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Impact of *BRCA1* and *BRCA2* Gene Mutations in Prostate Cancer in Thies

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Abstract

Prostate cancer (CaP) is a public health problem among men worldwide, particularly those over the age of 50, and its incidence continues to rise. Despite improvements in early detection methods, a large proportion of patients succumb to the disease. Studies have shown that men with *BRCA1/BRCA2* gene mutations in prostate cancer are likely to have more severe disease and a poorer prognosis. A *BRCA2* gene mutation is known to confer the highest risk of prostate cancer (8.6 times in men ≤ 65 years of age) while *BRCA1* presents an increased risk, albeit to a lesser extent (3.5 times); making *BRCA* genes a conceivable genomic biomarker for prostate cancer risk. It is in this context that we will examine the impact of *BRCA1/BRCA2* gene mutations in prostate cancer in Thiès. Our study is conducted between January 2020 and December 2022 with 59 patients diagnosed with a prostate tumor in the urology department of the Thiès regional hospital and the Saint Jean de Dieu hospital in Thiès. The variables studied were age, PSA levels, Gleason score and histological grades. Total DNA from prostate tissue was extracted using the Qiagen protocol (Qiagen Dneasy Tissue Kit) and the three primers for the *BRCA1-185delAG*, *BRCA1-5382insC* and *BRCA2-6174delT* genes were amplified. The results indicate a frequency of 62.71% of patients diagnosed with prostate cancer versus 37.29% with the lesion of benign prostatic hyperplasia. *BRCA1-5382insC* and *BRCA2-6174delT* mutations showed higher frequencies (2-3 fold) in patients with CaP than in those with the BPH lesion, with 62.7% vs. 37.3% and 65.1% vs. 34.9% respectively. Gleason score 8 was more represented with a rate of 44% corresponding to grade IV according to WHO-ISUP 2016. However, individuals carrying mutations (*BRCA1-5382insC; BRCA2-6174DelT*) could be associated with a higher risk of prostate cancer, and are also likely to have a poor survival rate.

Keywords: *Prostate cancer; Mutations; BRCA1, BRCA2*

Introduction

Prostate cancer (CaP) is the second most common cancer diagnosis in men (14.1%) and the fifth leading cause of death (6.8%) worldwide in 2020 [1]. Every year, Africa records around 1.1 million new cases of cancer and up to 700000 deaths from the disease [2]. Many men with prostate cancer are diagnosed by a biopsy and analysis of the prostate, a prostate specific antigen (PSA) test and a digital rectal examination. Risk factors for prostate cancer include family risk, ethnicity, age, obesity and other environmental factors [3]. Demographic expansion and improved life expectancy worldwide are expected to contribute to an increase in the number of cases of CaP [4]. making it a major global health problem. Prostate cancer is a heterogeneous disease, both epidemiologically and genetically. The interaction between genetics, environmental and social influences results in lower estimates of prostate cancer survival rates by race, which explains the differences observed in the epidemiology of prostate cancer in different countries [3]. There is documented evidence of a genetic contribution to prostate cancer. Hereditary prostate cancer and genetic predisposition to prostate cancer have been studied for years. One of the most predisposing genetic risk factors for prostate cancer is family inheritance. Twin studies and epidemiological studies have both demonstrated the role of heredity in CaP [5]. Many researchers have investigated the possible role of genetic variations in androgen biosynthesis and metabolism, as well as the role of androgens [6,7]. Genomics research has identified molecular processes that lead to certain cancerous developments, such as chromosomal rearrangements [3]. Although new treatments have emerged in the last decade, prostate cancer is still a major source of cancer deaths in men [8]. Advanced age is the main risk factor, with more than three-quarters of CaP detections made in men over 65 [9]. Prostate cancer susceptibility genes are genes involved in the androgen pathway and testosterone metabolism. The development of the prostate epithelium and prostate cancer cells depends on the androgen receptor and testosterone signalling pathway [10]. The identification of cancer biomarkers and the targeting of specific genetic mutations can be used for the targeted treatment of prostate cancer. Biomarkers that can be used for targeted therapy include tumour biomarkers, DNA biomarkers and general biomarkers [11]. Family history and genetic predisposition such as *BRCA1/BRCA2* pathogenic variants

have also been identified as important risk factors [12,13]. It is known that a mutation in the *BRCA2* gene confers the highest risk of prostate cancer in men (8.6 times higher in men aged 65 years, while *BRCA1* shows increased risk, although to a lesser extent (3.5 times) [14]. These genes have attracted much attention from researchers, but their role in the clinical assessment and treatment of prostate cancer remains complex. The aim of this study is to examine the impact of *BRCA1/BRCA2* gene mutations in prostate cancer in Thiès.

