessment. Subgingival biofilm samples were taken from at least three sites of 44 women who had breast cancer. The mean levels and proportions of 40 bacterial species were determined by checkerboard DNA-DNA hybridization. Spearman correlation was used to assess possible associations between the mean levels of bacterial species and clinical conditions.

Results: The five species found at the highest levels were *Prevotella nigrescens*, *Actinomyces gerencseriae*, *Neisseria mucosa*, *Porphyromonas gingivalis* and *Tannerella forsythia*. The species detected in the lowest counts were *Propionibacterium acnes*, *Streptococcus constellatus*, *Streptococcus intermedius*, *Eubacterium saburreum* and *Streptococcus anginosus*. No significant association between levels and proportion of bacterial species and clinical parameters were found.

Conclusion: In conclusion, the results of the present study found no direct association between the subgingival microbiota and breast cancer and an indirect pathway should be addressed in further studies.

Trial registration: Retrospectively registered.

Keywords: Breast cancer, Periodontitis, Subgingival microbiota, Risk factor, Cancer

Clinical relevance

Scientific rationale for study: Periodontitis is an extremely prevalent disease and has been associated with a risk factor for breast cancer. However, up to now, no studies have aimed to analyze the subgingival microbiota of women with breast cancer who also had periodontitis. **Principal findings:** The subgingival biofilm was colonized predominantly by Gram-negative species. Two species from the red complex *P.gingivalis* and *T.forsythia* were the species with the highest mean counts. **Practical implications.** Although no association between subgingival microbial profile and breast cancer was found, subgingival

microbiota can increase the expression of virulence and this relation should be investigated.

Background

Chronic periodontitis (ChP) is characterized by polymicrobial infection and inflammation of the periodontium that result in loss of connective tissue and alveolar bone surrounding the teeth [1, 2]. It has been associated with increased risk of systemic illnesses, including diabetes mellitus [3–5], cardiovascular disease [6, 7] respiratory disease [8, 9] and rheumatoid arthritis [10–12]. Indeed, ChP promotes systemic inflammation via translocation of oral bacteria, bacterial toxins, and inflammatory mediators through frequent transient bacteremia that would heighten the systemic burden and could promote cellular differentiation [4, 13]. In addition, ChP has also been associated with cancers of the head and neck [14, 15], pancreas [16], lung [17], and more recently breast cancer [18, 19].

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Breast cancer is an important public health disease. New estimates indicate that it is the second most common cancer around the world and the most frequent cancer among women [20]. Some prospective studies have observed associations between periodontal disease and breast cancer [18, 19, 21]. Freudenheim et al. [18] observed a higher risk of breast cancer among study participants who self-reported having periodontal disease, using data from 73,737 postmenopausal women followed up for 6.7 years. Sfreddo et al. [19] in a case control study, reported that women diagnosed with periodontitis had two to three times higher odds of breast cancer than women without periodontitis. Some hypotheses have been suggested to explain a possible association between cancer and periodontitis. The most frequently advocated biological plausibility is that persistent periodontal infection and inflammation induce a chronic systemic inflammatory state, which could act in a protumour fashion at distant sites [14]. However, no studies to date have analyzed the microbial profile of the subgingival biofilm of women with breast cancer and periodontitis. Therefore, the aim of this study was to explore the microbial composition of women diagnosed with breast cancer, who also had periodontitis.

Materials and methods

Subject population

This cross-sectional study was performed between November 2014 and April 2015 at the Department of Gynecology at the University Hospital Cassiano Antônio de Moraes (HUCAM) Vitoria, Brazil. The study was conducted according to the declaration of Helsinki and was approved by the Committee on Ethics in Research with Human Beings of the Health Sciences Center (UFES) (IRB:862.952). Accordingly, the study protocol was explained to each subject, and a signed informed consent was obtained. Forty-four women diagnosed with breast cancer (ICD-10 C50) at the Mastology Clinic were selected. No restrictions regarding cancer staging and cancer treatment were used.

Inclusion criteria

The inclusion criteria were as follows: women having breast cancer, aged between 35 to 75 years, > 10 teeth and at least one teeth with probing depth (PD) and clinical attachment level (CAL) ≥ 4 mm. Breast cancer had been diagnosed by board-certified gynaecologists specialized in mastology using standard diagnostic procedures defined by Brazilian National Institute of Cancer (INCA) which included mammograms, ultrasounds, fine needle aspiration, core needle biopsy and excisional biopsy, as needed. Biopsy specimens were evaluated by medical pathologists.

