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ORIGINAL ARTICLE

Role of *Cutibacterium acnes* and *Bacteroides fragilis* in Prostate Cancer: a Turkish Population-Based Case-Control Study

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ABSTRACT

Background: **Recent studies suggest that *Cutibacterium acnes* may be involved in prostate carcinogenesis. The potential association between *Bacteroides fragilis* and prostate cancer (PC) is still under investigation. This study aimed to determine the levels of *C. acnes* and *B. fragilis* in prostate biopsies from patients with PC and healthy controls (HCs) and to evaluate the possible roles of these bacteria in the etiopathogenesis of PC.**

Methods: **This age-matched case-control study was conducted between 2020 and 2022. Prostate biopsies were collected from 60 patients with PC and 60 HCs divided in two age groups of 55 - 65 years and 66 - 75 years, respectively. *C. acnes* and *B. fragilis* levels were determined using real-time quantitative polymerase chain reaction (qPCR).**

Results: ***C. acnes*** **was detected in 58 (96.6%) biopsies from PC patients and in 39 (65%) from HCs ($p < 0.001$), *B. fragilis* was detected in 9 (15%) biopsies from PC patients and in 4 (6.7%) from HCs ($p = 0.142$). Compared with HCs, *C. acnes* abundance was significantly higher in PC patients aged 55 - 65 years ($p = 0.002$). No significant difference in *B. fragilis* abundance was found between the two groups in either age category ($p = 0.211$).**

Conclusions: **Our findings suggest that *C. acnes* may contribute to the etiopathogenesis of PC, particularly in patients aged 55 - 65 years. In contrast, our data do not support a clear association between *B. fragilis* and PC. Larger, prospective, molecular-based studies are needed to clarify the potential role of these bacteria in prostate carcinogenesis.**

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INTRODUCTION

Prostate cancer (PC) has become the most frequently diagnosed cancer among men in both developed and developing countries in recent years [1,2]. Unlike other common cancers, its occurrence is directly related to age, and its incidence increases with age in men [2]. Recent studies on PC have consistently demonstrated the presence of acute and chronic inflammation in benign and malignant prostatectomy samples, prostate tumor tissues, transurethral resection samples of the prostate and histopathological examinations of prostate biopsies [1]. Studies have shown that patients with PC often experience inflammation in multiple areas, and the inflammation observed throughout the peripheral area of the gland has been attributed to a factor present in the prostate microbiota [1,2].

The development of many diseases today is often the result of multiple contributing factors acting together [3]. PC is influenced by factors such as age, ethnicity, family history, genetics, and environmental conditions including inflammation, diet, and lifestyle [4]. A common theory suggests that dormant or migrating microorganisms in the prostate may increase the risk of PC by triggering an inflammatory environment [2,5]. Microorganisms affect angiogenesis signaling by producing toxins that cause DNA abnormalities. Consequently, apoptosis-resistant cells promote cell growth. Recent studies have shown that prolonged inflammation may initiate cancer [6]. However, the specific pathogenic mechanism of PC is still poorly understood compared with that of other common cancers.

Cutibacterium acnes (formerly *Propionibacterium acnes*) is a non-spore-forming, gram-positive, anaerobic rod-shaped bacterium [7]. It is recognized as the most common microorganism in prostate tissue, and some studies suggest that it may contribute to the inflammatory response [7]. Histopathological analyses have shown that this bacterium is frequently present in the prostate gland and is strongly associated with chronic inflammation [7,8]. Furthermore, *C. acnes* can induce inflammation by activating NF-κB and potentially affecting the cell cycle via a thiopeptide molecule [9,10]. It has also been hypothesized that the propionic acid produced by *C. acnes* can exert immunosuppressive effects, reducing the immune system's ability to eliminate tumor cells. In this microenvironment, enhanced epithelial cell regeneration and the proliferative nature of the inflammatory milieu may promote the development of abnormal prostate epithelial lesions [8].

Bacteroides fragilis, a gram-negative, rod-shaped, obligate anaerobic bacterium, is normally found as a commensal organism in the human colonic microbiota [11, 12]. Recent studies suggest an association between *B. fragilis* colonization of the male urethra and suppurative infections of the male genitourinary tract [13].

Additionally, a notable increase in anaerobic bacteria has been observed in urine samples collected after prostate massage, with *B. fragilis* reported as the most frequently isolated anaerobic bacteria in these studies [13, 14]. Toxin-producing *B. fragilis* has been shown to induce chronic intestinal inflammation and tissue injury by activating specific inflammatory pathways and it plays an important role in the development of colorectal cancer (CRC) [15,16]. Although evidence linking the genus *Bacteroides* to prostate cancer suggested in a pivotal 1999 study, the role of *B. fragilis* in prostate cancer has not yet been established [17]. However, recent investigations into its contribution to colon carcinogenesis have prompted questions about its possible involvement in prostate cancer as well [17]. Interest in this topic has grown significantly since 2018 [18,19].

