INTRODUCTION

With a rapidly evolving incidence, breast cancer is currently the first female cancer in sub-Saharan Africa followed by cervical cancer. Recent reviews have reported that most breast cancers in Sub-Saharan Africa are triple negative, prognostic stage III tumours, with average age at diagnosis at late 40s, resulting in a high-mortality rate. Overall, 5–10% of breast cancers are inherited and could be associated with ovarian cancers. The risk is linked to two high-penetrance susceptibility genes: BRCA1 (17q21) and BRCA2 (13q12). Both are tumour suppressor genes involved in double strand break DNA repair. Women who have inherited mutations in BRCA1 or BRCA2 are at higher risk of developing breast and/or ovarian cancers. Risk increased with the number of affected women within the family, early age at diagnosis and the degree of relationship with other affected women. The cumulative risk of breast cancer by age 80 years was estimated to 72% for BRCA1 carriers and 69% for BRCA2 carriers. For ovarian cancer, cumulative risk at age 80 years was estimated to 44% for BRCA1 carriers and 17% for BRCA2 carriers. Many studies in different populations have identified pathogenic variants that have been stored in BRCA Consortia databases (CIMBA http://cimba.ccge.medschl.cam.ac.uk/, UMD http://www.umdb.org/BRCA1/, BIC http://research.nhgri.nih.gov/bic/, ENIGMA https://enigmaconsortium.org/, BRIDGE https://bridges-research.eu/). Some variants are at very high frequencies in specific ethnic groups suggesting their founder effect. In Ashkenazi Jewish women, BRCA1 c.66_67delAG (p.Glu23Valfs) and c.5266dupC (p.Gln1756Profs) founder mutations conferred a life-time risk to breast/ovarian cancer, ten times higher compared with general population. In Africa few studies have reported specific founder

RESULTS

Age at diagnosis and tumor characteristics

Mean age at breast cancer diagnosis was 39.5 years (range from 21 to 67 years). Overall, 88.8% of recruited patients were diagnosed before age 50. Of patients with information on tumor
stage (94.1%), most were diagnosed at advance stage (stage II = 58.9% or stage III = 35.2%). Tumour hormone receptors and HER2 status showed that 42.8% had triple negative breast cancer followed by HER2 enriched tumors, 28.5% (Table 1).

Identification of a recurrent pathogenic variant of BRCA1 gene

Mutation screening identified a recurrent pathogenic variant at heterozygous state of the BRCA1 gene in 15 probands out of 27 recruited. This is a duplication of ten nucleotides (c.815_824dupAGCCATGTGG, p.Thr276AfS) located in exon 11 of BRCA1 according to the HGVS nomenclature (Fig. 1). This pathogenic variant leads to a frameshift and a spurious stop codon 14 amino acids further down. It was detected in six index cases of a first group of 15 index cases by mutation screening of all coding exons of BRCA1 gene, and later in nine additional index cases from a second group of 12 patients by PCR genotyping (Supplementary Fig. 1). The allelic frequency was then estimated at 27.7% in hereditary breast cancer cases. The pathogenic variant was also detected by genotyping in a control population of sporadic breast cancer cases and healthy controls free from any cancer (allelic frequency estimated at 5% and 0.55%, respectively), and in ten healthy relatives from selected studied families (Table 2, Fig. 2). The PCR genotyping method is now available for first routine screening of the recurrent pathogenic variant in women at risk in our laboratory (Fig. 3).

Any other pathogenic variant of the BRCA1 gene was identified in the remaining nine index cases of the first group while one of them had a novel BRCA2 pathogenic variant.23

An ancient founder haplotype linked to the recurrent pathogenic variant

As the pathogenic variant is recurrent in our study population, we searched for its founding effect by haplotype analysis. We genotyped seven microsatellite markers flanking the BRCA1 gene and distributed in 2.15 Mb in ten index cases with the pathogenic variant, and 15 unrelated healthy controls. Haplotype analysis showed that specific alleles sizes 144, 156, and 173 bp of three microsatellite markers D17S855, D17S1323, and D17S1325, respectively segregated together in the index cases, and constituted a common haplotype of ~400 kb. This haplotype is not found in any of the healthy controls studied. This common haplotype suggested a founder effect of the pathogenic variant in the study population (Table 3).

We then estimated the age of the pathogenic variant in number of generations, using the following formula $G = \log(\delta)/\log(1 − θ)$ as described in the methodology. The pathogenic variant is supposed to appear in Senegal 55.5 generations ago, ~1400 years.

**DISCUSSION**

Breast cancer in sub-Saharan Africa has a clinical epidemiology characterized by an early age at diagnosis (<50 years), aggressive tumors with poor prognosis.2,24,25 This particular epidemiology has been observed in our study population. The average age of diagnosis was 39.5 years and is the lowest reported in sub-Saharan Africa: 45 years in Senegal and Nigeria,25 46 years in Mali,26 and 49 years in Ghana.27 In Canada, the US, and Australia there has been an average age at diagnosis of about 45 years for sporadic breast cancer and 39.9 years for inherited breast cancer.28 A study conducted in Senegal in 2017 has reported a mean age at diagnosis of 47.5 years in women with sporadic breast cancer.29 The average age observed in this study is then concordant with that reported in inherited breast cancer over the world.

