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Research Article

Genetic Variability and Differentiation of the BRCA1 and BRCA2 Genes in Female Breast Cancer in Senegal

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Abstract

Breast cancer constitutes a major public health problem. In Senegal, this pathology ranks second in terms of incidence and third in terms of mortality among cancers. BRCA1 and BRCA2 are two susceptibility genes for breast and/or ovarian cancer, implicated in hereditary breast cancer cases. These genes have been the subject of extensive research in the context of germline mutations; however, data on their role in sporadic breast cancer, particularly in sub-Saharan African populations such as Senegal, remain scarce or unavailable. To address this gap, the present study analyzed 51 surgical specimens of healthy and cancerous breast tissue to characterize the genotypic profile of BRCA mutations in Senegalese women. Three loci corresponding to founder mutations described in the Ashkenazi Jewish population BRCA1-185delAG, BRCA1-5382insC, and BRCA2-6174delT were targeted. The objectives were to determine the genotypic profile of each population at each locus and assess potential differences, to test genetic equilibrium, and to evaluate genetic differentiation between BRCA1- and BRCA2-associated breast cancer. Comparison of wild-type and mutant allele profiles between the two tissue types revealed no significant difference. Analysis of genetic diversity between healthy and cancerous tissues showed a heterozygote excess at both BRCA1 loci and a heterozygote deficit at the BRCA2 locus. Low genetic differentiation was observed between control and tumor tissues, attributable to the BRCA1-185delAG mutation, with an Fst value of 0.0072. These findings suggest that the BRCA1-185delAG mutation, despite its low penetrance, may be implicated in breast cancer among Senegalese women.

Keywords

Breast Cancer, BRCA1, BRCA2, Genetic Diversity, Founder Mutation, Senegal

1. Introduction

Breast cancer represents a major public health problem [1]. In Senegal, a sub-Saharan African country, breast cancer ranks second after cervical cancer in terms of incidence, and third in terms of mortality after liver and cervical cancer. Moreover, 16% of new cases were diagnosed in the same year, among which 12% resulted in death [2]. However, the etiology of breast cancer remains poorly understood. It results from an association between exogenous risk factors (environmental pollution) and endogenous factors such as genetic predisposition. In particular, genetic variations in the DNA sequence, such as mutations affecting oncogenes, tumor suppressor genes, and genes involved in DNA repair, can lead to alterations in normal cells, which may subsequently progress to cancerous cells [3]. Nevertheless, two genes conferring high susceptibility to breast cancer, BRCA1 and BRCA2, have been the subject of numerous inves-

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tigations [4-6]. These are tumor suppressor genes, first identified in the early 1990s as breast cancer susceptibility genes [7, 8]. They are located on the long arm of chromosome 17 (17q21, BRCA1) and chromosome 13 (13q12-13, BRCA2) [9]. Any alteration in the nucleotide sequence that is not corrected, or incorrectly repaired, would result in loss of heterozygosity, there by increasing the risk of malignant transformation into cancer [10-12]. Three founder mutations — 185delAG in exon 2 and 5382insC in exon 20 of the BRCA1 gene, and 6174delT in exon 11 of the BRCA2 gene — have been identified in breast tumors [13]. These mutations show a high prevalence among Ashkenazi Jewish women [14]. Indeed, approximately 2% of the Ashkenazi Jewish population carry one of these three mutations — BRCA1 (185delAG, 5382insC) or BRCA2 (6174delT) [15]. Furthermore, approximately 10% of breast cancers and more than 30% of ovarian cancers among Ashkenazi Jewish women are attributable to a genetic predisposition linked to germline mutations in the BRCA1 and BRCA2 genes [15]. More broadly, hereditary mutations in a single allele of the BRCA genes can confer a familial risk of breast cancer in women, with probabilities ranging from 50% to 55% [16]. The BRCA1-185delAG mutation is one of the most common mutations, located in exon 2 [17]. It occurs specifically at codon 23, causing a frameshift that leads to a premature stop codon at codon 39, resulting in truncation at the beginning of the RING zinc-binding domain. Mutations within the RING domain have been reported to predispose to BRCA1-associated cancer [18]. The BRCA1-5382insC mutation is a cytosine insertion at position 5382 of the gene, within exon 20. This mutation causes a frameshift and premature termination of amino acid chain elongation in the protein, rendering the protein non-functional [19]. Three domains of the BRCA1 protein are frequently mutated in cancer patients: the N-terminal RING region, encoded by exons 2 to 7, where the 185delAG mutation is located; the region spanning exons 11 to 13; and the C-terminal BRCT region, spanning exons 16 to 24, where the 5382insC mutation is located [20]. The 6174delT mutation constitutes a single base-pair deletion of thymine at codon 1982 in exon 11 of the BRCA2 gene. It creates a termination codon at position 2003. Mutations at this exon increase the risk of ovarian cancer [21]. Given the high susceptibility conferred by BRCA genes in breast cancer and their essential function in repairing double-strand DNA breaks within the cell, the present study aims to investigate the genetic variability of the BRCA1-5382insC, BRCA1-185delAG, and BRCA2-6174delT loci in sporadic breast cancer cases in Senegal.

2. Methodology

2.1. Ethical Considerations

This study was approved by the Research Ethics Committee (REC) of Cheikh Anta Diop University (protocol reference 0272/2018/CER/UCAD).

2.2. Study Population

The study population consisted of women of all ages managed at Aristide Le Dantect Hospital. Patients with histologically confirmed breast carcinoma were included, whereas those with a history of cancer other than breast cancer within the preceding five years were excluded. Control individuals with no cancerous or chronic pathology and normal blood test results were included in the study.