This study provides the first data on the presence of *C. acnes* and *B. fragilis* in prostate biopsy samples from our country and aims to evaluate the potential roles of these bacteria in the etiopathogenesis of PC.

MATERIALS AND METHODS

Study population

This study was conducted as a planned case-control clinical trial between March 2020 and December 2022. It was conducted at the Department of Medical Microbiology, Cerrahpasa Faculty of Medicine, Istanbul, Türkiye, with prostate biopsies taken from 60 patients with PC and 60 HCs who were followed in the urology department of the same faculty. The study was approved by the Ethics Review Board of the Cerrahpasa Faculty of Medicine (Approval No.: 2019/54138). All patients were informed about the study, and written informed consent was obtained.

Adult patients, who were diagnosed with PC based on histopathological examination, who had no other cancer diagnosis, were not receiving chemotherapy or radiotherapy, and did not use antibiotics within the last 2 weeks prior to biopsy collection, were included in the study. The HC group consisted of adult individuals with no cancer diagnosis who had also not used antibiotics within the last 2 weeks before biopsy collection. The American Institute for Cancer Research reported that 97% of patients diagnosed with PC in the United States (USA) are over 50 years of age, with a mean age of 65 years [20]. Patients and HCs were divided in two age groups (55 - 65 years and 66 - 75 years) according to age ranges determined by the U.S. Preventive Services Task Force (USPSTF) regarding the rate of PC diagnosis [21]. The study was conducted by age-matching the patient and HC groups ($p > 0.05$).

Sample collection

Two needle biopsy samples were taken from both the right and left median lobes of each patient's prostate via transrectal ultrasound. One of these biopsies was placed in sterile Eppendorf tubes, then immediately transferred to the microbiology laboratory and stored at -20°C until DNA extraction. The second sample was sent to the pathology department of the same faculty. Based on the

histopathological analysis report, biopsy samples from patients diagnosed with prostate adenocarcinoma were included in the patient group, and samples that were without adenocarcinoma and contained fibroblastic tissue were assigned to the control group.

Nucleic acid extraction and quantitative assessment of microbial abundance

Total genomic DNA was extracted from biopsy samples with a QIAamp® DNA Mini Kit (Qiagen, Hilden, Germany). Extraction was performed according to the kit's instructions. The extracted DNA was stored at -20°C until further use. The concentrations and purities of the extracted DNA samples were measured with a Nanodrop One spectrophotometer (Nanodrop Technologies, Wilmington, DE). The 260/280 ratio was used as an indicator of the purity of the DNA samples. Absorbance was recorded at 260 and 280 nm.

The amplification of genomic material, for the quantitative assessment of microbial abundance, was performed using the Microbial DNA qPCR Analysis Kit for *C. acnes* and *B. fragilis* (Qiagen, Hilden, Germany) with the Rotor-Gene Q 5plex HRM, a qPCR system (Qiagen, Hilden, Germany) and its corresponding software.

The kit contains a mixture of two polymerase chain reaction primers (10 µM each) targeting *B. fragilis* (accession no. FJ367787.1) and *C. acnes* (accession no. NZ_ADJL01000005.1) along with a 5'-hydrolysis probe (5 µM) to enable qPCR. Each 25 µL qPCR mixture contained 5 µL of genomic DNA, 12.5 µL of Microbial qPCR Mastermix ROX, 1 µL of primer/probe mixture, and 6.5 µL of DNA-free water. Fluorescence from fluorescein amid was detected in a 36-well rotor disk, and data were analyzed by setting the green channel threshold to 0.02. The amplification conditions included an initial activation step at 95°C for 10 minutes, followed by 40 cycles of denaturation at 95°C for 15 seconds and annealing/extension at 60°C for 2 minutes. A threshold line cycle value of 37 was set as the limit of detection, and fold change values were calculated via the $^{\Delta\Delta}$CT method with Template Excel Software. Standard curves were generated from 10-fold serial dilutions of plasmids ranging from 10^5 to 10^9 copies μL^{-1}.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 21 (Statistics Windows, IBM Corp., Armonk, NY, USA). Categorical data were presented as frequencies and percentages, and continuous data were presented as means with standard errors. p-values for the univariate relationship between the presence of *C. acnes* and *B. fragilis* in cases and HCs were determined using Pearson's chi-squared tests. The Mann-Whitney U test was used to determine whether the median amounts of *C. acnes* and *B. fragilis* differed between patients and HCs. A $p < 0.05$-value was considered statistically significant.