Materials and Methods

This study covers 59 patients with prostate tumours. These patients were recruited from the urology department of the Thiès regional hospital and the Saint Jean de Dieu hospital in Thiès between January 2021 and December 2022. Inclusion criteria were a suspicious digital rectal examination (DRE) with a PSA level greater than 4 ng/ml, followed by biopsies for histopathological diagnosis. After review in accordance with the rules laid down by Senegal's National Health Research Ethics Committee (SNHREC) and in compliance with the procedures established by Cheikh Anta Diop University in Dakar (UCAD) for all research involving human participants, ethical approval was obtained for this study. The objectives of the study, the protocol, the benefits and the confidentiality criteria were explained to each patient to give them the opportunity to accept or refuse to take part. In the case of acceptance, a duly completed and signed informed consent form was required for admission to the study. For data collection, we collected demographic data (surname, first name, age, ethnicity, reason for consultation), PSA levels and medical history from routine family files.

DNA Extraction and Amplification of the *BRCA1* and *BRCA2* Genes

Total DNA from each sample was extracted using the Qiagen protocol (Qiagen Dneasy Tissue Kit). DNA quality was checked by electrophoretic migration on a 1.5% agarose gel. For a given gene, the conditions for DNA amplification are the same whatever the pathology and for both tumour tissues and controls. PCR amplification conditions included a 1st step of a 12 minute of initial denaturation at a temperature of 95°C, followed by a 2nd step consisting of 35 cycles of 15 seconds of denaturation and hybridization at 94°C and 57°C respectively, primer elongation at 72°C/1 minute, and a 3rd step: final elongation or polymerization at 72°C for 5 min. PCR products were checked by electrophoretic migration on 1.5% agarose gel from 5 µl of amplicons. The size of each amplified gene was estimated using a 500 bp SmartLadder size marker.

The primer sequences and corresponding amplicon sizes are shown in Table 1.

Three founder mutations in the *BRCA1* and *BRCA2* genes were identified for PCR: 185delAG in exon 2 and 5382insC in exon 20 of the *BRCA1* gene, and 6174delT in exon 11 of the *BRCA2* gene [15-17]. Germline mutations in the *BRCA1* and *BRCA2* genes have been reported in several studies of different ethnic populations [16,18,19]. For each mutation, three primers (one common, one specific for the mutant and one specific for the wild-type allele) were used. The competing mutant and wild-type primers were designed to differ in size by 20 bp, allowing easy detection of the PCR products by routine electrophoresis. Both the mutant (long) and wild-type (short) primers contain a mismatched base sequence near the 3' end. The long (mutant) primer also incorporates two additional mismatched bases at two contiguous positions corresponding to the 5' end of the short (wild-type) primer. During the final cycles of the PCR reaction, heteroduplexes can be formed from the short and long products, but the contiguous mutagenic sequences in the long product prevent the short product from being filled in using the long strand as a template. If a mutation is present in one of the alleles, two bands will be present. PCR conditions were optimised for each primer pair and applied uniformly to all samples. Amplifications were performed in a reaction volume of 25 µl. The composition of the reaction mixture is given in Table 2.

Results and Discussion

Results

For 59 patients recruited, 37 (62.71%) were diagnosed with prostate cancer (CaP) and 22 (37.29%) with benign prostatic hyperplasia (BPH). With regard to the *BRCA1* (185delAG and 5382insC) and *BRCA2-6174delT* mutations, the frequency of *BRCA1-185delAG* mutations in patients with CaP was 40% compared with 60% in those with a BPH lesion, indicating that this mutation shows no significant difference in men with CaP and probably does not contribute to the incidence of this cancer. However, the other two *BRCA1-5382insC* and *BRCA2-*

Table 1: Primers used.

Primers	Primers sequences	Amplicon size
	BRCA1-del185AG	
Foward	5′ggttggcagcaatatgtgaa 3′	
Reverse wild	5′gctgacttaccagatgggactctc 3′	335pb
Reverse mutant	5′cccaaattaatacactcttgtcgtgacttaccagatgggacagta 3 ′	354pb
	BRCA1-5382insC	
Foward wild	5′aaagcgagcaagagaatcgca 3′	271pb
Foward mutant	5′aatcgaagaaaccaccaaagtccttagcgagcaagagaatcacc3′	295pb
Reverse	5′gacgggaatccaaattacacag 3′	
	BRCA2-6174delT	
Foward wild	5′gtgggatttttagcacagctagt 3′	151pb
Foward mutant	5′cagtctcatctgcaaatacttcagggatttttagcacagcatgg 3′	171pb
Reverse	5′agctggtctgaatgttcgttact 3′	

Table 2: Composition of the PCR reaction medium for each gene.