2.3. Sampling

A total of 51 individuals, including 25 controls and 26 cases managed at Aristide Le Dantec Hospital, were enrolled in this study. For each patient, a tissue sample was collected from the tumor site, whereas a blood sample was collected for the control group. Following collection, samples were preserved in 96% ethanol and transported to the UCAD Genomics Laboratory for genetic analysis.

2.4. Genomic DNA Extraction and Allele-Specific PCR for BRCA1 and BRCA2 Mutations

DNA extraction from blood (controls) and tissue (cancer cases) was performed using the Zymo Research kit for blood samples and the Qiagen DNeasy Tissue kit for cancerous tissue samples, according to the manufacturer's protocol. Amplification of the BRCA1-5382insC, BRCA1-185delAG, and BRCA2-6174delT loci was carried out in a total reaction volume of 25 µL using the OneTaq Quick-Load 2X Master Mix kit. To detect the presence or absence of the 5382insC, 185delAG, and 6174delT mutations and to distinguish between wild-type and mutant genomic profiles, three primers were used for each gene in this study (two sense primers, one wild-type and one mutant, together with one antisense primer for 5382insC and 6174delT; and two antisense primers together with one wild-type sense primer for 185delAG). The reaction mixture consisted of 8.75 µL of water, 12.5 µL of master mix, 0.25 µL of each primer, and 1.5 µL of $MgCl_2$. The nucleotide sequences of the primers are presented in Table 1. PCR was performed using an Eppendorf thermocycler under the following amplification conditions: an initial denaturation at 95 ℃ for 12 min to separate the two DNA strands across the entire genome, followed by denaturation at 94 ℃ for 15 seconds targeting the region of interest, annealing at 57 ℃ for 15 seconds, and extension at 72 ℃ for 30 seconds. The denaturation-to-extension steps were repeated for 35 cycles. PCR was completed with a final extension at 72 ℃ for 5 min.

Table 1. Nucleotide sequences of the primers and amplicon sizes of the BRCA loci obtained after PCR (Abou-El-Naga et al., 2018).

Locus	Primers Amplicon size	
BRCA1-185delAG	F: 5'-GGTTGGCAGCAATATGTGAA-3'	335
	Rw: 5'-GCTGACTTACCAGATGG GACTCTC-3'	
	F: 5'-GGTTGGCAGCAATATGTGAA-3'	354
	Rm: 5'CCCAAATTAATACACTCTTGTCGTGACTTACCAGATGGG ACAGTA-3'	
BRCA1-5382insC	Fw: 5'-AAAGCGAGCAAGAGAATCGCA-3'	271
	R: 5'- GACGGGAATCCAAATTAC ACAG-3'	
	Fm: 5'AATCGAAGAAACCACCAAAGTCCTTAGCGAGCAAGAGAATCACC-3'	295
	R: 5'- GACGGGAATCCAAATTAC ACAG-3'	
BRCA2-6174delT	Fw: 5'-GTGGGATTTTTAGCACGCTAGT-3'	151
	R: 5'-AGCTGGTCTGAATGTTCGT TACT-3'	
	Fm: 5'-CAGTCTCATCTGCAAATACTTCAG GGATTTTTAGCACAGCATGG-3'	171
	R: 5'-AGCTGGTCTGAATGTTCGT TACT-3'	

After PCR, 10 µL of the PCR product from each sample was subjected to electrophoresis on a 3% agarose gel (3 g of agarose in 100 mL of TAE buffer), to which 15 µL of Safe-View (a DNA-staining agent) was added, for 35 min for BRCA2-6174delT, 45 min for BRCA1-5382insC, and 50 min for BRCA1-185delAG, under a voltage of 100 V, in order to achieve clear separation of the wild-type and mutant bands. A 100-base-pair molecular weight marker was loaded onto the agarose gel to assess amplicon size. For each mutation, the profile was determined after gel electrophoresis by comparison with the molecular weight marker (a single band indicating a homozygous wild-type or mutant profile, and two bands indicating a heterozygous profile).

2.5. Genetic Analyses

2.5.1. Genetic Diversity

Genetic analyses were performed to characterize the distribution of BRCA1 and BRCA2 variants among breast cancer patients and healthy controls. Three recurrent pathogenic variants were investigated: BRCA1 c.68_69delAG (185delAG), BRCA1 c.5266dupC (5382insC), and BRCA2 c.5946delT (6174delT). Each locus was analyzed independently.

Allele frequencies and genotype frequencies were calculated for each variant in cases and controls using GENEPOP version 4.8.3 [22]. Differences in allele and genotype distributions between groups were assessed using Fisher's exact test, which is appropriate for sparse contingency tables and low-frequency variants. Statistical significance was set at $P < 0.05$.

To describe within-group genetic diversity, the following parameters were estimated using GENETIX version 4.05.2 [23]: observed heterozygosity (Ho), expected heterozygosity (He), unbiased expected heterozygosity (He), and Wright's fixation index (FIS). Because the investigated loci correspond to biallelic pathogenic variants, allelic richness was reported for descriptive purposes only.

2.5.2. Hardy–Weinberg Equilibrium and Linkage Disequilibrium

Departure from Hardy–Weinberg equilibrium (HWE) was assessed for each locus using the exact test implemented in GENEPOP version 4.8.3. Owing to the potential influence of disease status on genotype frequencies, HWE was primarily evaluated in the control population. A probability value of $p \geq 0.05$ indicated conformity with Hardy–Weinberg expectations, whereas $p < 0.05$ indicated significant deviation.

Pairwise linkage disequilibrium (LD) between loci was also tested using exact tests implemented in GENEPOP. Statistical significance was defined as $P < 0.05$.