RESULTS

The mean ages of patients with PC and HCs were 64.08 ± 6.66 years and 61.85 ± 5.81 years, respectively. In the 55 - 65 year age group, the mean ages of patients with PC and HCs were 59.29 ± 4.09 years and 57.93 ± 2.23 years, respectively, and in the 66 - 75 age group, the mean ages were 70.04 ± 3.75 years and 66.72 ± 5.18 years, respectively.

C. acnes was detected in 58 (96.6%) of the 60 patients with PC and 39 (65%) of the 60 HCs. The presence of *C. acnes* in the patient group was significantly higher than that in the HCs ($p < 0.001$) (Table 1). No statistically significant difference was detected between the groups regarding *C. acnes* abundance (log10/25 mg, 6.14 ± 1.02 in PC and 4.53 ± 2.63 in HC) ($p = 0.161$) (Table 1).

Meanwhile, *B. fragilis* was detected in 9 (15%) of 60 patients with PC and 4 (6.7%) of 60 HC samples. No statistically significant difference was found between the groups in either the presence or abundance of *B. fragilis* (2.18 ± 0.22 for patients with PC and 1.79 ± 0.15 for HCs) ($p = 0.142$ and $p = 0.211$, respectively) (Table 1).

Analyses of the presence and abundance of bacteria according to age group revealed that *C. acnes* was detected in all (100%) PC patients and in 18 (58.1%) HC subjects in the 55 - 65-year age group. In terms of the presence and amount of *C. acnes* (6.38 ± 0.07 in patients with PC and 3.92 ± 2.59 in HCs), a highly statistically significant difference was observed between patients and HCs in this age group ($p < 0.001$ and $p < 0.002$, respectively). No statistically significant difference was found between patients and HCs in the 66 - 75-year age group regarding the presence or amount of *C. acnes* ($p = 0.315$ and $p = 0.271$, respectively) (Table 1).

The results obtained for *B. fragilis* were different. In the 55 - 65-year age group, *B. fragilis* was observed in 5 (16.1%) PC samples and 3 (9.7%) HC samples. No statistically significant difference was observed for the presence or amount of *B. fragilis* in this age group ($p = 0.378$ and $p = 0.418$, respectively) (Table 1). A similar result was observed in the 66 - 75-year age group. No statistically significant difference was found in the presence or amount of *B. fragilis* ($p = 0.291$ and $p = 0.313$, respectively) between patients and HCs. (Table 1).

DISCUSSION

Human cancer was previously considered a genomic disease. Recent studies have shown that disruptions in the healthy microbiota may play a significant role in the development of PC and many other diseases [22,23]. Over the past two decades, numerous studies have been conducted to elucidate the role of the prostatic and genitourinary microbiome in the development of PC [23]. Furthermore, clinical and epidemiological studies indicate a strong link between inflammation, chronic infec-

Table 1. The number, the rate and the amounts (log10/25 mg) of *C. acnes* and *B. fragilis* in patients and controls according to age groups.

Bacteria	Age Groups	Patients (PC) n: 60		Controls (HC) n: 60		p
		Positive: n (%) Negative: n (%)	Amount	Positive: n (%) Negative: n (%)	Amount	
C. acnes	55 - 65	31 (100) 0 (0)	6.38 ± 0.07	18 (58.1) 13 (41.9)	3.92 ± 2.59	0.002 *‡ < 0.001 **†
	66 - 75	27 (93.1) 2 (6.9)	5.88 ± 0.25	21 (72.4) 8 (27.6)	5.19 ± 0.47	0.271 * 0.315 **†
	All ages	58 (96.6) 2 (3.4)	6.14 ± 1.02	39 (65) 21 (35)	4.53 ± 2.63	0.161 *‡ < 0.001 **†
B. fragilis	55 - 65	5 (16.1) 26 (83.9)	2.29 ± 0.33	3 (9.7) 28 (90.3)	1.85 ± 0.20	0.418 *‡ 0.378 **†
	66 - 75	4 (13.8) 25 (86.2)	2.05 ± 0.31	1 (3.4) 28 (96.6)	1.72 ± 0.21	0.313 *‡ 0.291 **†
	All ages	9 (15) 51 (85)	2.18 ± 0.22	4 (6.7) 56 (93.3)	1.79 ± 0.15	0.211 *‡ 0.142 **†

PC: prostate cancer, HC: healthy controls. * amount ** presence.
The *Mann-Whitney U test* ‡ was used for the amount of bacteria, and *Pearson's chi-squared test* † was used for the presence of bacteria.

tion, and cancer [24,25].

