

The Role of Oral *Fusobacterium nucleatum* in Female Breast Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Breast cancer is the most popular malignancy worldwide, predominantly targeting post-pubertal females of all ethnicities. As of late, oral *Fusobacterium nucleatum* species have been detected within malignant human breast tissue, thus highlighting the importance of microbes in cancer development and progression.

Objectives: To evaluate the potentiality of oral *Fusobacterium nucleatum* species as biomarkers for female-specific breast cancer.

Methods: A strict set of criteria for article inclusion were adhered to by all authors, with favorable acceptance of articles recording and evaluating women between the ages of 18-96 years with established breast cancer and gingivitis/periodontal disease from their respective medical and dental health care specialists. Data was independently extricated by all authors, creating a meta-analysis focused on risk estimation measurements of interconnections between oral *Fusobacterium nucleatum* species and breast cancer within females, determined from 95% confidence intervals and calculated relative risks.

Results: 78.70% of articles demonstrated positive correlations between oral *Fusobacterium nucleatum* and female breast cancer as depicted in the AXIS tool analysis. A rise in the prospect of breast cancer development was demonstrated in females with clinically visible signs of gingivitis/periodontitis due to the presence of abundant microbial levels of oral *Fusobacterium nucleatum* (95% confidence interval=1.63-1.91, relative risk=1.78). Statistical heterogeneity of low-moderate levels was detected ($I^2=41.39\%$; $P=0.02$), and the significance of periodontal health on breast cancer development and progression was elucidated (95% confidence interval=1.01-1.30, relative risk=1.24).

Conclusion: Oral *Fusobacterium nucleatum* species are credible biomarkers for female specific breast cancer as elevated levels are a grave risk for its dissemination.

Keywords: Oral *Fusobacterium nucleatum*, Periodontal disease, Breast cancer, Oral cavity

Description

In 2020, a staggering 2.261,419 million females were documented with confirmed breast cancer diagnoses resulting in 684,966 recorded deaths, alongside further estimations that 1 in 8 women will be diagnosed during their lifetime [1].

Oral Fusobacterium nucleatum, Periodontal Disease and Breast Cancer

The significance, functionality and understanding of the human microbiome are derived primarily from a catalogue of studies into the human gut-whereby an estimated 99% of the microbial mass has its origin. However, few studies have explored the importance of the oral microbiome. The oral cavity is a cornucopia of microorganisms, with circa 700 identifiable bacterial species [2].

The generation of dental plaque accumulates intraorally creates microbial dysbiosis activating the body's inflammatory responses thus leading to gingivitis. Prolonged periods of dental plaque accumulations initiate chronic inflammatory responses, causing periodontal disease. Approximately 45%-50% of adults over 30 years old and more than 60% of people aged over 60 years old suffer from periodontal disease [1,3]. *Fusobacterium nucleatum* is an imperative periodontal disease-causing virulent

pathogen. Identified as one of the most common gram negative anaerobic oral microbial species, it possesses an unusual spindle-shape, is non-spore-forming, with appreciable contributions to dysbiotic alterations and biofilm development [4].

Numerous murine model studies have demonstrated breast cancer progression in the presence of *Fusobacterium nucleatum* species with additional observance in cancerous human breast tissue. This is because the by-products of *Fusobacterium nucleatum* are adept in combining with pro-inflammatory cytokines (IL-1, IL-6, and IL-8) to infiltrate the systemic circulatory system, aiding cancer progression in distant bodily sites. This highlights this oral pathogen's prominent role in creating a proinflammatory microenvironment demonstrated in periodontal patients and its link to female-specific breast cancer [3,5].

The Importance of Adequate Periodontal Surgical Techniques in Preventing Female-Specific Breast Cancer Development

Minimal invasive surgery is a novel approach respecting hard and soft tissues *via* minimal flap reflections. It advantageously reduces postoperative pain, promotes healing, and improves clinical outcomes. Modification of the single flap methodology to a more minimally invasive approach in 2007 has since created a better technique for the correction of periodontal osseous defects.