2.5.3. Genetic Differentiation

Genetic differentiation between breast cancer patients and healthy controls was investigated using Wright's fixation indices (FIS, FIT, and FST) estimated with GENETIX version 4.05.2 [23]. Nei's genetic distance [24] was also calculated to provide an exploratory assessment of genetic differentiation between the two groups.

The statistical significance of fixation indices was evaluated using 95% confidence intervals generated by the software. Given the limited sample size and the low frequency of the investigated pathogenic variants, these differentiation analyses should be considered exploratory and interpreted with caution.

3. Results

3.1. Genotypic Analysis of the BRCA1-5382insC, BRCA1-185delAG, and BRCA2-6174delT Mutations

Following agarose gel visualization, 44 out of the 51 individuals exhibited at least one genotypic profile corresponding to the three loci studied, including 21 out of 25 controls (i.e., 84%) and 23 out of 26 cancer patients (i.e., 88.46%). For the remaining individuals, no profile was observed for one of the three loci. These results are presented in Figure 1 below.

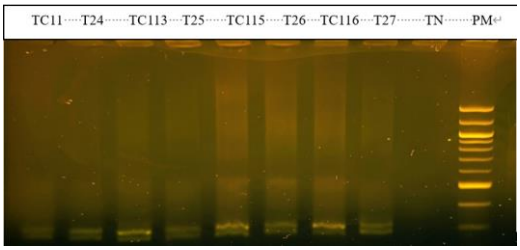

Figure 1. *Migration profiles after 45 minutes on a 3% agarose gel of BRCA1 (5382insC) amplicons from DNA extracts of breast cancer tissue and control samples.*

Different alleles were obtained for each locus. For each locus, one wild-type allele and one mutant allele were identified. The wild-type and mutant alleles for each locus are presented in Table 2.

Table 2. *Different alleles obtained per locus.*

Locus	BRCA1-185delAG	BRCA1-5382insC	BRCA2-6174delT
Wild-type allele	335	271	151
Mutant allele	354	295	171

3.2. Genetic Analyses

3.2.1. Genetic Diversity

(i). Estimation of Allelic Frequencies per Locus and per Population

For the BRCA1-185delAG and BRCA2-6174delT loci, corresponding to the 354 bp and 171 bp mutant alleles, cancerous tissues exhibited higher frequencies than control tissues. However, for the BRCA1-5382insC locus, in the 295 bp mutant allele, controls showed a higher frequency compared with cancerous tissues. For the 335 bp and 151 bp wild-type alleles of the BRCA1-185delAG and BRCA2-6174delT loci, controls exhibited higher frequencies compared with cancerous tissues. In contrast, for the 271 bp wild-type allele of the BRCA1-5382insC locus, cancerous tissues showed a higher frequency compared with control tissues. Nevertheless, a non-significant Fisher's exact test p-value of 1, greater than 0.05, was obtained, indicating no significant difference in allelic frequencies per locus and per population.

Table 3. *Allelic frequency per locus and per population.*

Populations	Counts	Loci					
		BRCA1-185del AG		BRCA1-5382insC		BRCA2-6174 delT	
		335	354	271	295	151	171
TC	23	0,556	0,444	0,523	0,477	0,147	0,853
T	21	0,571	0,429	0,5	0,5	0,308	0,692
P-value de Fisher		1	1	1	1	1	1

Note: TC: cancerous tissue, T: healthy tissue.

According to the dbSNP database, allelic frequencies are reported only for the BRCA2-6174delT mutation. For this mutation, nearly all individuals in Europe are wild-type, at a frequency of approximately 0.99937, while the mutant type is rare, at approximately 0.00063, on this same continent. In Asia, all individuals are wild-type. In Africa, and more specifically in Senegal, the mutant type is more frequently reported, at approximately 0.853. However, the distribution of allelic frequencies between countries, for both the mutant and wild-type alleles, yielded a non-significant p-value of approximately 1. There is therefore no significant difference in the distribution of wild-type alleles, nor of mutant alleles, between countries. These results are presented in Table 4.

Table 4. Aggregated ALFA allele frequency for the BRCA2-6174delT locus.

Populations	Locus BRCA2-6174 delT		p-value
	T	delT	
Europe	0,99937	0,00063	
Asie	1,000	0,000	1
Sénégal	0,147	0,853	

(ii). Estimation of Genotypic Frequencies

The distribution of genotypic frequencies by population and by locus reveals a higher frequency of heterozygous genotypes at both BRCA1 loci (BRCA1-185delAG and BRCA1-5382insC) in both the cancerous tissue and control populations. However, for the BRCA2-6174delT locus, a higher genotypic frequency of the homozygous mutant profile was found in both tissue types. Comparison of the significance of genotypic frequencies between cancerous and control tissues using Fisher's exact test yielded a non-significant p-value of 1, greater than 0.05, thereby indicating equality in the distribution of genotypic frequencies between the two populations. These results are presented in Table 5 for the genotypes identified, and in Table 6 for the genotypic frequencies.

Table 5. Presentation of the genotypes identified in the study.

Genotype Locus	Homozygous wild-type	Heterozygous	Homozygous mutant
BRCA1- 185delAG	335-335	354-335	354-354
BRCA1- 5382 ins C	271-271	295-271	295-295
BRCA2-6174 delT	151-151	171-151	171-171

Table 6. Genotypic frequencies per locus and per population.

