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Research Article

Prostate Specific Antigen and the Risk of Prostate Cancer on Prostate Biopsies in Libreville, 2018-2020

L'antigène spécifique de la prostate et le risque de cancer de la prostate sur les biopsies prostatiques à Libreville 2018-2020

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Mots clefs : risque de cancer de la prostate, antigène spécifique de la prostate, Biopsie prostatique, Libreville.

ABSTRACT

Introduction. Prostate cancer is the most common cancer in men over 60 worldwide and as well as in Gabon. Its diagnosis is made histologically, nevertheless, can be suggested by a serum total prostate-specific antigen value greater than 4 ng/mL. However, this value can be elevated in the presence of any prostate pathology. The objective of this study was to assess the risk of a diagnosis of high-grade prostate cancer with elevated prostate-specific antigen. **Methods.** This was a case-control study that took place in January 2022 in the Pathology Anatomy Department's lab of the Faculty of Medicine of Libreville. Serum total prostate-specific antigen levels were compared to histological analyzes of biopsies from 2018-2020. **Results**. 232 biopsies were studied including 134 prostate cancers and 89 benign prostatic hypertrophies. There was an increasingly positive correlation between the level of prostate-specific antigen and the histological diagnosis of cancer. The risk of high-grade cancer was 37 times greater with a total prostate-specific antigen level above 100 ng/mL. **Conclusion**. The relationship between the level of total prostate-specific antigen and the risk of high-grade prostate cancer is clearly visible in this study. Nonetheless, there is a high number of patients with an elevated serum total prostate-specific antigen value associated with an absence of histological lesions of cancer.

RÉSUMÉ

Introduction. Le cancer de la prostate est le cancer le plus fréquent chez les hommes de plus de 60 ans dans le monde et au Gabon. Son diagnostic est histologique mais peut être évoqué devant une valeur d'antigène spécifique de la prostate total sérique supérieur à 4 ng/mL. Cependant, cette valeur peut être dépassée devant toute pathologie de la prostate. L'objectif de cette étude était d'évaluer le risque d'un diagnostic de cancer de la prostate de haut grade avec un antigène spécifique de la prostate élevé. **Méthodologie.** Il s'agissait d'une étude cas-témoins qui s'est déroulé de janvier 2022 dans le Service d'Anatomie pathologie de la Faculté de médecine de Libreville. Les tests d'antigènes spécifiques de la prostate total sérique ont été comparés aux analyses histologiques des biopsies de 2018-2020. **Résultats.** 232 biopsies ont été étudiées dont 134 cancers de la prostate et 89 hypertrophies bénignes de la prostate. Il existait une corrélation positive croissante entre le niveau d'antigène spécifique de la prostate et le diagnostic histologique de cancer. Le risque de cancer de haut grade était 37 fois plus important avec un niveau d'antigène spécifique de la prostate total supérieur à 100 ng/mL. **Conclusion.** La relation entre le niveau d'antigène spécifique de la prostate total et le risque de cancer de la prostate de haut grade est bien visible dans cette étude. Toutefois, il existe un nombre élevé de patients avec une valeur d'antigène spécifique de la prostate total sérique élevée associé à une absence de lésion histologique de cancer.

HIGHLIGHTS OF THE STUDY

What is already known on this topic?

Serum PSAt levels greater than or equal to 4 ng/mL recommend prostate biopsies

What question this study addressed?

The question was to find out what is the risk for a man aged 45 and over of being diagnosed with high-grade prostate cancer when he had a serum PSAt level greater than or equal to 4 ng/mL

What this study adds to our knowledge?

A threshold of 4-10 ng/mL of PSAt for prostate biopsies remains debatable. It is associated with a low sensitivity which does not discriminate between men with high-grade prostate cancer and men with indolent cancer.

How this is relevant to practice, policy or further research?

The thresholds for performing a prostate biopsy could be adjusted upwards to ensure a specificity of the PSAt level below 5%.