Physical trauma, microbial colonization along with diet are exogenous factors that may introduce carcinogenic substances and lead to hormonal imbalances. When these substances damage the prostate, cytokines that promote epithelial cell proliferation and angiogenesis in inflammatory cells are stimulated. Ultimately, these processes lead to chronic inflammation and precancerous lesions called proliferative inflammatory atrophy. Bacteria may promote cancer through their direct effects on cell transformation or via the production of toxic, carcinogenic metabolites. It is widely accepted that the accumulation of somatic genetic and epigenetic changes through these interactions, along with the inactivation of tumor suppressor genes and the activation of oncogenes, leads to PC development. Therefore, chronic inflammation is considered a major driver of prostate carcinogenesis [26].

C. acnes, a member of the skin's commensal microbiota has recently been increasingly reported in the literature as an opportunistic agent. Owing to its lipophilic structure, it can be abundantly found in both sebaceous and non-sebaceous skin areas and can colonize tissues and biomaterials causing complications such as orthopedic implant infections, sarcoidosis, progressive macular hypomelanosis, and chronical disorders [22]. Furthermore, in recent years, it has been suggested that this bacterium may contribute to the development of PC through an inflammatory mechanism [22,26].

Most studies reporting the role of *C. acnes* in the etiology of PC are molecular-based studies that compare the presence of this bacterium between tumor tissues from PC patients and healthy tissue samples [27]. For example, Sfanos et al. [28] demonstrated the presence of *C. acnes* in prostate biopsy samples from 30 patients via 16S rDNA gene sequence analysis. Alexeyev et al. [29] investigated the presence of *C. acnes* in a study of 352 prostate biopsies by 16S DNA nested polymerase chain reaction sequence analysis. Additionally, integrated metagenomics, metatranscriptomics, shotgun-based analysis, pyrosequencing, and 16S rRNA amplicon sequencing were among the methods used to detect *C. acnes* in tissue samples [7,30,31,32].

When we review the studies investigating the role of *C. acnes* in the etiology of PC, we noted that Ugge et al. [33] reported a 61% (60/99) detection rate of *C. acnes* in cancerous prostate tissues in Sweden in 2018. Yow et al. [31] reported in 2017 in Australia that *C. acnes* was present in 95% of prostate tissue samples from PC patients. In 2015, Chen and Wei [7] reported the presence of *C. acnes* in 100% of tumor samples from 42 PC patients, similarly Fassi Fehri et al. [6] reported in 2010 in Germany that, via in situ immunofluorescence, *C. acnes* was present in all cancerous prostate samples.

In contrast, Mak et al. [34], in a study conducted in the United States, detected *C. acnes* in only 23% of cancerous prostate tissues. Davidsson et al. [35] reported the presence of *C. acnes* in tumor tissues of 73 of 137 PC patients (53.2%) in a study conducted in Sweden in 2012.

We observed that our findings were very similar to those reported by Yow et al. [31], Chen and Wei [7], and Fassi Fehri et al. [6]. Furthermore, our findings are close to the upper end of the prevalence range reported in the literature and are particularly similar to findings from studies conducted with molecular or immunohistological methods.

When we examined the age range of patients in studies conducted to detect the rate of *C. acnes* in cancerous prostate tissues, we observed that in the study by Bae et

al. [36] the age range was between 50 and 78 years in PC patients and between 50 and 80 years in HCs. In the study by Radej et al. [37] the age range was reported as 64 years and Olender et al. [38] included 20 organ-confined PC patients aged 52 - 78 years to investigate the presence of *C. acnes.* Chen and Wei [7] studied 20 Western patients with prostate tumors aged between 48 - 73 years and 14 Chinese patients aged between 52 - 80 years who were diagnosed with PC. Mak et al. [34] studied 30 PC patients with a mean age of 57 (range 43 - 74) years to investigate the presence of *C. acnes.* Fassi Fehri et al. [6] investigated the presence of *C. acnes* in prostate tissues from 71 PC patients aged between 51 - 77 years. Consistent with these studies and in accordance with the USPSTF recommendations, the patients and controls in our study were within an acceptable age range of 55 - 75 years.