Exclusion criteria

Women who needed antibiotic prophylaxis prior to oral examinations, or who were wearing fixed orthodontic appliances, using medications associated with gingival overgrowth (nifedipine, cyclosporine and phenytoin), diagnosed with psychomotor disorders, had taken antibiotics drugs within 6 months before the clinical examination were not included.

Data collection and clinical monitoring

A trained interviewer (VRB) used a structured questionnaire to collect data on demographic characteristics, socioeconomic status, lifestyle exposure and medical history. In addition, data including cancer diagnosis, treatment type and duration, and medications were collected from each participant's medical record using a standardized form. Clinical monitoring was performed by one calibrated examiner (VRB). Visible plaque index (VPI presence or absence), bleeding on probing (BOP; presence or absence), PD (mm) and CAL (mm) were measured at 6 sites per tooth (mesiobuccal, buccal, distobuccal, distolingual, lingual and mesiolingual) in all teeth, excluding third molars. The PD and CAL measurements were recorded to the nearest millimeter using a North Carolina periodontal probe (Hu-Friedy, Chicago, IL, USA).

Microbiological monitoring

Subgingival plaque samples were collected from 3 to 4 non-contiguous interproximal sites per subject with PD ≥ 4 mm. After the clinical parameters had been recorded, the supragingival plaque was removed and the subgingival samples were taken with individual sterile mini-Gracey curettes (#11–12) and immediately placed in separate Eppendorf tubes containing 0.15 ml of TE (10 mM Tris-HCl, 1 mM EDTA, pH 7.6). One hundred microliters of 0.5 M NaOH was added to each tube and the samples were dispersed using a vortex mixer. Counts of 40 bacterial species were determined in each sample, using the checkerboard DNA–DNA hybridization

Table 1 Demographic characteristics and mean (\pm SD) full-mouth clinical parameters of the subjects in experimental group

Variables	Chronic periodontitis
Subjects (n)	44
Age (years)	51.0 \pm 7.0
Probing depth (mm)	2.23 \pm 0.45
Clinical attachment level (mm)	2.51 \pm 0.69
Mean number of sites with PS ≥ 4 mm	13.0 \pm 11.1
% sites with	
Plaque	40 \pm 45
Bleeding on probing	22 \pm 22

SD Standard deviation

Table 2 Mean (\pm SD) clinical parameters of the sites analyzed microbiologically

Variables	Chronic periodontitis
Number of samples	144
Probing depth (mm)	4.7 \pm 0.4
Clinical attachment level (mm)	2.0 \pm 2.6
% sites with	
Plaque	80 \pm 12
Bleeding on probing	92 \pm 10

SD wStandard deviation

technique [22, 23] at the Laboratory of Microbiology of Guarulhos University.

Briefly, samples were boiled for 10 min and 800 μ l of 5 mol/L ammonium acetate was added to promote bacterial lyses and consequent suspension of DNA in solution. A nylon membrane (15 X 15 cm), with positive charge (Hybond N⁺-Amersham, GE Healthcare Limited, Buckinghamshire, England, UK), was placed in a MiniSlot 30[®] (Immunitics, Cambridge, MA, USA) and 1000 μ l of each suspension was placed into the

extended slots of the MiniSlot 30[®] and fixed to the membrane by baking it at 120 $^{\circ}$ C for 20 min. In each membrane 28 samples are placed and the last two channels of Minislot 30[®] are reserved for the placement of controls, containing a mixture of species of microorganisms that have been investigated by DNA probes, in two concentrations, 10⁵ and 10⁶ bacterial cells. A Miniblotter 45[®] (Immunitics, Cambridge, MA, EUA) device was used to hybridize the digoxigenin-labeled whole-genomic DNA probes perpendicular to the lanes of the clinical samples. Prior to the examination of the samples, the probes are tested to calibrate the controls.

