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The Prediagnosis of Prostate Cancer Risk is Possible with the Evaluation of BRCA1 Primary Exons in Men

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Abstract Prostate cancer is a public health concern among men older than 50 years worldwide and its incidence keep rising as younger men are now diagnosed with this affliction. It is triggered by genomic instability or epigenetic modifications impacting genes and proteins involved in DNA repair, cell growth regulation and tumor suppression. In sub-Saharan African countries, few data are available on prostate cancer and the loss of BRCA1function. Recent studies have associated BRCA1 mutations to prostate cancer. Men with prostate cancer have symptoms like nocturia, poor urinary flow, hematuria, erectile dysfunction all of which affect their familial and social life. The main objective of our study is to assess the association between the instability of BRCA1 primary exons and the occurrence of prostate cancer, with the motivation to contribute to its early prescreening, prevention and treatment. Thus, to assess the functionality of BRCA1 we have investigated the integrity of exon 1,2,3 and 5 in male diagnosed with prostate cancer in three west African countries (Benin, Nigeria and Niger). Materials and methods: Peripheral blood was collected from men diagnosed with prostate cancer in urological service of three hospitals respectively in Benin (n= 20), Nigeria (n= 16) and Niger (n = 20) subsequent to ethical comity authorization (CLERB-UP) and signed informed consent from participants. Control samples (n= 20) were from healthy male students and university professors older than 25 years. Chloroform/isoamyl alcohol method was used to extract DNA before quantification with spectrophotometer. Polymerase chain reaction (PCR) was used to amplify exon 1, 2, 3 and 5 from 50 ng DNA, before migration on 1% agarose gel. Results and discussion: In all samples exon 2 and exon 5 were not amplified in 31.34% and 31.63% respectively; while Exon 1 and exon 3 were not amplified in 17.53% and 19.5% respectively. All of which could be due to deletion or spontaneous mutation. Conclusion: BRCA1 mutation should also be investigate in routine exam for prostate cancer prevention and treatment in sub-Saharan African population to prescribed the proper drug accordingly.

Keywords: *prostate cancer, pre-diagnostic, BRCA1*

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1. Introduction

Cancer is the second leading cause of death in the world and is likely to surpass that of infectious diseases in Africa, in the next two decades [1]. In 2020 nearly 10 million deaths were linked to Cancer [2]. Each year, Africa registers about 1.1 million new cases of cancer and up to 700,000 deaths from the disease [2]. Prostate cancer remains the leading cause of morbidity and mortality among men in sub-Saharan Africa [3]. Its genesis is linked to several sources such as genetic factors, family history, environment, etc. Although mutations in tumor suppressor genes (genetic factors) were known risk factors for this disease, epigenetic modifications were also involved in the initiation of prostate cancer. Thus, prostate cancer is triggered by genome instability or epigenetic modifications impacting DNA repair and tumor suppression genes and proteins [3]. One of the tumor suppressor gene being investigated is BRCA1 which inactivation could be triggered by genome instability or epigenetic modifications impacting DNA repair processes and suppression of tumor cells. Specifically, multitude of mutations of BRCA1 was reported through its 24 exons but nevertheless, no study has investigated the instability of the primary exons of BRCA1. The BRCA1 gene is located on chromosome 17 (17q21), bears 22 coding

exons that could not all be investigated at once as it is costly and time consuming [4].

Beside genetic factor underlying this disease, we can also incriminate environmental and nutritional factors.

Environmental Exposures to **Bisphenol A** (BPA) which is a diethylstilbestrol initiates also cancer [5,6]. Exposure to chlordecone which is an organochloride pesticide used for banana agriculture [7,8]. Organochlorine insecticides are endocrine disruptors that accumulate in fatty tissue, providing ongoing endocrine disruption that may increase prostate cancer risk [9].