Pop	Count	Loci BRCA1-185 del AG			BRCA1-5382insC			BRCA2-6174delT		
		335-335	354-335	354-354	271-271	295-271	295-295	151-151	171-151	171-171
TC	23	2	6	0	3	17	2	1	3	13
T	21	5	6	3	3	14	13	4	0	9
p-value F		1		1		1	1	1	1	1

(iii). Estimation of Heterozygosity Rates in Each Population

Both BRCA1 loci exhibited observed heterozygosity (Ho) rates higher than the unbiased expected heterozygosity (Hnb) and expected heterozygosity (He) rates, in both cancerous tissues (TC) and control tissues (T). In contrast, for the BRCA2-6174delT locus, Ho rates were lower than Hnb and He rates in both TC and T. Notably, controls showed a Ho equal to 0.

These results are presented in Table 7.

Table 7. *Mean number of alleles per locus and heterozygosity in each population.*

Loci	N_A	H_O		H_{nb}		H_e	
		TC (23)	T (21)	TC (23)	T (21)	TC (23)	T (21)
BRCA1-185delAG	2	0,8889	0,6429	0,5079	0,4524	0,4938	0,4362
BRCA1-5382insC	2	0,7727	0,7000	0,5106	0,5128	0,4990	0,5000
BRCA2-6174delT	2	0,1765	0,0000	0,2585	0,4431	0,2509	0,4260

N: total number of individuals studied; NA: number of alleles; Ho: observed heterozygosity; Hnb: unbiased heterozygosity; He: expected heterozygosity.

(iv). Hardy–Weinberg Equilibrium and Linkage Disequilibrium

1) Hardy–Weinberg Equilibrium

Our results show that for the BRCA1 loci (BRCA1-185delAG, BRCA1-5382insC), cancerous tissues exhibited statistically significant p-values, indicating a departure from Hardy-Weinberg equilibrium. In contrast, controls followed Hardy-Weinberg equilibrium for both loci, with non-significant p-values. Furthermore, cancerous tissues followed Hardy-Weinberg equilibrium for the BRCA2-6174delT locus, with a non-significant p-value, whereas controls did not follow this equilibrium for the same locus, showing a significant p-value. These results are presented in Table 8.

Table 8. *Hardy-Weinberg equilibrium test per locus for each population.*

Population P-value	TC	T
BRCA1-185delAG	0,0023*	0,6209
BRCA1-5382insC	0,0291*	0,1760
BRCA2-6174delT	0,2884	0,0005*

Note: TC: cancerous tissue; T: controls. *= p-value < 0.05.

The global Hardy-Weinberg test under the heterozygote excess hypothesis yielded, for the cancerous tissue population, a significant p-value below 0.05, indicating that this population is not in Hardy-Weinberg equilibrium (HWE), whereas the control population showed a non-significant p-value, indicating that this population is in Hardy-Weinberg equilibrium. These results are presented in Table 9.

Table 9. *Global Hardy-Weinberg test per population.*

Populations	TC	T
P-value H	0,0006	0,8946

The global test for the BRCA1 loci yielded significant p-values across the entire population set, whereas the BRCA2-6174delT locus showed a non-significant p-value. These results indicate that the BRCA1 loci are not in Hardy-Weinberg equilibrium across the overall population, whereas the

BRCA2 locus is in equilibrium across the overall population. These results are presented in Table 10.

Table 10. Global Hardy-Weinberg test per locus.

Locus	BRCA1-185delAG	BRCA1-5382insC	BRCA2-6174delT
P-value H	0,0406	0,0023	0,9996

2) Linkage Disequilibrium

The linkage disequilibrium test yielded non-significant p-values in cancerous tissues, indicating an absence of linkage between loci in this population. In contrast, a significant p-value (p-value = 0.039472) was found in the control population between the two BRCA1 loci (BRCA1-5382insC, BRCA1-185delAG), indicating linkage between them.

Table 11. Linkage Disequilibrium Between Loci.

Populations	Locus 1	locus 2	P-value
TC	BRCA1-185delAG	BRCA1-5382insC	1
TC	BRCA1-185delAG	BRCA2-6174delT	1
TC	BRCA1-5382insC	BRCA2-6174delT	0,373268
T	BRCA1-185delAG	BRCA1-5382insC	0,039472*
T	BRCA1-185delAG	BRCA2-6174delT	0,773246
T	BRCA1-5382insC	BRCA2-6174delT	0,726698

Note: TC: cancerous tissue, T: control; red color: significant p-value.

(v). Genetic Differentiation

Nei's genetic distance between controls and cancerous tissues yielded negative values for the BRCA1-185delAG and BRCA1-5382insC loci, indicating that the populations are very closely related at these loci. This is confirmed by the overall distance between populations, which was null. For BRCA2-6174delT, a positive distance was found, indicating that the populations are not closely related at this locus. The TC (cancerous tissue) population differs from the T (control) population. These results are presented in Table 12.

Table 12. Nei's (1978) genetic distance between tissues and controls.

Locus Distance	BRCA1-185delAG	BRCA1-5382insC	BRCA2-6174delT	Total
TC-T	-0,001	-0,024	0,011	0,000
T-T	0	0	0	0
TC-TC	0	0	0	0

The Fis (inbreeding coefficient) yielded significant values ($p < 0.05$) in the diseased populations (TC) for the BRCA1 loci (0.0023 for BRCA1-185delAG, 0.0291 for BRCA1-5382insC), and in the healthy (non-cancerous, T) populations for the BRCA2-6174delT locus, at approximately 0.0005. Furthermore, the significant Fis values obtained in cancerous tissues at the BRCA1 loci were negative (-0.7895 for 185delAG, -0.5322 for 5382insC), indicating heterozygote

excess, whereas the significant Fis value obtained in the control population at the BRCA2 locus was 1, indicating that all individuals in this population were homozygous at this locus. In summary, at the BRCA1 loci, the cancerous tissue po pulation exhibited a low degree of inbreeding, whereas the control population was 100% inbred at the BRCA2 locus.