A 2013 study on minimally invasive surgical techniques reported nominal bone loss when compared with conventional surgeries. The single flap approach has a superfluity of advantages to lower the risk of periodontal disease instigating bacteria prospectively enhancing breast cancer development *via* reduction of post-operative recessions, prevention of blood clot contaminations, acceleration of wound-healing, minimization of post-operative pain and allowing flap repositioning with concomitant adherence to undetached papilla [6].

The Human Oral Microbiome Database and Metagenomics/Meta-Transcriptomics

Over the past decade, much focus has been placed into understanding the impact of oral microbial burdens on overall systemic health. In 2005, The Human Oral Microbiome Database was set up for the purpose of imparting vital data on bacterial niche typologies observed within the oral cavity. As many as 1,576 genomes and 784 different taxa have been discovered, with FN species notably being identified as one of the more common phyla [7].

However, questions remain unanswered. For example, how do microbial dysbiosis and fluctuating oral microbial compositions activate periodontal disease? And do specific microbial characteristics relate to other systemic diseases?

Recent emergence of meta-transcriptomics and meta-genomics has permitted high throughput analysis of microbial communities, aiding understanding. Customarily, microbial recognition and detection of microbes relied heavily upon culture methodologies, nevertheless, introduction of metagenomics involves detailed evaluations of all microbial diversities, population structures, communities, functional-relationships and their interactive behaviours within their respective environments [8]. Despite the technology's positives, there are some shortcomings with respect to inadequate study designs and sample sizes, poor sampling methodologies and deficient follow up durations.

Possible Mechanisms of Oral *Fusobacterium nucleatum* in Breast Cancer Development

Extensive analysis of microbial communities in both benign and malignant growths originating from breast tissue samples of female patients, were extensively evaluated in a comparative study published in 2016. The study disclosed a direct relationship between breast cancer malignancies and a microbial abundance of *Fusobacterium nucleatum* species-the mechanisms of which remain unclear. In 2022, a review article examined how oral *Fusobacterium nucleatum* species colonised lactiferous ducts within breast tissue and a 2020 article illustrated the capability of FN to inhabit cancerous tumours through its coupling to Gal-GalNAc receptors allocated on tumour cell surface membranes. This implied that oral *Fusobacterium nucleatum* species could reach other Gal-GalNAc-displaying tumours with the same mechanism, augmenting haematogenous Gal-GalNAc levels thus accelerating female-specific BC pathogenesis [9,10].

Future Prospects

Despite our investigation, there is still inadequate data available. Further analysis into this field with more focused assessment objectives would be useful, taking the following into consideration.

- IIF approach-“Identification-Isolation-Flag-up”. A meth-

od to recognize varying subtypes of the *Fusobacterium nucleatum* species, observed in different sections of breast tissue samples taken from female patients with confirmed breast cancer diagnoses at different disease developmental stages from least to most severe (GRADES I-IV). This would allow evaluation of the activity levels and the proportions of species subtype present, which would later provide a clearer indication of their respective contribution to breast cancer pathogenesis.

- Consequently, the IIF approach would be duplicated and implemented on a female population presenting clinically with oral inflammatory conditions (gingivitis and periodontitis), and again thorough analysis of *Fusobacterium nucleatum* subtypes would be undertaken at different disease progression stages for both conditions (mild-moderate-severe).

It is our firm conviction that multiomics possesses immense promise for our proposal in differentiating and understanding the relational complexities between the human microbiome and cancer predisposition. At present, the evaluation of microbiome data fabricated *via* multiomics methodologies is still a challenge as a consequence of unsatisfactory tool availability. In order to overcome this obstacle, supplementary well-designed Randomized Controlled Trails (RCT's) incorporating longer follow-up periods would assist in the validation of whether meta-genomic/meta-transcriptomic changes are feasible contributors in periodontal therapy personalization. This collective approach could revolutionize oral healthcare, driving a structured, informed and supportive environment for patients and clinicians-potentially saving lives.

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