Nutritional factors: change in lifestyle induced a shift towards an increased incidence of prostate cancer especially increase in animal fat diet and low fruits and vegetable diets [10]. Diet rich in poly-unsaturated fat, particularly omega-6 (ω-6) fatty acids largely from vegetable oils, is also associated with an elevated risk of prostate cancer [11]. Conversely, intake of ω-3 fatty acids primarily from fish is associated with a reduced risk of prostate cancer [12]. Calcium from dairy products is also incriminated in prostate cancer development and progression [13,14]. Vitamin D deficiency was shown to increase the risk of prostate cancer development [15]. Consumption of Vitamin E has demonstrated anti prostate cancer properties [16,17]. Vitamine B12 and B9 (folate) are involved in DNA methylation, synthesis and repair [18]. Unbalanced level of vitamine B12 and B9 (folate) could also lead to uncontroled DNA methylation leading to epigenetic modification of tumor suppressor gene and subsquently to cancer [19,20]. Heavy alcohol consumption is associated to several types of human cancers, including prostate cancer [21,22]. Exposures (passive and active) to cigarette smokes predispose also to prostate cancer [23,24]. The prostate cancer strategy involves several identified biomarkers for prostate cancer screening. Among the biomarkers used in prostate cancer screening, the most common and widely adopted being prostate-specific antigen (PSA), which has been approved by the Food and Drug Administration [25] from the United States in 1986 [26,27]. PSA screening has had a significant impact on trends in prostate cancer incidence and mortality and its widespread adoption has been scrutinized since its discovery 40 years ago [28,29].

Although PSA screening appeared to be very beneficial, the question arises whether it improved survival or simply detected earlier stage of prostate cancer, leading to overtreatment [30]. Recent data from the US Preventative Services Task Force (USPSTF) reported evidence that PSA screening offers a potential benefit in reducing the risk of death in old men of 55 to 69 years [30]. Additional biomarkers have been developed recently, including the Prostate Health Index (PHI) that has been approved by the FDA, combines free and total PSA and pro-PSA 2-isoform (p2PSA). The PHI test is intended to reduce the number of unnecessary prostate biopsies in men tested for PSA [31]. Similarly, Prostate Cancer Antigen-3 (PCA3) is a known urinary biomarker for prostate cancer. It is a non-coding, prostate-specific mRNA that is highly overexpressed in 95% of prostate cancer cells. The non-invasive nature of the PCA3 urine test makes it attractive to clinicians, giving its superiority over several alternative biomarkers with similar or greater specificity, the 4Kscore showed superiority over PSA in the diagnosis of indolent versus aggressive prostate [32]. Despite these new advances, PSA currently remains the international gold standard for screening and monitoring but the results do not always corelated with prostate cancer. Thus, our study compared both PSA. BRCA1 malfunction and the onset of prostate cancer.

Although genetic testing for BRCA1 is widely spread in developed countries before prostate cancer treatment, this strategy is unknown in most west African countries. In sub-Sahara African countries, few or no data are available on prostate cancer and the loss of BRCA1 function subsequent to mutation in primary Exon 1, 2, 3 or 5. The general objective of this study is to assess the association between BRCA1 instability in prostate cancer patients and healthy controls in three west African countries including Benin (Cotonou), Nigeria (Ogun State) and Niger (Zinder), in order to develop molecular biomarker tools for reliable pre-screening of prostate cancer onset.

2. Materials and Methods

2.1. Type of Study

Observational and case/control study

In a first part, this study consists in demonstrating that there is an association between the instability of the BRCA1 gene and the occurrence of prostate cancer. This is an observational case-control study, the cases will be men with prostate cancer and the controls will be those who are not sick.

In a second part, this study consists in demonstrating that BRCA1 gene mutations and epigenetic inactivations are responsible for the occurrence of prostate cancer.

2.2. Inclusion and Non-inclusion Criteria

The selection of the study population was made according to a well-defined questionnaire.

Inclusion criteria: subjects who gave their informed consent to participate in the study. As such, men of 30 years or older diagnosed with prostate cancer and age matched controls.

Non-inclusion criteria: subjects who did not give their informed consent to participate in the study; Men under 30; The women; Anemic, bedridden men and men afraid of blood tests.

2.3. Sampling

The blood samples were collected in EDTA tubes in order to be able to recover the peripheral white blood cells and proceed to the analysis of the biomarkers (BRCA1).

2.4. DNA Extraction

DNA extraction was carried out according to the methods described previously [33].

To extract the DNA, the blood was collected in EDTA tube and centrifuged at 2000 rpm for 10 min. The Buffy Coat was collected directly into a 15ml falcon tube. The lysis buffer was added to the latter, closed and agitated by

inversion for 5 minutes. We left the mixture to stand for 15 minutes at room temperature, before centrifuging at 2000 rpm for 15 min and removing the supernatant (this process was repeated 3 times).