Table 13. Estimation of Fis parameters per locus for each population.

Locus	BRCA1-185delAG		BRCA1-5382insC		BRCA2-6174delT	
Populations	TC	T	TC	T	TC	T
Fis Value	-0,7895	0,1613	-0,5322	-0,3782	0,3239	1,0000
Fis p-value	0,0023*	0,6209	0,0291*	0,1760	0,2884	0,0005*

Estimation of Fis values after allele permutation within each population showed, for the BRCA1 loci, negative actual Fis values in controls (-0.444 for 185delAG, -0.378 for 5382insC) and in cancerous tissues (-0.789 for 185delAG, -0.532 for 5382insC), indicating heterozygote excess in both populations at these BRCA1 loci. The distribution of Fis values expected under Hardy-Weinberg equilibrium for these BRCA1 loci in both the TC and T populations confirmed this result, with a higher proportion of values exceeding the actual value (100% and 83.7%) for the BRCA1-185delAG locus, and (98.000% and 89.800%) for the BRCA1-5382insC locus. For the BRCA2-6174delT locus, the positive actual Fis value obtained in cancerous tissues (0.323) indicated a heterozygote deficit. Meanwhile, a Fis value of 1 found in controls revealed a population that was fully homozygous at this locus. The distribution of Fis values confirmed this result, with 71.4% and 100% of values lower than the actual value in cancerous tissues and controls, respectively. In summary, for the BRCA1 loci, a homozygote deficit was observed, indicating a low degree of inbreeding within both populations at these loci, whereas the BRCA2 locus showed a homozygote excess, indicating a higher degree of inbreeding within both populations at this locus. These results are presented in Table 14.

Table 14. Estimation of Fis values after allele permutation within each population, and F-statistics across the overall set of populations and loci. Number of permutations: 1,000.

Population Locus	TC				T			
	Réel	%val>	%val<	%val=	Réel	%val>	%val<	%val=
BRCA1-185delAG	-0,789	100,000	0,000	0,000	-0,444	83,700	0,000	16,3000
BRCA1-5382insC	-0,532	98,000	0,000	2,000	-0,378	89,800	1,100	9,1000
BRCA2-6174delT	0,323	1,5000	71,400	27,100	1,000	0,000	100,000	0,000
Total	-0,456	100,000	0,000	0,000	0,050	34,600	65,400	0,000

%val>: percentage of values higher than the actual value; %val<: percentage of values lower than the actual value; %val=: percentage of values equal to the actual value.

The F-statistics across the overall population and the three loci yielded a negative Fis and a negative Fit, attesting to a heterozygote excess both among individuals within populations and among individuals in the total population. This reflects a low rate of homozygosity between the two populations. However, the Fst value of 0.00712 indicates very low genetic differentiation between the two populations.

Table 15. F-statistics in the total population after 1,000 permutations.

F statistique	FIS	FST	FIT
Values (1000 permutations)	-0,22091	0,00712	-0,21222

Estimation of Weir and Cockerham's F-parameters using the jackknife method yielded positive Fis and Fit values of 0.01692 and 0.01653, respectively, when excluding the BRCA1-185delAG locus. This indicates a high rate of homozygosity among individuals within populations and among individuals in the total population when this locus is excluded. However, Fis and Fit were negative when the BRCA1-5382insC and BRCA2-6174delT loci were omitted. Furthermore, an Fst of -0.00040 was found when excluding the BRCA1-185delAG locus. This value was lower than that obtained after excluding the BRCA1-5382insC and BRCA2-6174delT loci (0.01857 and 0.00390, respectively). Consequently, the BRCA1-185delAG locus appears to be responsible for the low genetic differentiation observed between cancerous and control tissues. These results are presented in Table 16.

Table 16. Estimation of Weir and Cockerham's F-parameters using the jackknife method per locus in the two populations.

F statistique Locus	FIS	FIT	FST
Sans BRCA1-185 delAG	0,01692	0,01653	-0,00040
Sans BRCA1-5382insC	-0,07421	-0,05426	0,01857
Sans BRCA2-6174 delT	-0,55066	-0,54462	0,00390

Estimation of Fis values according to Weir and Cockerham yielded negative values after omitting loci in the cancerous tissue population, thereby indicating heterozygote excess in this population. However, this excess decreased further when the BRCA1-185delAG locus was removed, yielding a Fis value of -0.24020. In the control population, by contrast, heterozygote excess was observed when the BRCA2 locus was removed, represented by a Fis value of -0.40916. Heterozygosity is therefore maintained in the cancerous tissue population by the BRCA1-185delAG locus, whereas it is maintained in the control population by the BRCA2-6174delT locus. These results are presented in Table 17.

Table 17. Estimation of Fis values according to Weir and Cockerham using the jackknife method per population.

Population Locus	TC	T
Sans BRCA1-185delAG	-0,24020	0,27793
Sans BRCA1-5382insC	-0,40593	0,29091
Sans BRCA2-6174delT	-0,65986	-0,40916

Estimation of F-statistics between populations by allele yielded negative Fis and Fit values for both alleles of BRCA1-185delAG (-0.64881 and -0.61523). These values were higher than the Fis and Fit values for the other BRCA1 allele of 5382insC (-0.45875 and -0.47631) and for the BRCA2 allele, which were positive (0.71143 and 0.71608). Thus, the BRCA1-185delAG locus exhibited the highest heterozygosity across populations. Similarly, an Fst of 0.02037 found for both alleles of the BRCA1-185delAG locus indicated low genetic differentiation. This value was higher than that of the BRCA1-5382insC locus alleles, which recorded an Fst of -0.01204, and of the BRCA2 locus, which recorded an Fst of 0.01611.