Volume to be sampled for a PCR with a reaction volume of 25 µl.			
Reagents	Gènes amplifiés		
	BRCA1-185delAG	***BRCA1-5382insC***	***BRCA2-6174delT***
Water	8,75 µl	8,75 µl	8,25 µl
Master mix	12,5 µl	12,5 µl	12,5 µl
Fw	0,25 µl	0,25 µl	0,25 µl
Fm	0,25 µl	0,25 µl	0,25 µl
R	0,25 µl	0,25 µl	0,25 µl
Mgcl2	1 µl	1 µl	1,5 µl

Table 3: Association between Gleason scores and *BRCA1 /BRCA2* mutations.

Gleason score/ BRCA mutations	*BRCA1-185delAG*	*BRCA1-5382insC*	*BRCA2-6174delT*
	N individuals	N individuals	N individuals
Gleason score 6	0	5	4
Gleason score 7	4	12	9
Gleason score 8	6	13	11
Gleason score 9	0	2	2

6174delT mutations showed higher frequencies (2 to 3 times) in patients with CaP than in those with the BPH lesion, with respectively 62.7% versus 37.3% and 65.1% versus 34.9%. For individuals with adenocarcinoma of the prostate, most cases had a Gleason score greater than or equal to 7 (87%); with 13% of individuals having a Gleason score equal to 6. Gleason scores for prostate tumours were classified into subgroups <7 and ≥7. This threshold was chosen based on clinical experience and previous literature suggesting that the clinical outcome for prostate cancer of Gleason score 7 is more similar to that of Gleason score 8 to 10 than for Gleason score <7 disease2 [20]. Table 3 shows the association between Gleason scores and *BRCA1/BRCA2* mutations. Individuals with cape with *BRCA1/2* germline mutations were more frequently associated with Gleason score ≥ 8, at stage T3/T4. *BRCA1-5382insC* and *BRCA2-6174delT* mutation carriers conferred a 2 to 3-fold increased risk of high-grade prostate cancer. Although the *BRCA1-185delAG* mutation has not been associated with prostate cancer, it may be associated with high Gleason score tumours. These results must be carefully taken into account in genetic counselling.

Discussion

When analysing the genetics of CaP, it is essential to distinguish between localised, high-risk and metastatic disease. Firstly, due to the widespread adoption of PSA, the majority of new CaP diagnoses are low-grade localised disease with an excellent prognosis. These diagnoses are clinically distinct from the comparatively fewer diagnoses of advanced metastatic CaP [21] which are known to have the potential for a poor outcome. Several studies have shown that the genomic/genetic landscape of metastatic castration-resistant CaP (mCRPC) is different from that of localised [22,23]. It is difficult to obtain meaningful clinical predictions by examining CaP as a whole, given the great clinicopathological heterogeneity of the disease. This can be illustrated by germline mutations in *BRCA2* which have been underestimated as a driver of hereditary prostate cancers. Genomic profiling of CaP was initially extrapolated from material acquired during unselected prostatectomies and genetic abnormalities were therefore considered rare [24]. As a result, verification bias prevented reporting the true prevalence of pathogenic genetic mutations in advanced metastatic cape. This work was designed to assess the impact of *BRCA 1* and *BRCA 2* mutations in prostate cancer in the Thiès region with the association of the three founder mutations *BRCA1-185delAG* and *BRCA1-5382insC* and *BRCA2-6174delT*. This study revealed that the highest frequency of *BRCA1* mutations in CaP patients was *BRCA1-5382insC* (62%) followed by BRCA1 185-delAG (40%). The frequency of *BRCA1* mutations in patients with a BPH lesion was 60% for *BRCA1-185delAG* and 38% for *BRCA1-5382insC.* In addition, the global *BRCA2-6174delT* mutation was identified in 65.1% of patients with cape versus 34.9% of those with a BPH lesion. These results suggest that the *BRCA2-6174delT* and *BRCA1-5382insC* mutations are likely to contribute to the incidence of prostate cancer in the Thiès region, which is not the case for the *BRCA185-delAG* mutation, which shows no significant difference in patients with CaP. Our results are comparable to those of Gallagher et al. in 2010 [24] and Agalliu et al. in 2009 [25] where they found mutation frequencies for the *BRCA1-5382insC* and *BRCA2-6174delT* genes to be largely predominant in individuals with CaP. Studies of breast cancer by Abou El Naga et al. reported contradictory results, with the two mutations (*BRCA1-5382insC and BRCA2-6174delT)* showing higher frequencies in healthy controls than in breast cancer patients [26]. In addition, we found that the risk of prostate cancer associated with carrying these mutations was higher in men diagnosed at an older age (65 or over) and in particular in those with the *BRCA2-6174delT* and *BRCA1-5382insC* mutations.