The supernatant mixture, TKM1 (tris-Kcl-Mgcl2) (5ml) and 4 drops of triton are added then stirred by inversion until the mixture is completely dissolved. This mixture was centrifuged at 2200 rpm for 15 minutes in order to recover the pellet. TKM1 (1ml) was added, stirred and transferred to a 1.5ml Eppendorf tube. This mixture is centrifuged again for 5 min to harvest the pellet before lysis with 400 µl of lysis buffer (TKM2) and 25 µl of 10% SDS. Then mixed until completely dissolved and incubated in a water bath for 30 minutes at 55°C. After the incubation of the mixture, 180 µl of NaCl (5 M) was added, stirred, left to stand at room temperature for 20 minutes then centrifuged at 12000 rpm for 5 min. The supernatant containing the DNA was removed and transferred to a new eppendorf tube. The chloroform / isoamyl alcohol (SEVAG) mixture (800 µl) was added and centrifuged at 12000rpm for 5 min. The supernatant containing DNA was removed and transferred to an Eppendorf tube. Sodium acetate (3 M PH 2.5) at 10% and 100 µl of absolute ethanol (96°) with ice are added. The mixture was centrifuged at 12000rpm for 3 min then the supernatant was removed and 1000 µl of ice-cold 76° ethanol was added, stirred and centrifuged at 12000rpm for 5 min. The supernatant was discarded and then the DNA was left to dry at room temperature. The DNA suspension was made in 300 µl of sterile distilled water and then stored at -20°C.

2.5. Quality Control and Assay of Extracted DNA

The DNA concentration is estimated by the optical density at 260nm knowing that one unit of optical density at 260nm corresponds to 50 µg of DNA/ml.

The degree of DNA purification was evaluated with a spectrophotometer optical densitometry (OD) and the OD ratio 260nm /280nm which requires only 3-5 µl of the sample.

In short, the purity of the extracted DNA is evaluated by the ratio of its optical density: DO260nm/DO280nm which must be between 1.8 and 2.1. A lower value indicates contamination by proteins and a higher value indicates contamination by heavy metals.

Polymerization Chain Reaction (PCR) program is specified in Table 1.

Table 1. PCR program for exon 1, 2, 3 and 5 of BRCA1 gene amplification

Stage	Temperature	Time
Thermal denaturation	94°C	30 seconds
Hybridization (30 cycles)	94°C 65°C 68°C	30 seconds 60 seconds 1 min/kb
Elongation	68°C	5 minutes
Conservation	4–10°C	

The One Taque-Load 2X Master Mix with Standard Buffer was used to perform the PCR

The primers sequences were detailed in Table 2 as follows.

Table 2. The primers used according to [34]

Embarrassed		Primers
Name	exon	Sequences 5' ………………………..…………………3'
BRCA1	1	**Forward:** TAG CCC CTT GGT TTC CGT G
		Reverse: TCA CAA CGC CTT ACG CCT C
BRCA1	2	**Forward:** GAA GTTG TCA TTT TAT AAA CCT TT
		Reverse: TGT CTT TTC TTC CCT AGT ATG T
BRCA1	3	**Forward:** TCC TGA CAC AGC AGA CAT TTA
		Reverse: TTG GAT TTT TCG TTC TCA CTT A
BRCA1	5	**Forward:** CTC TTA AGG GCA GTT GTG AG
		Reverse: TTC CTA CTG TGG TTG CTT CC

2.6. Electrophoresis

The PCR products were subjected to migration on an agarose gel. The latter was prepared using Tris Borate EDTA (TBE 1x) then poured into the tray of the electrophoresis tank with a comb arranged for the creation of sample deposit wells in the gel. The exon staining was made with an addition of SafeView nucleic Acid Stains (5 µl). The electrophoresis tank is filled to 2/3 with tri Borate EDTA (TBE 1x) and 10 µl of the DNA size marker (Quick-Load Purple 100bp Ladder) is placed in the first well. Then a mixture of 10 µl of distilled water and One Taque-Load 2X Master Mix with Standard Buffer was placed in each well. The first well was loaded with a DNA size marker (DNA ladder). Then a mixture of 10 µl of amplified DNA was deposited in each of the remaining wells. Our innovation in this method is to have used only the master mix 2X (One Taq-Load 2X Master Mix with Standard Buffer), without our usual loading buffer (Gel Loading Dye Blue Purple 6X) for better visibility of migrated amplicons on electrophoresis gel. The electrophoresis tank was connected to a generator. After migration for 30 min at 100 mV, the bands were revealed by ultraviolet [35] observation. The following section presents the results obtained with these methods.