These results indicate that the low genetic differentiation between the two populations originates from the BRCA1-185delAG locus. Furthermore, the Fis, Fst, and Fit values between populations were equal for each allele within each locus, indicating that each allele within each locus contributed equally to genetic diversity. Indeed, for the BRCA1-185delAG locus, which is the source of the low genetic differentiation between the two populations, both the wild-type allele (335) and the mutant allele (354) contributed equally to genetic differentiation. These results are presented in Table 18.

Table 18. *Estimation of F-statistics per allele.*

F statistique Alleles	FIS	FIT	FST
BRCA1 335	-0,64881	-0,61523	0,02037
BRCA1 354	-0,64881	-0,61523	0,02037
BRCA1 271	-0,45875	-0,47631	-0,01204
BRCA1 291	-0,45875	-0,47631	-0,01204
BRCA2 151	0,71143	0,71608	0,01611
BRCA2 171	0,71143	0,71608	0,01611

The Nm (gene flow) derived from migration between TC and T, at 34.88, is low. This indicates little or no gene exchange between TC and T. Reynolds' distance, which depends on genetic drift, yielded a very low value of 0.00714. This result reflects an absence, or a very low degree, of divergence between the cancerous and control populations attributable to genetic drift. These results are presented in Table 19.

Table 19. *Estimation of Fst, gene flow (Nm), and Reynolds' distance between tissues and controls (Weir & Cockerham).*

Parameters	Valeur
FST	0,00712
Nm	34,88
D Reynold	0,00714

4. Discussion

An analysis of genetic variability and genetic differentiation was performed in Senegalese patients with breast cancer, based on two nuclear markers, BRCA1 and BRCA2, in which three loci were targeted: two for BRCA1 (BRCA1-5382insC, BRCA1-185delAG) and one for BRCA2 (BRCA2-6174delT). A population genetics approach was used to analyze DNA extracted and genotyped from 26 tumor tissue samples (TC) and 23 control tissue samples (T). After genotyping the three BRCA loci, 44 individuals exhibited at least one genotypic profile, namely 21 out of the 25 controls studied (84%) and 23 out of the 26 cancerous tissues (88.46%). At both BRCA1 loci, the wild-type allele was the most frequent, whereas at the BRCA2-6174delT locus, the mutant allele was the most frequent, in both tissue types (controls and cancerous). In cancerous tissues, the mutant alleles of BRCA1-5382insC and BRCA1-185delAG were present at frequencies of 47.7% and 44.4%, respectively. These results are consistent with those of [25] who, in a study of the frequency of these three mutations in breast cancer among Egyptian women, found a higher frequency (11.6%) of the mutant allele at the BRCA1-5382insC locus compared with the mutant allele at the BRCA1-185delAG locus (2.3%). Furthermore, [26] after studying the contribution of these mutations to breast cancer in Egypt, also found that the BRCA1-5382insC locus was more frequently mutated than the BRCA1-185delAG locus, with frequencies of 66.7% and 15.6%, respectively, among breast cancer patients [26]. A potential pioneering role for the BRCA1-5382insC mutation in BRCA1-associated breast cancer has been proposed [26]. Our results are also consistent with those of Bhatta et al. in terms of dominant allele frequency. Indeed,

after studying the prevalence of BRCA1-185delAG in the Nepalese population, these authors found a ratio of 92% for the wild-type allele and 8% for the mutant allele [27]. The high frequency of the wild-type profile and the low frequency of the mutant profile in that study, compared with our study (0.556 wild-type profile, 0.444 mutant profile), could be explained by the sample size, sample type, and mutation-detection technique used. Indeed, Bhatta et al. used the RFLP technique to detect the mutation, and also had approximately twice as many cancer samples as our study — 50 samples versus 26. In addition, their cancerous tissue samples were of blood origin, whereas our diseased samples were tissue samples. Furthermore, a higher frequency of the mutant type at the BRCA2-6174delT locus was found in cancerous tissues. This result contrasts with that of [28] who found a higher incidence of BRCA1 founder mutations in the Slavic population after testing 8533 women with breast cancer [28]. However, the non-significance of Fisher's test in our study shows that the frequencies of the wild-type and mutant alleles were the same in both tissue types for all three BRCA loci. Thus, the distribution of allelic frequencies of these loci between populations does not allow a specific allele type to be attributed to either cancerous tissues or controls. The distribution of aggregated allelic frequencies indicates that the mutant and wild-type forms of the BRCA2-6174delT locus occur in populations of African, Afro-European, and Asian ancestry. These frequencies are similar to those found in Senegal (in our study) and on other continents (Europe and Asia). Likewise, the mutant forms are comparable across continents, showing a null or low frequency of this mutation. These results are consistent with those of [25]. Indeed, the latter found an absence of the BRCA2-6174delT mutation in a study of breast cancer comparing three different groups of Egyptian women: patients, their healthy first-degree relatives, and unrelated controls. Chakraborty et al. found the same results in the eastern region of India, among a total of 231 patients with malignant breast tumors (130 with a family history and 101 sporadic cases) [29]. [30] found the same result in Libya, among 18 patients with familial breast cancer and 67 sporadic cases [30].

Regarding genotypic frequencies, the heterozygous genotype was the most frequently found at the BRCA1 loci in both tissue types, whereas at the BRCA2 locus, the homozygous mutant genotype was the most common. Also, for the predominant heterozygous genotype at the BRCA1 loci, only BRCA1-5382insC showed a non-significant frequency difference between healthy and cancerous tissues. Furthermore, at the BRCA2-6174delT locus, the predominant homozygous mutant genotype was the most frequent in both cancerous and healthy tissues. No genotype specific to either of our populations was found for these three loci, as confirmed by a non-significant Fisher's test.