Conceptualizing the relationship between *C. acnes* and PC, our research supports the idea that *C. acnes* may cause an inflammation-based neoplastic process by activating NF-κB via TLR2/TLR4 in prostate epithelial cells, leading to the release of proinflammatory cytokines such as IL-6, IL-8, and TNF-α [2,35]. This process may also contribute to the development of a carcinogenic mechanism such as DNA damage, cell proliferation, and inhibition of apoptosis in prostate cells. Furthermore, it has been suggested that *C. acnes* contributes to the immunosuppression-mediated carcinogenesis process by increasing the number of regulatory T (Treg) cells and M2-type macrophages, and that the short-chain propionic acid synthesized by the bacteria during its metabolic process may also reduce antitumor activity in some immune cells such as CD8+ CTLs, and NK cells) through an immunosuppressive effect. [9,35]. The most important risk factors for PC are advanced age, race, genetic factors, geographic location, and family history [4,39]. In addition to these factors identified as specific risk factors by the CDC, in recent years, different lifestyle and nutritional habits including low human development and low education indices, living in countries with low gross national income per capita and high life expectancy at birth, exercise, diabetes, diet, obesity, smoking, exposure to chemicals, a history of sexually transmitted infections, vitamin E supplementation, and vasectomy, have also been cited among the risk factors for PC [4,39]. Following the increasing incidence of PC and the recommendations published by the USPSTF in 2012, it has become clear that age is a significant risk factor for PC, with the highest incidence occurring in older men (> 65 years) [40]. In fact, studies have shown that men aged 50 - 70 years are more likely to develop PC, and older white US adults aged 75 - 79 years are 100 times more likely to develop PC than those aged 45 - 49 years [39]. Furthermore, the risk of PC has been observed to increase after age 50 in American individuals without a family history of PC, and the risk increases after age 40 in African American individuals, regardless of their family history. Consequently, regular PC screening is strongly recommended for men with a family history of PC starting at the age of 45 [39].

Bacteroides spp. were known to be commensal bacteria and constitute approximately 30% of the human intestinal microbiota. Recent studies have identified a subtype of some *B. fragilis* strains that can carry a metalloprotease enterotoxin called *B. fragilis* toxin or BFT. These strains, also called ETBF, are known to infect children and adults and cause acute and chronic intestinal diseases, and when examining the population they affect, it is thought that they may play a role in the etiology of CRC [9,11,12]. The first study demonstrating a possible association between the genus *Bacteroides* and PC was published in 1999 [17]. Since then, owing to the increased interest in this topic especially since 2018, particularly following studies addressing the role of *B. fragilis* in the etiology of CRC, the role of this bacterium in PC has been the focus of research. However, the number of studies investigating the role of *B. fragilis* in the etiology of PC remains limited. Salachan et al. [23] demonstrated the presence of *B. fragilis* in the prostate tissue of 94 patients diagnosed with PC. Feng et al. [30] conducted a study on the genus *Bacteroides* using biopsy samples from 22 PC patients. These sample sizes indicate that the number of samples included in our study is sufficient to discuss our results in comparison with these studies. However, in our study, contrary to the findings of Salachan and Feng, we isolated *B. fragilis* from only 9 (15%) of 60 PC patients aged between 55 - 75 years. These results suggest that the prevalence of *B. fragilis* in prostate tissues may vary from study to study, depending on the location of the sample, the testing method, geographic location and eating habits. The possible etiopathogenesis between *B. fragilis* and prostate cancers has been linked in the literature to the enterotoxin synthesized by *B. fragilis* strains targeting the E-cadherin protein in epithelial cells, weakening interepithelial junctions, thus facilitating the entry of local immune cells, related inflammatory agents and microbial products into the prostate stroma from the disrupted mucosal structure. This, in turn, results in the loss of prostate epithelial-mechanical barriers, leading to an inflammatory process and tissue damage, which are proposed as possible causes of neoplastic transformation [16]. Another view proposed regarding this process is that neoplastic transformation may occur due to increased proinflammatory IL-17A and IL-6 cytokine induction in immune cells caused by ETBF antigenic stimulation and activation of the STAT3 signaling pathway, resulting in increased prostate epithelial cell proliferation [15, 16]. This study has some limitations. Although the numbers of patients and controls are consistent with those in similar studies, more robust results could have been achieved with a larger number of participants. Additionally**,** if we had been able to cultivate *C. acnes* and *B. fragilis* from the collected biopsy samples, it would have been very useful to perform their genome analyses and better understand their virulence profiles to more clearly explain the link between these bacteria and PC.

CONCLUSION

Our findings suggest that *C. acnes* plays a role in the etiology of PC, particularly in patients aged between 55 and 65 years, whereas *B. fragilis* is not involved in the etiology of PC in the Turkish population in which we performed this study**.** We believe that the results obtained in this pilot study, the first of its kind in our country, will inform future studies with more comprehensive case-control groups.

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Declaration of Interest:
The authors declare that they have no known competing personal or financial interests.

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