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**Low prevalence of *Cutibacterium acnes* in prostatic tissue biopsies in a French hospital**

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34   **Abstract:** 53 words

          We evaluated the *Cutibacterium acnes* prevalence in prostatic biopsies and characterized the  
36   strains at a molecular level. 18 out of 36 biopsies (50%) were sterile after seven days in  
          culture. *C. acnes* was observed in only two biopsies. Its prevalence was low (5.6%). Finally,  
38   the molecular characterization revealed diverse clusters including phylotypes IA<sub>1</sub>, IB and II.

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**Note : 941 words**

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Prostatic adenocarcinoma remains one of the most frequent tumors for male patients. The  
62 persistence of microorganisms leading to a chronic inflammation of the prostate gland has  
been suspected to be responsible for the carcinoma process [1]. Viruses or bacteria such as  
64 *Cutibacterium acnes* have been reported for their remanence in prostatic tissues, especially in  
Asia and Northern Europe [2,3]. *C. acnes* prevalence in prostatic samples has been reported  
66 from 23% to 95%, depending on the method used [4]. However, the relationship between *C.*  
*acnes* detection and prostatic cancer or chronic prostatitis remains controversial. Currently, no  
68 study has been conducted in France. The aim of this monocenter prospective study was to  
assess *C. acnes*' prevalence within prostatic biopsies.

70 During a four-month period at Nantes University hospital, 36 patients were included  
prospectively during their urology consultation. These patients were admitted for prostatic  
72 biopsies as part of the adenocarcinoma diagnosis associated with prostatitis or not. The tissue  
sampling, using a transrectal approach with a 400 mg ofloxacin antibioprophylaxis, was  
74 realized with a biopsy sterile gun. The first needle was meant for the bacteriology analysis  
while the 12 other cartography prostatic biopsies were used for histological analysis. Prostatic  
76 biopsies were placed in sterile conditions, using physiological water. After grinding with  
glass beads for 15min, 50 µL of the sample were seeded on a Schaedler agar plate incubated  
78 in anaerobic condition at 37°C for 7 days. A first look was performed at day 2 and another  
one at day 7 (D7). At each time, suspect colonies were identified using MALDI-TOF mass  
80 spectrometry as previously described [5]. For each *C. acnes* strains detected, a molecular  
typing was performed [6].

Patients' median age was 69.5 and the median PSA level was 7.5 ng/mL (N <4,50 ng/mL). Prostatic adenocarcinoma was diagnosed for 23 patients (64%) with a Gleason score ranging from 6 to 10.

Regarding the microbiological analysis, 18 out of 36 biopsies (50%) were sterile at D7 in culture including 7/13 (54%) in the non-cancer group and 11/23 (48%) in the adenocarcinoma group (**Figure 1**). The 18 remaining samples were tested positive, mostly with a polymorphic flora, including *Bifidobacterium sp.* (n=4) or *Mobiluncus curtisii* (n=3).

A positive *C. acnes* culture (usually a few colonies) was observed in only two biopsies representing a prevalence of only 5.6%. One patient (non-cancer group) had two different types of *C. acnes* (hemolytic and non-hemolytic) associated with *Escherichia coli* and *Streptococcus salivarius* group. The other patient (adenocarcinoma group) had a *C. acnes* associated with *Collinsella aerofaciens* and *Fingoldia magna*, both present in the gastrointestinal tract. Regarding these three strains' molecular types, three different lineages were found. For the first patient, a phylotype IB, a SLST-type H1 belonging to clonal complex CC36 (hemolytic) and a phylotype II, SLST-type K16 belonging to CC53 (non-hemolytic), generally detected in prosthetic joint infections [7,8]. For the second patient, a phylotype IA<sub>1</sub>, SLST-type K1 belonging to CC18, usually found on the skin [9]. Interestingly, *Cutibacterium avidum* was also found in the three samples either alone (adenoma patient) and with *C. aerofaciens* and *Mobiluncus curtisii* (non-cancer patient). At last, no microorganism or mixed flora was found in patients presenting a prostatitis diagnosis, regardless of adenocarcinoma's presence.

The role of *C. acnes* in the inflammatory stimulation prostatitis and the carcinogenesis process remains under debate. Compared to the existing literature and despite crushing prostatic biopsies, the prevalence of *C. acnes* remains surprisingly low in this work series. In the review of Capoor et al, the detectable *C. acnes* prevalence varied within cancer tissue

samples significantly from 23 to 95% depending on the method used [4]. This is a key finding. Indeed, it seems really difficult to compare microbiological culture methods, universal 16S rRNA amplification, specific *C. acnes*-target PCR, Next Generation Sequencing approach, histologic observations, *in situ* fluorescence microscopy or antibody methods to detect viable or alive *C. acnes*. These methods allow to distinguish infection, colonization and skin contamination [4]. Moreover, 16S rRNA PCR is probably not the best molecular target to assess *C. acnes* presence [10,11]. Therefore, notwithstanding our expertise in orthopedic-device related infections and skin proinflammatory disease [8,9], as far as our ability to detect *C. acnes* strains in prostatic specimens is concerned, we question a possible difference regarding the ecology of the prostatic biopsies analyzed. Indeed, we detected for almost 50% of the samples, a polymorphic flora. This seemingly implies that we would have found a higher positivity rate with a higher microbial diversity using other methods, including molecular and sequencing ones as previously reported [12]. If certain *C. acnes* strains may likely play a role in either chronic inflammation of prostatic tissue or prostatic tumor [4], we did not find a specific tropism of a phylotype or a specific lineage as stressed by Mak *et al.* [13]. A different ecology hypothesis across ethnicities has been previously suggested concerning viruses detected in prostatic biopsies, [2] but the differences are still to be confirmed by a large scale, cross-center prospective study.

A major limitation of this study is its small sample size at a single location. However, grinding should have helped detecting the intracellular *C. acnes* bacteria [14]. Another limit ties to the fact that only one biopsy per patient was analyzed. A cartography, using different prostatic biopsies, would have allowed to collect more accurate data. Conducting further studies in different European countries using the same methodology would also help. As a reminder, this methodology entails (i) analyzing the potential differences in *C. acnes* frequency in prostatic tissues, (ii) characterizing at a molecular level the strains involved and

determining a potential specific tropism and finally (iii) better understanding the correlation between *C. acnes* presence and either prostatic inflammation or cancer development.

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**Conflict of interest:** nothing to declare

### **Ethical approval**

The human biological samples collected during the treatment of patients undergoing prostate biopsies were stored in the microbiology laboratory of the Nantes University Hospital. These samples integrated into the collections of human biological samples attached to the "Infectiology" research program declared on 05/09/2011 under the n° DC-2011-1399 and in the following amending declarations (DC-2012-1555; DC-2013-1832; DC2014-2206 and DC-2017-2987 currently pending) at the Ministry of Research and having obtained a favorable decision from the CPP Ouest IV on 07/04/2015.

Data collection followed the principles outlined in the Declaration of Helsinki; all patients had signed an informed consent agreement to deliver their own anonymous information for future studies.

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**Fig1. Flow chart of the study, polymorphic flora including microorganisms from the gut flora:**  
*E. coli*, *E. faecium*, *Collinsella aerofaciens*, *Bifidobacterium* spp., *Mobiluncus curtisii* and *Finegoldia magna*