Regarding heterozygosity rates, our results show that cancerous tissues exhibited a higher heterozygote excess at the BRCA1 loci compared with controls, whereas a heterozygote deficit was found at the BRCA2-6174delT locus in cancerous tissues, versus a complete absence of heterozygosity in controls. These results are consistent with those of [31]. Indeed, after studying the frequency of 20 pathogenic variants (BRCA1, BRCA2, PALB2) associated with breast cancer in the French-Canadian population, these authors found more heterozygous BRCA variants in cancerous tissues (21) compared with controls (5 heterozygotes). The 5 heterozygous variants found in controls concerned only male individuals, which could explain the absence of heterozygosity observed among controls in our study at the BRCA2-6174delT locus. However, the frequency of BRCA2 variants was higher than that of BRCA1 variants in both cancerous tissues and controls in their study, which contrasts with our findings. It should be noted that our variants were not included in the study by [31]. Similarly, Maxwell, after studying 160 breast cancer cases, also found a higher heterozygosity rate at the BRCA2 locus (46%) compared with the BRCA1 locus (10%). This difference may be explained by sample size and the germline nature of Maxwell's study. However, despite this low heterozygosity, BRCA1 tumors with a heterozygous profile retained BRCA1 protein expression, which could be associated with an increased mutational burden in BRCA1 breast tumors (repair mechanism). In contrast, BRCA2 tumors showing high heterozygosity were characterized by a low mutational burden [32].

The Hardy-Weinberg (HW) equilibrium test for each population, per locus, shows that the TC population is not in Hardy-Weinberg equilibrium at the BRCA1 loci, whereas the control population is in Hardy-Weinberg equilibrium at these same loci. At the BRCA2 locus, the cancerous tissue population followed Hardy-Weinberg equilibrium, whereas controls did not follow Hardy-Weinberg equilibrium at this same locus. In the literature, we found no study that tested Hardy-Weinberg equilibrium for these three mutations in the context of breast cancer. However, a population in HW equilibrium is closed to evolutionary forces, whereas a population not in equilibrium is open to these same forces. Based on the evolutionary force of mutation, we can state that, in our study, at the BRCA1 locus, there is more mutation in the TC population, which is open, compared with the control population, which is closed and shows less mutation. In contrast, at the BRCA2 locus, the TC population is closed to mutation (i.e., less mutated) compared with the T population (more prone to mutation). These results contrast with those of [33]. Indeed, after studying the prevalence of pathogenic variants in the BRCA1 and BRCA2 genes in breast cancer, this author found more mutations in controls compared with cancerous tissues at the BRCA1 locus (8 versus 7). At the BRCA2 locus, more mutations were found in cancerous tissues (20 versus 8). However, the findings of Zeng are consistent with ours for the BRCA1 loci, but not for the BRCA2 locus [34]. Indeed, this author found a higher number of mutations at the BRCA1 gene in TC compared with controls (13 versus 3), whereas at the BRCA2 locus, the same author found more mutations in TC compared with T (31 versus 0), following an evaluation of pathogenic mutations in breast cancer predisposition genes, including

BRCA1 and BRCA2. The discrepancy between these two studies and ours may be explained by the origin of the study populations. Indeed, [33] targeted the French-Canadian population, whereas Zeng targeted the Chinese population. The latter supports this perspective by confirming a higher risk associated with the BRCA1 gene in populations of African ancestry for breast cancer, compared with the BRCA2 gene. Moreover, [33] study did not target the mutations examined in our study.

The linkage disequilibrium test shows that, in controls, the two loci BRCA1-185delAG and BRCA1-5382insC are linked, whereas in TC (cancerous tissues), these two loci are not linked. Linkage disequilibrium has several causes, including chance, selection, and mutation. The fact that the BRCA1 loci are linked in controls may be due to a predominance of the BRCA1 loci relative to the BRCA2 locus, resulting either from chance or selection. The selection hypothesis would imply that the BRCA1 loci are selectively advantageous for the control population compared with the BRCA2 locus. This is not entirely accurate. Indeed, in some studies, the BRCA2 gene confers the greatest predisposition to breast cancer, as observed in China [34], and in French Canada [33], whereas in Tunisia [35] and in western Washington State [36], it is BRCA1 that confers the greatest predisposition. We therefore hypothesize that this linkage disequilibrium is due to chance.

Regarding inter-population genetic diversity parameters, Nei's genetic distance between controls and tissues gave a value very close to that found at the BRCA1-185delAG locus. Wright's F-statistics, such as Fis, revealed low inbreeding at the BRCA1 loci in TC compared with T, where inbreeding was high. In controls, at the BRCA2-6174delT locus, complete inbreeding was found. These results are consistent with those of [37] who found greater inbreeding among controls compared with patients after studying the effect of consanguinity on breast cancer incidence in the Tunisian population [37]. Moreover, analysis of the distribution of homozygous and heterozygous BRCA1 haplotypes in 40 familial cancer cases, 46 sporadic cases, and 34 healthy control cases showed fewer homozygous haplotypes among patients compared with controls (6 and 13 versus 15). This author concluded that parental consanguinity appears to be protective against breast cancer. The Fit value revealed a heterozygote excess among individuals within our subpopulations and in the total population. The Fst value indicated low genetic differentiation between our populations. After estimating the F-statistics using the jackknife method, we found that this heterozygote excess in our populations, as well as the low genetic differentiation observed between TC and T, was linked to the BRCA1-185delAG locus. Moreover, this locus contained more heterozygosity among patients. Our results are similar to those of Sirisha. Indeed, this author found a high heterozygosity rate of 36% among patients versus 4% among controls for the 185delAG mutation, in a study of 100 women with ovarian cancer in southern India (32 familial and 68 sporadic cases) [38]. Moreover, this mutation has been reported in several countries, such as India, by [30]. According to [39]., this mutation is recurrent and more frequent in South Asia [39]. Hedau et al. reported 6 patients presenting BRCA alterations among 100 sporadic cancer cases [40]; among these 6 patients, 2 carried the 185delAG mutation.