3. Results

3.1. Sample Size

This research work took place on 80 subjects including forty cases (40) of prostate cancer with twenty (20) cases from Benin and twenty (20) from Niger. To compare our results, we chose forty (40) healthy controls, twenty (20) from Benin and twenty (20) from Niger.

3.2. Presentation of the Results According to the Age

In our study, samples from 40 prostate cancer patients were screened for BRCA1 primary exon mutations. An informed consent survey was conducted among these patients to record their ages as shown in Figure 1.

The Figure 1 shows the distribution of the study population according to their age. The distribution of prostate cancer varies according to the age and the frequencies were 8.88%; 41.17% and 49.94% respectively for age 30 - 50; 50 -70 and 70 – 90 years. The higher

frequency was observed for people with age between seventy (70) to ninety-nine (90). The global analysis of our results shows that the average age of prostate cancer patients was 60 ± 5 years. Additional prostate cancer screening parameter includes a dosage of the prostate-specific antigen (PSA) (Figure 2).

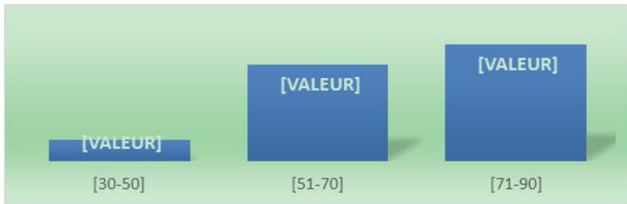

Figure 1. Histogram summarizing the survey data. The distribution of prostate cancer by age group shows that majority of patients are above 71 years followed by 51 to 70 years. Younger than 50 years patients were among the study population

3.3. Presentation of PSA Results

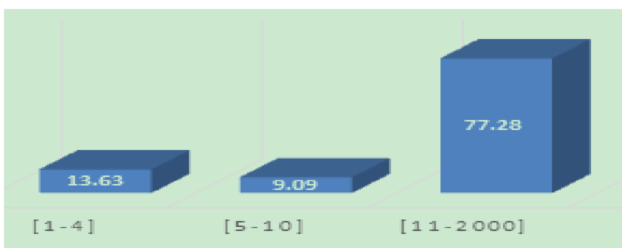

Figure 2. Histogram showing total PSA level distribution from low to high value among prostate cancer patients. *Normal PSA is lower than* 4 ng/ml, suspect PSA is between 4 - 10 ng/ml while prostate cancer related PSA is abnormally higher than 10 ng/ml

The histogram on Figure 2 presents the amount of PSA according to three intervals. In our study population normal PSA was observed in 13.63% of patient, suspect PSA was observed in 9.09% of them while the majority of them (77.28%) high PSA levels; which are respectively in the intervals [1 - 4 ng/ml], [5 - 10 ng/ml] and [11 - 2000 ng/ml]. The average PSA is 585.75 ng/ml.

Investigation of BRCA1 exon 1, 2, 3 and 5 amplification with specific primer in Table 2.

Prostate cancer is interconnected with BRCA1 gene mutation where exon disruption is the main etiology.

3.4. Presentation of PCR Results

The Figure 3 represents agarose gel electrophoresis with PCR products. The presence of the 315 bp and 250 bp fragments correspond respectively to exon 1 and exon 2. The absence of one or both fragments indicates the loss of these exons. Exon 1 of BRCA1 is absent in 17.53% of samples as shown by sample N5, and present in the other people where bands are seen. Exon 2 of BRCA1 is absent in 31.33%. of samples as shown by samples B2, N1, N3 while it is present in the other samples where bands are seen. After these two exons, we also evaluated exons 3 and 5 in our study population (Figure 4).

The electrophoresis gels of exons 3 and 5 are shown in Figure 4. The presence of fragments of 340 bp and 278 bp correspond respectively to exon 3 (above) and exon 5 (bottom). The absence of one or both fragments indicates the loss of these exons. Thus, the analysis of this Figure 4. shows the absence of exon 3 and 5 in samples B2 and N5. There is a loss of exon 5 in samples N4 and N5. The prevalence of the loss of exon 3 is 19.5% while it is 31.63% for exon 5. Globally, there is more of a deletion of exon 5 in our study population.