INTRODUCTION

When first described in 1979, prostate-specific antigen total (PSAt) was considered a good marker for assessing responses to treatment and monitoring patients with prostate cancer. After the publication of reports of several series in which the PSAt level determined whether or not one does a biopsy, the PSA level was set as a recognized screening tool [1,2]. The experiment led to a consensus that a prostate-specific antigen level of more than 4.0 nanograms per milliliter (ng/mL) has predictive value for the diagnosis of prostate cancer [3,4]. Despite this primary role, the information of recent years seems to refute its premises in the diagnosis of prostate cancer. Indeed, the discordant results between the value of the specific antigen of the prostate and the presence of cancer are not seldom in the literature [5,6]. Two prospective studies have investigated the appropriateness of mass screening for prostate cancer, with conflicting results. The "Prostate Lung Colorectal and Ovarian Cancer Screening Trial (PLCO)" study, launched in 1996 in North America, randomized more than 76,000 patients followed for at least ten years. Surprisingly, the cancer-related mortality rate of the group of screened patients was similar to that of the group with no evidence of screening [7]. The "European Randomized Study of Screening for Prostate Cancer (ERSCP)" study, 182,000 patients followed for more than ten years, already showed in its first publication a substantial reduction in the specific prostate cancer mortality rate of 20% [8]. The difficulty of shared and informed decision-making appears high when the value of the prostate-specific antigen increases above four ng/mL. In Gabon, as in the world, PSAt is used for prostate cancer diagnosis. The upper threshold limit is 4ng/mL. However, to our knowledge, no studies in the country have assessed the risk of being diagnosed with prostate cancer from a threshold of 4 ng/mL of PSAt in our populations. In this context of the lack of data on the risk for diagnosing high-grade prostate cancer for a man over 45 years following an increase in the value of serum PSAt above 4 ng/mL, we carry out the present study carried out. Testing the hypothesis that there would be a PSAt value in men in Gabon above which prostate cancer was essentially high-grade, we assessed the risk of being diagnosed with prostate cancer of high grade for men with a total prostate-specific antigen value greater than 4 ng/mL in Libreville between 2018 and 2020.

MATERIALS AND METHODS

Study design

Our study was case-control. It took place within the framework of a multidisciplinary project that aims to study the immunity of prostate cancer in Libreville.

Population

The samples studied came from 232 patients, 143 of whom had malignant lesions of the prostate (cases), and were compared to 89 control patients with benign prostatic hypertrophy (controls). For both groups, the inclusion and non-inclusion criteria were as follows:

Inclusion criteria

Have been subjected to a prostate biopsy with samples of 10-12 carrots.

Have been diagnosed with confirmed prostate cancer or benign prostatic hypertrophy, according to architectural and cytological criteria established by the International Society of Urological Pathology in 2014 [9].

Have a serum PSAt level greater than 4 ng/ml

Be over or equal to 45 years old.

Non-inclusion criteria

Be less than 45 years old. Have a history of prostate cancer and factors that may affect prostate-specific antigen concentration, such as previous transurethral resection of the prostate, treatment with drugs that may affect prostate-specific antigen concentration total prostate (5-α-reductase inhibitors and androgens), urinary tract infection contemporaneous with the blood sample, acute bacterial prostatitis in the three months preceding the biopsy.

An unspecified prostate-specific antigen value.

Course of the study

The patients were recruited from the Anatomy-Cytology-Pathology laboratory of the Faculty of Medicine of Libreville between January 2018 and December 2020. Our choice was maken because, until 2019, the Anatomy-Cytology-Pathology laboratory of the Faculty of Medicine has been the only pathology laboratoty in the country for decades, with a pathologist physician specialized in prostat cancer. To set the two groups, we included each patient in relation to their order of registration in the laboratory registers according to the diagnosis. Sampling was done in a simple random manner. The selection made it possible to constitute a representative population of men who came to have samples of prostate biopsies analyzed in the laboratory during the study period.

The study population was divided into five age groups corresponding to the age guideline groups for the serum total prostate-specific antigen test of the U.S. Prostate Cancer Screening Trial, lung, colon-rectum, and ovary

(PLCO) [7]. We have categorized the ranges of prostate-specific antigen values into five bands based on a modification of D'Amico Risk Groups and the National Comprehensive Cancer Network risk categories to fit our study [10,11].
The patients from whom all the retained samples came had signed consent for subsequent use for research purposes of their biological material. The consent procedure used was the same for both groups. This study received a positive opinion from the institutional ethics committee. (ref : CEI 2019/12)

Judgment criteria

The main judgment criteria was the risk of developing high-grade prostate cancer.
To assess the risk of presenting with high-grade prostate cancer, we recorded, for each patient, the age, the serum PSAt level, the Gleason score, and the diagnosis retained.
We evaluated the age of the patients from 45 years. We chose this age limit because, from the literature, prostate cancer most often appears after 45 years in black populations [12,13].
We evaluated the serum PSAt level from the threshold value of 4 ng/mL because, in the literature, further investigation, such as the realization of a prostate biopsy, is recommended from this value [14,15].
We defined high-grade prostate cancer by a Gleason greater than or equal to 7 (4+3) as defined by "The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason"[16,17] as well as benign prostatic hypertrophy by the presence of an adenomyofibroma lesion of the prostate [18]. The diagnosis retained could be a malignant or benign lesion.
The various socio-demographic and medical data concerning each patient were recorded at the time of the sample delivery to the laboratory based on the patient's speech and the request for examination. We collected the data relating to the retained histological diagnosis of the sample from the laboratory results registers, and we reported them on a data collection sheet developed for the study by the investigators.