Bound probes were detected through the use of phosphatase-conjugated antibodies to digoxigenin and chemiluminescence (CDP-Star Detection Reagent[™], Amersham, GE Healthcare Limited, Buckinghamshire, England, UK). The membranes were placed under a radiographic film (AGFA[®]-IBF, Duque de Caxias, RJ, Brazil) by approximately sixty minutes. The films were revealed shortly thereafter. Each probe produces a certain type of signal, which was visually compared to the

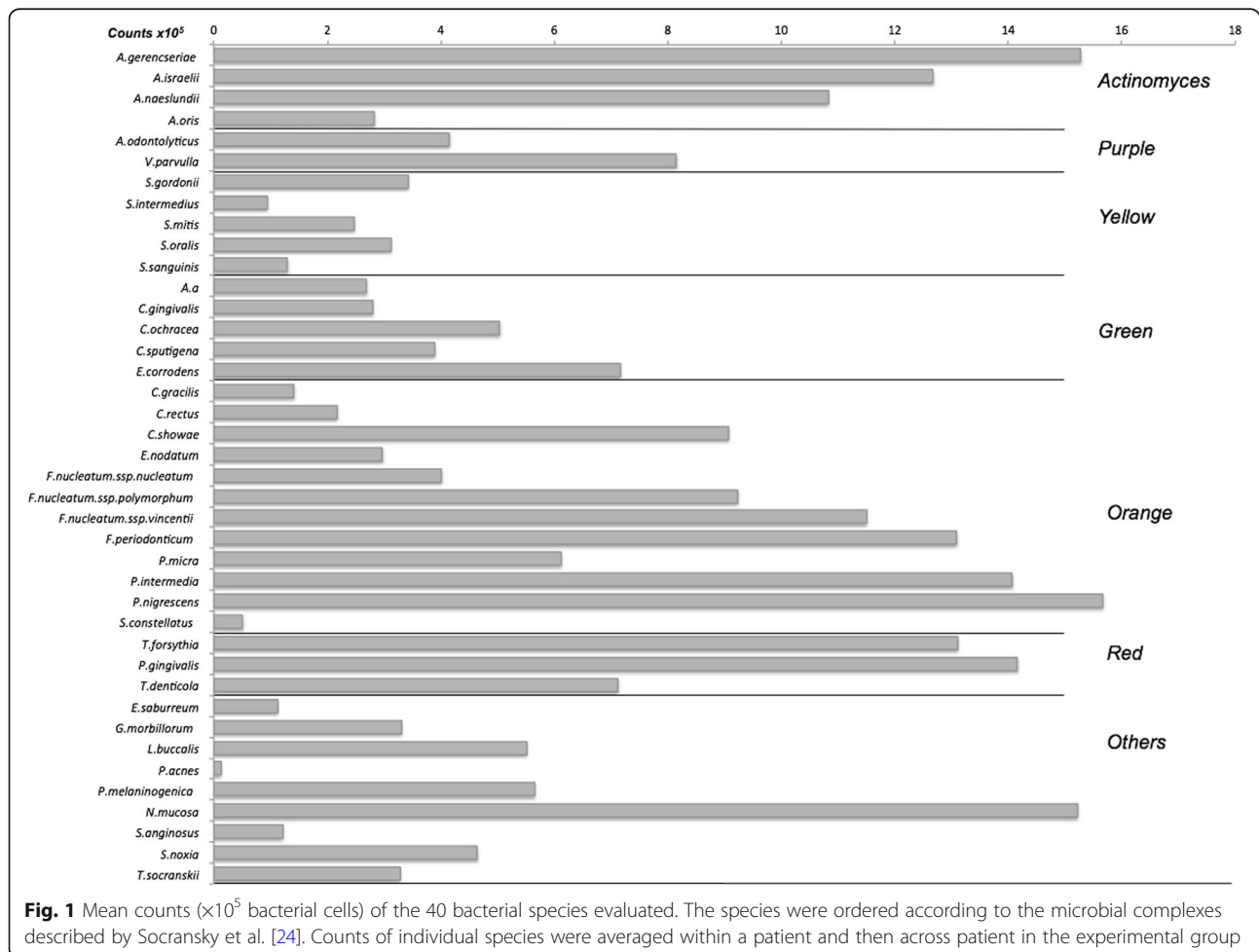


Fig. 1 Mean counts ($\times 10^5$ bacterial cells) of the 40 bacterial species evaluated. The species were ordered according to the microbial complexes described by Socransky et al. [24]. Counts of individual species were averaged within a patient and then across patient in the experimental group

signals produced by the probes in the two controls containing 10^5 and 10^6 bacteria. The signals were scored related to the count levels observed: (0) not detected; (1) $< 10^5$ cells; (2) nearly 10^5 cells; (3) between 10^5 and 10^6 cells; (4) nearly 10^6 cells; (5) $> 10^6$ cells. Signals were also coded for presence (0) or absence (1) of each tested bacterial species. The sensitivity of this assay permitted the detection of 10^4 cells of a given bacterial species by adjusting the concentration of each DNA probe.