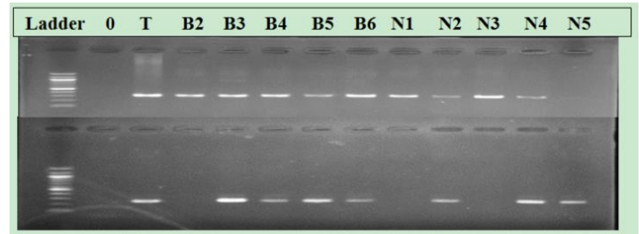

Figure 3. Agarose gel showing the amplification of exons 1 (above) and exons 2 (bottom) of the BRCA1 gene by PCR. *Absence of band is indicator of mutation on the targeted exon*. T: Witness, B: Benin, N: Niger

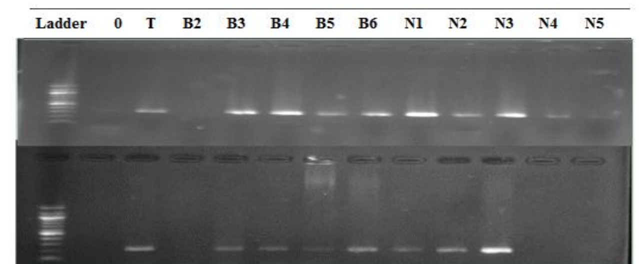

Figure 4. Gel showing the PCR product of BRCA1 exons 3 (above) and exons 5 (bottom). Sample B2 and N5 are missing exon 3 and exon 5 while samples N4 and N5 are missing exon 5 but not exon 3

Nevertheless, DNA duplication was observed in sample B16 and loss of exons 1, 2, 3 and 5 of BRCA1 was observed in sample B10, N6.

In summary, the percentages of the loss of exons 1, 2, 3 and 5 of BRCA1 in our study population are represented in the figure below:

Figure 5. Percentage of absence of exons 1, 2, 3 and 5 in our study population. Globally for Benin (B) and Niger (N) together [36] the loss was 17.53 % for exon 1 (Ex1); 31.34% for exon 2 (Ex2); 19.5% for exon 3 (Ex3) and 31.63 % for exon 5 (Ex5). Nos mutations was observed the control samples (Temoins)

Taken together, prostate cancer sample from Benin and Niger displayed higher mutation frequencies in exon 5 (31.63%) and exon 2 (31.34%) than in exon 3 (19.5%) and exon 1 (17.53). BRCA1 mutation analysis is very complex but defects in primary exons impact BRCA1 protein synthesis. Additional mutations may exist but we focused on the primary exons to evaluate their association to prostate cancer in west Africa.

4. Discussion

Cancer is caused by molecular alterations that may lead

to specific mutations. In men, prostate cancer was the most common cancer worldide in 2020 [37]. As shown with other cancers, genetic and epigenetic changes underly a higher risk of prostate cancer and its progression [38]. DNA damage is implicated in carcinogenesis and may be associated with environmental factors such as ionizing radiation, chemicals or toxins and ultraviolet radiation responsible for the production of reactive oxygen species [38]. DNA damage response pathways are in place to maintain genomic stability by monitoring DNA integrity and activating the DNA repair process or inducing cellular apoptosis when necessary [39]. Altered DNA damage response pathways lead to genomic instability through survival and proliferation of unrepaired cells and subsequently to tumorogenesis [40]. Among the germline and somatic mutations in prostate cancer, BRCA mutations are the most frequent mutations [41]. The BRCA1 gene is part of the large BRCA family whose mutation is associated with the risk of prostate cancer which one varies according to the type of mutation or the absence of the exons [41].

Molecular biology techniques have given strength to the study of useful biomarkers for the prognosis and prediction of cancer. In the context of our work based on prostate cancer, men of various ages were recruited to assess the determinant exons that can be used as molecular biomarker of BRCA1 defaulting in patients with prostate cancer in West Africa.

