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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 Northen 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.

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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  $\mu$ L 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].

82 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  
84 from 6 to 10.

Regarding the microbiological analysis, 18 out of 36 biopsies (50%) were sterile at D7 in  
86 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  
88 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  
90 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  
92 *Streptococcus salivarius* group. The other patient (adenocarcinoma group) had a *C. acnes*  
associated with *Collinsella aerofaciens* and *Finegoldia magna*, both present in the  
94 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  
96 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  
98 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  
100 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  
102 adenocarcinoma's presence.

The role of *C. acnes* in the inflammatory stimulation prostatitis and the carcinogenesis  
104 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  
106 the review of Capoor et al, the detectable *C. acnes* prevalence varied within cancer tissue

108 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  
110 Sequencing approach, histologic observations, *in situ* fluorescence microscopy or antibody  
methods to detect viable or alive *C. acnes*. These methods allow to distinguish infection,  
112 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  
114 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  
116 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  
118 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  
120 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.*  
122 [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  
124 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,  
126 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  
128 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  
130 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

132 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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136 **Conflict of interest:** nothing to declare

### 138 **Ethical approval**

The human biological samples collected during the treatment of patients undergoing prostate  
140 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  
142 "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-  
144 2017-2987 currently pending) at the Ministry of Research and having obtained a favorable  
decision from the CPP Ouest IV on 07/04/2015.

146 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  
148 future studies.

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152

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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 *Fingoldia magna***