Data entry and analysis

Data from the 232 patients were entered into an Excel spreadsheet and analyzed using SAS v.9.4 statistical software (SAS Institute, Cary, NC, USA). In the descriptive univariate analyses, the quantitative variables were expressed in median, first and third quartile. Mean confidence intervals were calculated using Student's law. The binary qualitative variables were expressed in number and percentage. In bivariate analyses, the independence between two quantitative variables was tested using Spearman's nullity test. The independence between a quantitative variable and a qualitative variable was tested using a Student test.

RESULTS

The study included 232 men (89 with benign prostatic hyperplasia and 143 with prostate cancer).
The median age of the patients was 67.3 (IQR: [61.75; 73]). The age group of 60-69 years was the most represented 93 (44%) patients. The age distribution according to the concept of cancer and benign prostatic hyperplasia was almost similar for a p-value of 0.741.
Patients with a prostate-specific antigen between 31-100 ng/mL were the most numerous, 100 (43.1%); however, 39 (16.8%) patients had a PSAt greater than 100 ng/mL.
The analysis of the average prostate-specific antigen varied according to the age groups (<50 years: 37 ± 54.8; 50-59 years: 336 ± 1198; 60-69 years: 142 ± 359; 70-74 years: 208 ± 1092; 74 and over 86 ± 164). However, the difference was not statistically significant for a p-value of 0.726. The characteristics of each group included in the study are presented in the table I.

Table I: Characteristics of the study population according to the results of the biopsy.

Characteristics	All Men (N=232)	Men with PBH (N=89)	Men with cancer (N=143)	P value
Age-groups (years)				0.741
-<50	3(1.3)	2(2.2)	1(0.7)	
-50-59	43(18.5)	15(16.9)	28(19.6)	
-60-69	102(44.0)	42(47.2)	60(42.0)	
-70-74	69(29.7)	24(27.0)	45(31.5)	
->74	15(6.5)	6(6.7)	9(6.3)	
PSAt (ng/mL)				0.001
Mean	192.36	23.1985	86	
Median	49.42	16.0000	100	
Min-Max	0.02-9129	0.20-183.54	4-9129.00	

PSAt : prostate specific antigen ; HBP : benign prostatic hyperplasia; Min : minimum ; Max : maximum

Characteristics of Prostate Cancer Patients

Value and percentage of total*serum PSA in prostate cancer

Gleason's score of 7 (4+3) was the most frequent in this population, with a percentage of 32.4%. Figure 1 shows the distribution of patients with a total prostate-specific antigen value between 4 and 9129 according to Gleason's score.

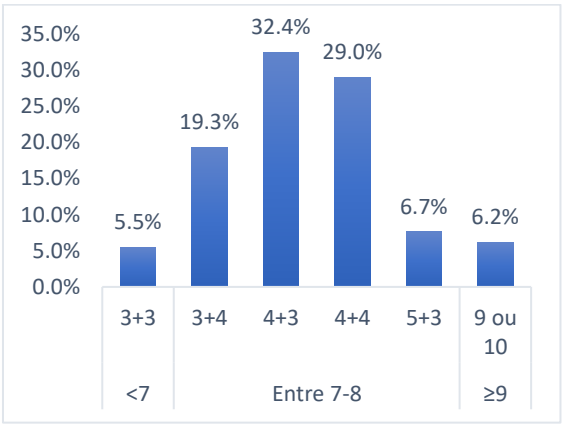

Figure 1: Distribution of percentage of total prostate-specific antigen (PSAt) in prostate cancer according to Gleason score.

The number of patients who had a Gleason greater than 7 (4+3) was the highest with about 75% of patients.

Total Prostate-Specific Antigen value and risk of high-grade prostate cancer

There was a direct correlation between total prostate-specific antigen values and the risk of high-grade cancer (r=0.34 p<0.0001). However, this correlation is not strong enough to affect the risk in the total prostate-specific antigen values between 30-100 ng/mL. For prostate-specific antigen values > 100, the effect on the selection for performing prostate biopsies in this population is significant, as in Table II.

Table II: estimation of high-grade prostate cancer risk based on prostate-specific antigen value in the 2018-2020 study population.