The analysis of our results showed that the average age of patients with prostate cancer was 60 ± 5 years. In Benin, a retrospective study carried out by Hounnasso and his collaborators in 2015 [42] on 84 patients showed that the average age of the patients was 70 years ± 9 years, which is above those of our results. This average age found in our study is related to that of Amégbor and his collaborators in 2009 in Senegal as well as other authors from Africa south of the Sahara. [43] and the Maghreb confirmed these results [44]. The work carried out in France revealed that there is no significant difference in the average age of 71.6 years [35]. These data from other studies reflect that prostate cancer remains a disease of the elderly. Also, in our results, we had 30-year-old patients. According to data from the Surveillance, Epidemiology, and End Results program and the Institute for Health Metrics and Evaluation Global Burden, men as young as 17 are experiencing an increasing incidence of prostate cancer in much of the world, including in the USA [45]. Thus, the occurrence of prostate cancer is not only related to the age rather, it could be correlated to lifestyles, environmental, genetic and epigenetic factors.

For the diagnosis of prostate cancer, PSA remains the cornerstone of biological testing in developing countries such as Benin. However, our results showed a discordance between the high value of the PSA and the existence or not of prostate cancer.

Nevertheless, our results showed a significant increase in the value of PSA in some patients suffering from prostate cancer, with values exceeding 10 ng/ml. The study carried out by Hounnasso and his collaborators in 2015 in Benin on patients suffering from prostate cancer, confirms our results [42]. Similarly, in Guinea, a high rate of PSA has been reported [46]. Thus, we can point out that there is a correlation between the value of PSA and the extension of prostate cancer in some people.

The results from our research work on the evaluation of exons 1, 2, 3 and 5 of BRCA1 show that 17.53%; 31.34%; 19.5% and 31.63% of our study population lack exons 1, 2, 3 and 5 respectively. In this research, losses of exons 2 and 5 had the highest incidence while defaulting exons 1 and 3 had the least incidence. The absence of these exons has not been widely studied in prostate cancer in sub-Saharan Africa. On the other hand, these BRCA1 exons have been sought in breast and ovarian cancers. [47].

The breakdown of our results by country shows that the loss of exons 2 was dominant in Benin while Exon 5 is predominantly lost in Niger.

This study, which is the first in Benin and Niger, shows us that BRCA1 gene instability is one of the causes of prostate cancer in West Africa, as several studies have shown [48]. BRCA1 and BRCA2 mutants predispose to breast and ovarian cancer in women as well as to breast and prostate cancer in men [48].

Ultimately, the first four (04) exons of the BRCA1 gene must be analyzed in all men over the age of 30 to detect molecular risk factors for genomic instability initiating carcinogenesis in Africa and elsewhere. Medicines as well as foods to control the evolution of these cancers are available [49].

Most African countries do not have access to treatment with PARP inhibitors like rucaparib (Rubraca) and olaparib (Lynparza) which are drugs used for cancer with defectif BRCA1.to slow PARP (poly(ADP)-ribose polymerase) activity are recommended in case of BRCA1 deficiency [25]. We are expecting that our study will contribute to the use of such drugs in sub-Saharan Africa if molecular analysis pointed out defectif primary exons of BRCA1 in prostate cancer DNA extracts or absence of BRCA1 protein in cell lysates.

5. Conclusion

Prostate cancer is a men affliction that could be prevented if diagnosed early. In west Africa the diagnosed is often late due to social, familial, and fiancial constraints. Diagnosis based on PSA often gives ambiguous results. Our study has shown for the first time in Benin and Niger that we can use the absence of certain BRCA1 exons as a biomarker of the integrity of this gene for prostate cancer prevention and personalized targeted therapy in Africa. This could help the life of people suffering from prostate cancer and prevent death caused by inappropriate treatments. Indeed, not all patients suffering from prostate cancer have the same BRCA1 exons impacted by mutations or deletions. According to our studies, it would be recommended for each patient to analyze at least the first five exons of the BRCA1 gene in addition to the PSA before medical receiving treatment. Studies have already shown that there are appropriate treatments for BRCA1 mutations. This is because drugs like rucaparib and olaparib are used to treat patients who have BRCA1 mutations or silencing. We have shown in our laboratory that it is possible to detect BRCA1 gene exon deficiencies in the blood. Also, we recommend to clinicians the use of these analyzes henceforth, independently of the PSA before any treatment against prostate cancer in the black Africans.

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SANI BOUKARI Souleimane

Ethique

This study project was evaluated by the LOCAL ETHICS COMMITTEE FOR BIOMEDICAL RESEARCH of the University of Parakou (CLERB-UP). The ethical approval of CLERB-UP was obtained under ref: 0416/CLERB-UP/P/SP/R/SA before the start of blood sampling.

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