A number of previous studies have examined the associations between these *BRCA1/BRCA2* mutations and prostate cancer [17,28-30]. Struewing et al. [27] estimated a lifetime risk of CaP of 16% for *BRCA1/BRCA2* mutation carriers and 3.8% for non-carriers. Our results reported that *BRCA2-6174delT* and *BRCA1-5382insC* mutation carriers had two to three times the risk of prostate cancer, and as indicated here, the *BRCA1-185delAG* mutation was not associated with prostate cancer. Our results contradict those of Giusti et al. [30] who found the *BRCA1-5382insC* mutation not to be associated with prostate cancer. The absence of a detectable effect for the *BRCA1-185delAG* mutation could be linked to its low prevalence in the population, or to the effects of allelic heterogeneity. In support of a role for prostate cancer-associated *BRCA2* mutations, studies of breast and/or ovarian cancer families harbouring disease-associated *BRCA2* mutations have reported that male family members carrying such mutations have an increased risk of prostate cancer [31-33]. A Finnish study [34] of breast and/or ovarian cancer families also reported a 5-fold increase in the risk of prostate cancer in men carrying *BRCA2* protein-truncating mutations. First-degree male relatives of breast cancer patients with protein-truncating *BRCA2* mutations had a 4.8% risk of prostate cancer [35]. In 2012, studies by Castro et al. [36] reported that *BRCA2* mutation status was found to be an independent predictor of median cause-specific survival. Interestingly, the non-carrier group also had a poorer outcome than other sporadic CaP series, suggesting that a family history of breast cancer could somehow affect the prognosis of prostate cancer patients.

In the present study, a major proportion of mutation carriers had a Gleason score ≥ 7 (87%); our results are similar to those of Gallagher et al. in 2010 [24] where 85% of mutation carriers had Gleason disease ≥7. Our results were striking, with 22 of 26 (84.6%) *BRCA2-6174delT* mutation carriers and 27 of 32 *BRCA1-5382insC* mutation carriers (84.3%) showing Gleason disease ≥7, representing a group with an aggressive phenotype and confirming this association reported by Agalliu et al. [25]. However, individuals carrying these two mutations may be associated with a higher risk of prostate cancer and are also likely to have poor survival as reported by Edwards et al. in 2010 [37]. This is also reflected in the study by Kote-Jarai et al. where the proportion of high grade CaP (Gleason score ≥ 8) was 63% significantly elevated [14]. The study by Gallagher et al. reported that *BRCA2* mutation carriers

had an increased risk of CAP and a higher histological grade and that *BRCA1* or *BRCA2* mutations were associated with a more aggressive clinical course [24] results confirmed by studies by Castro et al. in 2013 in a large retrospective cohort [38].

Conclusion

Prostate cancer is the second most common cancer in men worldwide and is a complex heterogeneous disease with high heritability. Our results showed that *BRCA2-6174delT* and *BRCA1-5382insC* mutations are strongly associated with a very aggressive form of prostate cancer. Molecular characterisation of CaP patients should be systematically integrated into healthcare structures in order to select patients who are more likely to respond to targeted agents. In addition, in the event of a family history of hereditary breast cancer (± hereditary ovarian cancer), it is recommended that the patient be referred to an oncogenetic consultation to look for a mutation in the *BRCA1* and *BRCA2* genes. In the case of aggressive prostate cancer (high Gleason score or locally advanced or metastatic stage) in a patient under the age of 50, it is recommended that the patient be referred to an oncogenetic consultation to look for a mutation in the *BRCA2* and *HOXB13* genes (level of evidence 2a) [39]. Further clinical trials would be needed to assess the impact of genomic nuances in reducing the morbidity and mortality prevalent with prostate cancer.

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Conflict of Interest

The authors have declared no conflicts of interest.

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