PSAt Level	Men with no high-grade prostate cancer ≤7(3+4)	Men with high-grade prostate cancer ≥7(4+3)	High-grade cancer risk ratio [IC 95%]	P value
4	0(0.0)	0(0.0)	1	
5-10	2(0.0)	2 (100)	1[1.92-1.96]	0.833
11-30	7(100)	14(0.0)	2.10[3.23-6.55]	0.453
31-100	23(97)	57(33.3)	2.47[1.15-1.72]	0.029
>100	1(87.2)	37(55.6)	37[1.33-1.87]	0.001

PSAt : total serum prostate-specific antigen

A serum PSAt level > 100 ng/mL was predictive of prostate cancer at 37 [95%

Comparison between prostate cancer vs HBP patients

PSA total*concentrations, Prostate cancer vs HBP patients

Serum prostate-specific antigen value was significantly higher in patients with prostate cancer than in patients with benign prostatic hyperplasia (Mann-Whitney U test p<0.001) (figure 2).

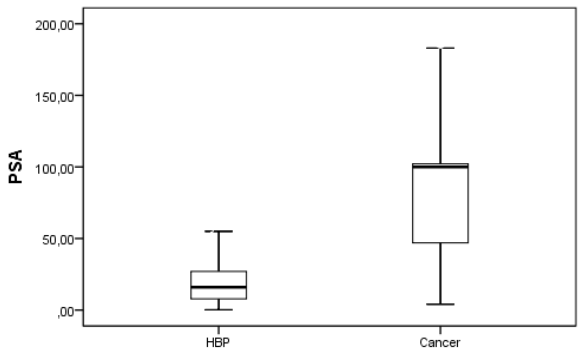

Figure 2 : serum total prostate-specific antigen value by diagnostic group.

Sensitivity and specificity of serum total* PSA in prostate cancer and benign prostatic hyperplasia.

A value strictly superior to 100 ng/mL offers a sensitivity of 87% and a specificity of 13% (i.e. it prevents 13% of men with benign prostate disease from an inappropriate biopsy), as shown in Table III.

Table III : Value and percentage of the sensitivity and the specificity of total PSA* in prostate cancer in Libreville 2018-2020.

PSA level	All men N=232 (%)	Men with cancer N=143 (%)	Men with high grade cancer ≥7 (4+3) N=93 (%)	Se	Sp
4	6 (2.6)	0 (0.0)	0 (0.0)	0.00%	93.26%
5-10	30 (12.9)	4 (2.8)	2 (11.1)	3%	96.66%
11-30	57 (24.8)	21 (14.7)	14 (13.33)	25%	75.43%
31-100	100 (43.1)	80 (55.9)	43 (33.3)	56%	44%
>100	39 (16.8)	38 (26.6)	34 (55.6)	87%	12.84%

A value strictly superior to 100 ng/mL offers a sensitivity of 87% and a specificity of 13% (i.e. it prevents 13% of men with benign prostate disease from an inappropriate biopsy).
Se: Sensitivity Sp: Specificity

DISCUSSION

Based on our knowledge, this is the first study in Libreville to compare histologically confirmed diagnoses from prostate biopsies to serum total prostate-specific antigen values.

The question to be answered by this study was to know the risk for a man aged more or equal to 45, to be diagnosed with high-grade prostate cancer when he had a serum value of prostate-specific requirement total greater than or equal to 4 ng/mL.

Analysis of the results of this study first showed a higher average prostate-specific antigen in prostate cancer than in benign prostatic hyperplasia. The difference was statistically significant for this population. This finding is consistent with studies that have shown that normal prostate cells, although they can express prostate-specific antigen, cancerous tissue releases approximately 10 times more antigen into the serum than hyperplasia tissue. Benign prostate or normal [19]. The release of prostate-specific-antigen is thought to be related to the disruption of normal prostate cell membranes that occurs in prostate cancer. However, the average prostate-specific antigen in this population was twice the averages found in studies of prostate-specific-antigen in Caucasians with prostate cancer, although it was similar to other sub-Saharan Africa [20,21]. This finding supports previous epidemiological studies which have shown that sub-Saharan African men have significantly higher plasma levels of prostate-specific antigen than European-American men, although prostate size is similar in both men groups [22,23]. This latter observation suggests that a generally enhanced androgenic and growth-promoting effect is not present in the gland of African men, which would explain the elevated levels of total prostate-specific antigen in the blood [24].