Statistical analysis

The mean age and mean percentage of sites with VPI and BOP as well as mean full-mouth PD and CAL and mean sample sites PD and CAL were computed for each subject and then averaged across subjects.

Microbiological data were express in proportions and levels of each species in each sample at the baseline visit. Mean counts $\times 10^5$ of each species were computed for each sample and then averaged across subjects. Spearman correlation was used to assess possible associations

between the mean levels of bacterial species and clinical conditions. The level of significance was set at 5%.

Results

The demographic characteristics and clinical parameters of the studied population and the sampled sites are presented in Tables 1 and 2, respectively. A total of forty-four women diagnosed with breast cancer participated in this investigation. This population presented a mean number of sites with $PD \geq 4$ mm of 13.0 ± 11.1 (Table 1) and the mean PD and CAL of the sites analyzed was 4.7 ± 2.6 mm and 2.0 ± 2.6 mm (Table 2), respectively.

The mean counts ($\times 10^5 \pm SEM$) and mean percentage of DNA probe counts (proportions) of the 40 species evaluated are presented in Figs. 1 and 2, respectively. The five species found at the highest levels ($10^5 \pm SEM$) were *Prevotella nigrescens* (15.6 ± 2.4), *Actinomyces gerencseriae* (15.2 ± 2.4), *Neisseria mucosa* (15.2 ± 2.3), *Porphyromonas gingivalis* (14.1 ± 2.7) and *Tannerella forsythia* (13.1 ± 2.5). The species detected in the lowest counts were *Propionibacterium acnes* (0.1 ± 0.02), *Streptococcus constellatus*