The BRCA1-5382insC mutation ranks second after the BRCA1-185delAG mutation in terms of genetic differentiation. Indeed, this mutation is highly prevalent in Central and Eastern Europe [41]. In Poland, it is found in 34% of familial breast cancer cases [42]; 14% in Russia; [43] 4% in Germany [44]; and 10% among Ashkenazi Jewish women [45].

The BRCA2-6174delT mutation does not appear to be responsible for the low genetic differentiation obtained in our study between our populations. Indeed, this mutation has been reported as absent in several countries. After comparing the frequency of this mutation between Jewish and non-Jewish women, Neuhausen et al. found that 6 out of 80 Jewish women carried this mutation, compared with 0 out of 90 non-Jewish women [46]. This demonstrates the rarity of this mutation even among Ashkenazi Jews, where this gene has a founder effect. Likewise, Abou-El-Naga et al. found an absence of this mutation in Egypt, after comparing three groups (patients, first-degree healthy relatives, and unrelated healthy controls [25]. Chakraborty et al. also found an absence of this mutation after estimating carrier frequency in a region of eastern India, among a total of 231 patients with malignant breast tumors (130 with a family history and 101 sporadic cases) [29]. The same results were found in Libya, following analysis of the presence of this mutation among 18 patients with familial breast cancer and 67 sporadic cases [30].

5. Study Limitations

The main limitation of this study is the relatively modest sample size, which may have reduced the statistical power of some genetic analyses, particularly those related to Hardy–Weinberg equilibrium, linkage disequilibrium, and genetic differentiation. Therefore, these findings should be interpreted with caution and confirmed in future studies involving larger cohorts.

6. Conclusion

The study of intra- and inter-tissue diversity between healthy and cancerous tissues for the BRCA1-185delAG, BRCA1-5382insC, and BRCA2-6174delT mutations reveals a difference between BRCA1 and BRCA2 tumors. Indeed, in BRCA1 tumors (185delAG and 5382insC), the wild-type profile predominates over the mutant profile; these tumors exhibit a heterozygote excess, low inbreeding, and are not in Hardy-Weinberg equilibrium. In contrast, in BRCA2 tumors (6174delT), the mutant profile predominates over the wild-type profile; these tumors exhibit a heterozygote deficit. In these tumors, the inbreeding rate is high, with controls being

100% inbred. Our study also shows low genetic differentiation between controls and tissues, attributable to the BRCA1-185delAG locus, followed by BRCA1-5382insC. Both of these mutations are founder mutations in the Ashkenazi Jewish population. The low-penetrance BRCA1-185delAG mutation could be involved in breast cancer among Senegalese women. However, it would be of interest to determine whether these two BRCA1 mutations have a founder effect in the Senegalese population, particularly the 185delAG mutation (potentially linked to a specific geographic area or ethnic group). Additionally, sequencing to assess the degree of pathogenicity of the BRCA1 (185delAG, 5382insC) and BRCA2 (6174delT) mutations in the Senegalese population would be valuable. Such an approach would enable clinicians to take appropriate measures and screen for these mutations, particularly in BRCA1 tumors, even in sporadic breast cancer cases — for a gene that is often overlooked in sporadic cases but extensively studied in germline cases. Looking ahead, this work paves the way for new research directions, namely investigating a founder effect for one of these mutations, primarily BRCA1-185delAG, and assessing the pathogenicity level of these three mutations in the Senegalese population. These research directions will help deepen our understanding of BRCA-related tumors. We recommend increasing the sample size in order to better assess the involvement of the BRCA1-185delAG mutation in breast cancer among women in Senegal.

Abbreviations

DNA	Desoxyribonucleic Acid
BRCA1	Breast Cancer Gene 1
BRCA2	Breast Cancer Gene 2
PALB2	Partner and Localizer of BRCA2
PCR	Polymerase Chain Reaction
RFLP	Restriction Fragment Length Polymorphism
bp	Base Pair(s)
TC	Cancerous Tissue
T	Controls (Healthy Controls)
REC	Research Ethics Committee
HWE	Hardy-Weinberg Equilibrium
LD	Linkage Disequilibrium
NA	Number of Alleles
Ho	Observed Heterozygosity
He	Expected Heterozygosity
Hnb	Unbiased (Expected) Heterozygosity
Fis	Inbreeding Coefficient (Within-population Fixation Index)
Fit	Total Fixation Index
Fst	Fixation Index (Between-population Genetic Differentiation)
Nm	Gene Flow
D	Genetic Distance (Nei's or Reynolds', Depending on Context)
185delAG	Deletion Mutation of AG Nucleotides (BRCA1, Exon 2)
5382insC	Insertion Mutation of a Cytosine (BRCA1, Exon 20)
6174delT	Deletion Mutation of a Thymine (BRCA2, Exon 11)

Author Contributions

Berenice Raissa Diallo: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft

Boubacar Cissokho: Data curation, Methodology, Software, Validation, Visualization, Writing – review & editing

Mbacke Sembene: Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing

Conflicts of Interest

The authors declare no conflict of interest.

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