Second in this population, with 4ng/mL of total serum prostate-specific antigen, as the upper threshold, we were able to histologically confirm the diagnosis of 61% of prostate cancer that is not negligible. However, further subgroup analysis shows a disparity in the different ranges. The diagnosis of high-grade cancer was made at the highest ranges. We were thus able to observe that to obtain a sensitivity of 87% of the test, a threshold of 100 ng/mL was necessary, but at the cost of 13% false positives. At ranges of total prostate specific-antigen below 30 ng/mL, the test had very low sensitivities, below 50%, but we still found 24% of high-grade cancer. If we take this value as a reference threshold for a more in-depth examination and a biopsy, for this population, we would miss 25% of high-grade cancer, but we would save 75% of men from undergoing anxiety and useless biopsies. The 25% of patients who would be missed in this range could be made up by systematically measuring total prostate-specific antigen and free prostate-specific antigen. The ratio of free PSA to total PSA usually expressed as a percentage (%fPSA), has been proposed to differentiate between benign and malignant prostate disease, improving specificity while maintaining sensitivity, especially in the gray zone diagnosis where the total prostate-specific antigen is between 4-30 ng/mL [25].

Another potential approach to improving the sensitivity and specificity of prostate-specific antigen tests when identifying high-grade prostate cancers is to incorporate genetic variant information. Hereditary factors are thought to explain 40-45% of the variability in prostate-specific antigen levels [26]. Gudmundsson [27] identified four single nucleotide polymorphisms (SNPs) that were primarily associated with total prostate-specific antigen values rather than prostate cancer risk. This identification was made in a genome-wide association study (GWAS) of serum prostate-specific antigen values in Icelandic men undiagnosed from prostate cancer. (PSA-SNP : TERT rs2736098, FGFR2 rs10788160, TBX3 rs11067228, KLK3 rs17632542). Men with a high number of PSA-SNP alleles that increase prostate-specific antigen levels were considered genetically "high" prostate-specific antigen producers, while those with one reduced number were genetically "inferior" prostate-specific antigen producers. They suggested that using the combined effect of these PSA-SNPs to genetically correct the measured prostate-specific antigen could improve the performance of total prostate-specific antigen as a diagnostic tool. high-grade prostate cancer [28–30]. Li et al. 2020, recorded SNPs that alter the functions of neighboring genes, resulting in age-specific effects and on the level of prostate-specific antigen [31]. The association of genetic polymorphisms in the organic anion transporter polypeptide superfamily, encoded by the SLCO2B1 and SLCO1B3 genes with the potential to transport adrenal androgens to prostate cells, has been shown to regulate antigen levels prostate-specific [32]. But one should not overlook that the literature suggests several factors associated with variation in the prostate-specific antigen's serum level, including demographics, body mass index, ethnicity, smoking, and consumption of alcohol [33–35]. However, variable multifactorial assessments associated with prostate-specific antigen, especially in cohorts from various continents, are not found in the literature as suggested by his study. Evaluation of factors associated with the level of prostate-specific antigen in prostate cancer cases and controls, in this population would see here all its importance.

threshold >100 ng/mL was required to present a 37-fold risk of being diagnosed with high-grade prostate cancer. It appears that the risk of high-grade prostate cancer in this population increases with the elevation of the prostate-specific antigen value. This level of ascending risk is found in the New Zealand and Taiwanese population by the multicentre study which evaluated the factors associated with the level of prostate-specific antigen in three regions [36]. However, other studies have shown that the slope of this relationship is flatter than previously thought, causing controversy as to what level of prostate-specific antigen should prompt a biopsy [37]. Because of this increasing risk with the value of prostate specific antigen, the threshold for prostate biopsy could be adjusted upwards to maintain a specificity of total prostate-specific antigen below 5%.

However, our study has limitations. First, in all the patients, no biopsy scheme was specified, whereas the interpretation of the level of total prostate-specific antigen strongly depends on the biopsy scheme. Second, the absence of transrectal ultrasound biopsies (TRUST). Indeed, the absence of transrectal ultrasound biopsies presents a higher risk of sampling errors during the biopsy with no ultrasound guidance.

CONCLUSION

In this study, the risk of being diagnosed with high-grade prostate cancer only appears for prostate-specific antigen values above 100 ng/mL. However, this threshold is still debatable because it is associated with a low sensitivity which does not make it possible to discriminate between men with a real risk of presenting high-grade prostate cancer and men with indolent cancer. A reasonable recommendation is to double the threshold value considered normal and interpret it as usual. Increasing the thresholds of measured prostate-specific antigen values considered pathological may improve the clinical usefulness of the test. As most of the patients in this population with total prostate-specific antigen values between 4.0 and 10.0 ng/mL have benign prostate disease, this represents a substantial number of patients who would avoid an inappropriate prostate biopsy if we increase the threshold limit to 10 ng/mL.

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Conflict of interest

All authors declare that they have no conflict of interest

Authors contribution

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Final article approval : Joel Fleury Djoba Siawaya et Maguette Sylla Niang

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