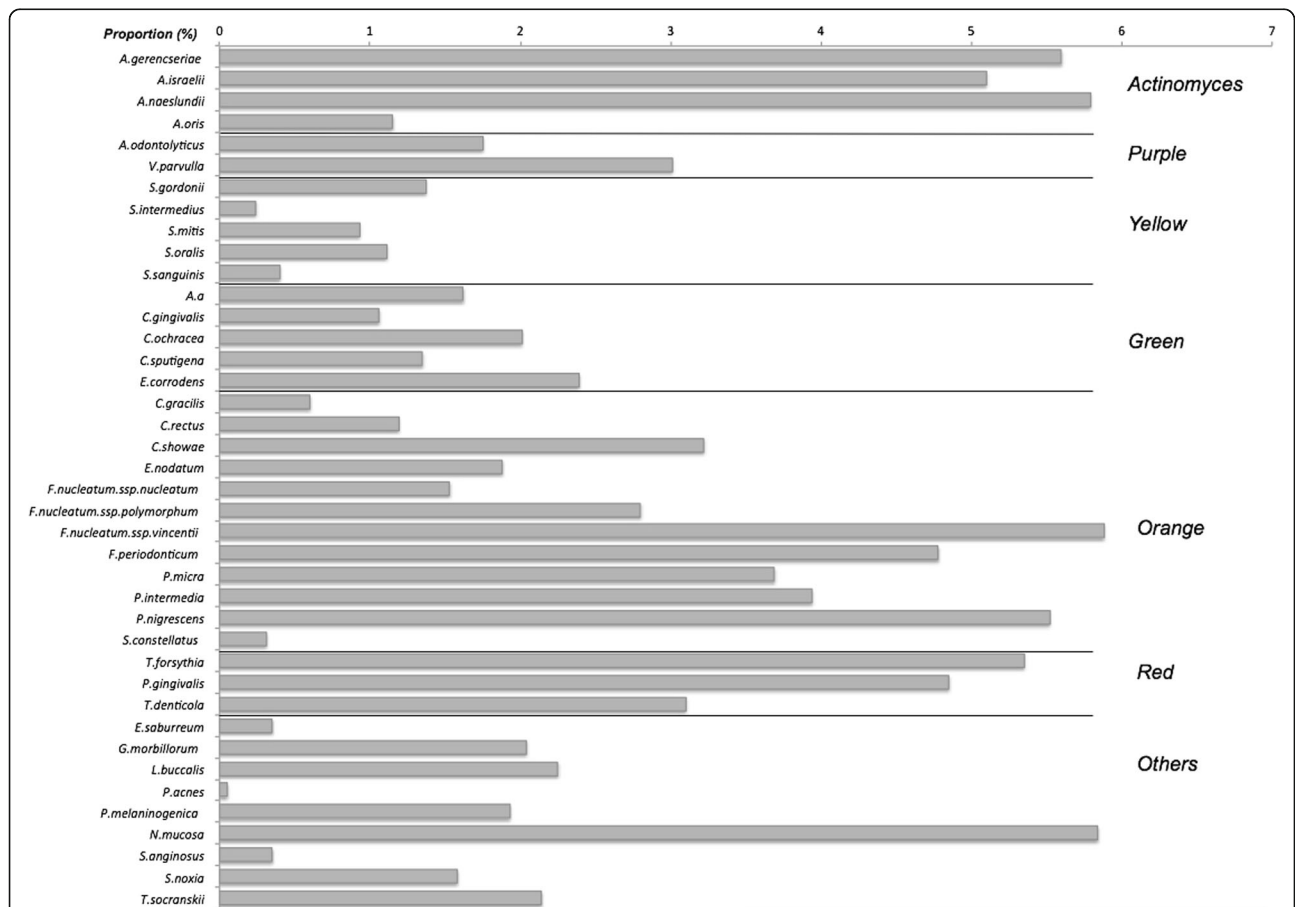


Fig. 2 Mean proportion (% of DNA probe counts) of the 40 bacterial species evaluated. The proportion of each species were ordered according to the microbial complexes described by Socransky et al. [24]. The proportion that each species comprised of the total DNA probe count was determined at each site, and then averaged within and across subjects in the experimental group

(0.5 ± 0.1), *Streptococcus intermedius* (0.9 ± 0.1), *Eubacterium saburreum* (1.1 ± 0.2) and *Streptococcus anginosus* (1.2 ± 0.2) (Fig. 1).

Seven species was found over 5% of the total of microbiota analyzed been *Fusobacterium nucleatum ssp nucleatum*, *N mucosa*, *Actinomyces naeslundii*, *A. gerencseriae*, *P. nigrescens*, *T. forsythia* and *P.gingivalis* (Fig. 2). The species found in the lowest proportion, below to 1% of the total of microbiota were *C. gracilis*, *Streptococcus sanguinis*, *E. saburreum*, *S. anginosus*, *S. constelattus*, *S. intermedia* and *P. acnes*.

The mean proportion of the microbial complexes presented in the subgingival biofilm of women with breast cancer are described in Fig. 3. The orange and red complex were found in almost 50% of the microbial load, 35.3 and 13.3%, respectively. *Actinomyces* species were found in 17.6% and others species not found in the microbial complex was found in 16.5%. No significant association between levels and proportion of bacterial species and clinical parameters were found.

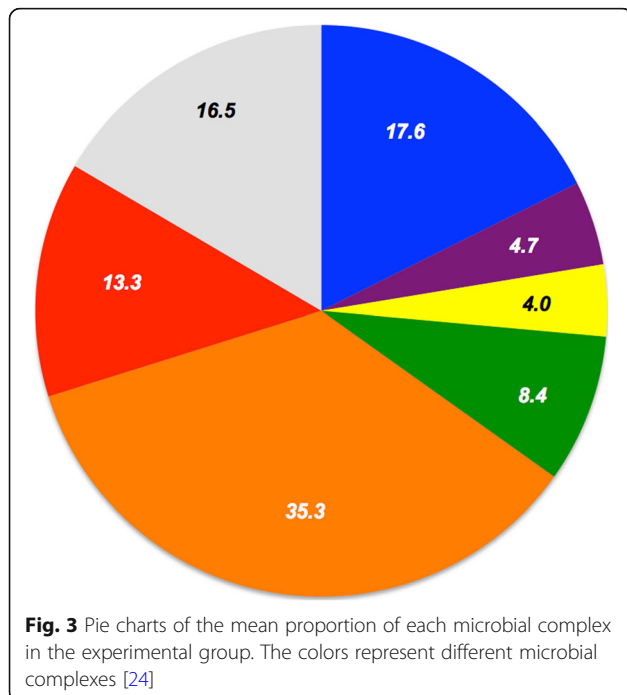
Discussion

Nowadays, a great deal of research effort has been dedicated to understanding the impact of the oral microbial burden on systemic health. It is well recognized that periodontal infection increases the level of inflammatory markers in the blood, and several studies [14–17] have linked this persistent inflammation to the development of different types of cancer, including breast cancer [18, 19, 25]. Therefore, defining the microbial profile of women with breast cancer and

periodontitis is important contributory data to our understanding of the relationship between periodontitis and this systemic condition. To our knowledge, this is the first report in which the composition of the subgingival microbiota of woman with breast cancer has been extensively evaluated. The levels and proportions of 40 bacterial species in 144 subgingival plaque samples from 44 subjects were analyzed.

The subgingival biofilm of our experimental group was colonized predominantly by Gram-negative species. Two species from the red complex *P. gingivalis* and *T. forsythia* were the species with the highest mean counts. In addition, higher levels of some putative periodontal pathogens from the orange complex were also found in the subgingival biofilm of women with breast cancer, especially species of *Fusobacterium* sp. and *Prevotella* sp. It is important to note that the microbial profile of our study population was in agreement with previous studies that found higher levels of these bacterial species in the subgingival biofilm of subjects with periodontitis [26–28] and no differences were observed between our data and the data provided by the literature. However, it is important to highlight that our study population presented a clinical profile compatible with mild periodontitis, and we also found a complex microbiota in their subgingival biofilm. Therefore, an indirect pathway from periodontitis and breast cancer could be hypothesized and the chronic inflammation resulting from the periodontal infection can be one of the risk factor for the development of this type of cancer. The relation with chronic inflammation and cancer was reported by Coussens and Werb [29]. Therefore, the presence of lipopolysaccharides (LPS) that are component of Gram-negative bacteria, which can cause chronic inflammation may be a potential candidate to connect periodontitis and breast cancer.

In according to Mager et al. [30], estimates have indicated that over 15% of malignancies worldwide could be related to infections. Some studies have reported association between oral bacteria species and different types of cancer [31, 32]. Gao et al. [32] reported an association of *P. gingivalis* and *T. denticola* with tumorigenesis of esophageal cancer. *Porphyromonas gingivalis* and *Fusobacterium nucleatum* has shown strong oral carcinogenic potential in vitro and in animal studies [14, 31, 33]. Mager et al. [29] reported that high salivary counts of *Capnocytophaga gingivalis*, *Prevotella melaninogenica* and *Streptococcus mitis* may be diagnostic indicators of oral squamous cell carcinoma. Therefore, during ‘dysbiosis’ these oral bacterial can increase the expression of virulence factors leading to an inflammation status of the host [14, 33] and produce a chronic inflammation through different pathways including the activation of the caspase-1 inflammasome [34].



Inflammasomes are multiprotein complexes localized within the cytoplasm of the cell [35]. According to Karki et al. [34] excessive inflammation driven by the inflammasome or the interleukin-1 (IL-1) signaling pathways can promote breast cancer, gastric carcinoma, fibrosarcoma, and lung metastasis. Kolb et al. [36] reported that caspase recruitment domain-containing protein 4 (NLRC4) inflammasome mediates expression of adipocyte-mediated vascular endothelial growth factor A (VEGFA), and accelerates the progression of breast cancer. Recently, it was found that *P.gingivalis* and *Fusobacterium nucleatum* [35], may develop different mechanisms to inhibit inflammasome activation and function, and therefore this systemic inflammation could indirectly contribute to systemic cancer such as breast cancer [29].

Despite the possible association between breast cancer and periodontitis [18, 19, 25], the components and products involved in the mechanisms of induction of carcinogenesis are unknown and further studies with a large sample size and a control group should be conducted with the purpose of elucidating this issue. Indeed, public data on this topic will be very important for public health assistance.

Conclusion

In conclusion, the results of the present study found no direct association between the subgingival microbiota and breast cancer and an indirect pathway should be addressed in further studies.

Abbreviations

BOP: Bleeding on probing; CAL: Clinical attachment level; ChP: Chronic periodontitis; DNA: Deoxyribonucleic acid; IL-1: Interleukin-1; MM: Millimeter; NLRC4: Domain-containing protein 4; PD: Probing depth; SD: Standard deviation; VEGFA: Vascular endothelial growth factor A; VPI: Visible plaque index

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Authors' contributions

VRB, MF, MFF, AF (concept, data acquisition, data analysis, writing manuscript, final review); MSS, MCMG, RGB, CJT (data acquisition, data analysis, writing manuscript); All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The Ethical Committee of Health Sciences Center/ UFES approved this study procedure on November 25, 2014 (Approval Number: 862.952). All patients recruited gave written consent to participate in the study.

Consent for publication

All authors agreed to publish.

Competing interests

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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