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**Table 1.** Age at diagnosis and tumor characteristics of studied population.

| Age at diagnosis | Number | Percentage % |
|------------------|--------|--------------|
| 20–35            | 11     | 40.7         |
| 36–50            | 13     | 48.1         |
| >50              | 3      | 11.1         |
| SBR stage        |        |              |
| I                | 1      | 5.9          |
| II               | 10     | 58.9         |
| III              | 6      | 35.2         |
| Hormone receptors and HER2 status | | |
| TNBC             | 6      | 42.8         |
| HER2 enriched    | 4      | 28.5         |
| Other phenotypes | 4      | 28.7         |
| ND               | 13     | 48.1         |

**Fig. 1** Chromatographic sequence of the BRCA1 gene exon 11 surrounding the identified pathogenic variant c.815_824dup.
Tumors characteristics showed a late stage diagnosis with aggressive tumors of bad prognosis mainly grade SBR II and III. This has also been reported in sporadic breast cancer in sub-Saharan Africa. This late stage diagnosis could be linked to the lack of awareness programs for breast cancer symptomatology and diagnosis, and the high cost of breast cancer therapy, most patients first resorted to traditional medicine.

Despite the need expressed by gynecologists and oncologists, molecular phenotyping of tumors is not available in most sub-Saharan African countries. Available data came from abroad at expensive costs inaccessible to most patients. For the few laboratories that have local facilities, the poor quality of biopsies, the inadequacy of fixation time, the lack of equipment and specialists, are pitfalls for achieving these analyzes. Our results showed that the majority of tumors were triple negative (42.8%) or Her2 enriched (28.5%), all considered as poor prognostic tumors. Added to this, is the young age at diagnosis with 40.7% of our population under 35 years of age. It has been reported that breast cancer diagnosed in women under 40 years with triple negative or Her2-enriched tumors, is of poor prognosis and high metastasis incidence. It therefore appears that breast cancer in young women could constitute a biologically different entity.

Germline mutations of BRCA1 and BRCA2 genes, and a familial aggregation are frequently observed in this case. Therefore, a BRCA gene mutation will be suspected, when an index case has a young age at diagnosis, and/or a family history of breast or ovarian cancer and a poor prognosis tumor. Patients in our study were relatively young (mean age 39.5 years) and all had at least

| Mutation status | Families | Healthy relatives | Sporadic cases | Healthy controls |
|-----------------|---------|------------------|---------------|-----------------|
|                 | Nb cases | Allelic frequency | Nb cases | Allelic frequency | Nb cases | Allelic frequency |
| c.815_824dup10+ | 6        | 27.7%            | 10       | 5%              | 1        | 0.55%            |
| c.815_824dup10− | 9        | 13               | 72       | 89              |
| Total           | 15       | 23               | 80       | 90              |

Fig. 2 Pedigrees of six families carrying the BRCA1 pathogenic variant c.815_824dup10 identified by Sanger sequencing. Blue color indicates individuals diagnosed with breast cancer. P: index case, E+: Individual with pathogenic variant, E−: Individual without pathogenic variant.

Fig. 3 4% agarose gel electrophoresis of PCR products for BRCA1 pathogenic variant c.815_824dup10 genotyping. PM molecular weight marker, TN DNA negative control, NM non-carrier index case, AB-FY-FGF-FW-ML-SN-WM-SM-NAG-AT: index cases carrying the mutation (AB-FY-FGF-FW-ML-AT belong to the first group of 15 index cases recruited and SN-WM-SM-NAG belong to the second group of 12 recruited index cases). This gel derived from a single experiment.
one affected relative, while 14.8% had associated ovarian cancer. These characteristics are in favor of *BRCA* genes inherited mutations and thus a genetic predisposition. Hereditary breast cancer accounts for 5–10% of breast cancers in women. Molecular genetics have led to a better understanding of the genetic basis of predisposition to breast/ovarian cancer. Several genes have been involved with two major genes *BRCA1* and *BRCA2* and minor genes PALB2, *P53*, *PTEN*, PALB2, *P53*, *PTEN*, CDH1, *RAD51*, *MLH1*, *MSH2*, *PMS2*, and *EPCAM*. Pathogenic variants of these genes play an important role in the genetic predisposition to breast or ovarian cancer. The cumulative risk of breast cancer for *BRCA1* carriers and 17% for *BRCA2* carriers.

Predisposition to inherited breast cancer has been conducted in European or American populations while in Africa particularly in sub-Saharan Africa, very few studies have been conducted. We report here for the first time in Senegal, a recurrent pathogenic variant of the *BRCA1* gene, c.815_824dup10 involved in the predisposition to hereditary breast cancer. Allelic frequency of the mutation was estimated to 27.7%. This is the highest allelic frequency of this mutation reported in a population. Review from the literature has shown that the variant has been described for the first time in a breast cancer patient from Ivory Coast living in the US, Later it was also reported in patients from Mexico and the Bahamas, among African-Americans and Hispanics living in the US, in Peru, but also in some European populations. Among African Americans with hereditary breast cancer, it is the most common mutation with a frequency of 16%. According to CIMBA database, 65 people carrying the variant have been identified worldwide, mostly of African or Hispanic origin. Studies in West Africa, particularly in Nigeria and Burkina Faso have not report it in these populations.

When a mutation is identified at a high frequency within a population, exploring for its founding effect becomes important for cancer prevention. Several founder mutations have been reported in different populations. Variants c.66_67delAG and c.5266dupC of *BRCA1* have been used for breast cancer prevention among Jewish women. In Africa, founder mutations have been reported in Yoruba population from Nigeria (c.303T>G; (p.Tyr101Ter)) in a series of four families, in Afrikaners from South Africa (c.2641G>T; (p.Glu881Ter)) in four families, and in Moroccan (c.5309G>T; (p.Gly1770Val)) in five families. The founding effect of the variant c.815_824dup10 was reported first in five nonrelated families from US and the mutation was supposed to be of West African origin.

When we screened for its founder effect in Senegal, we identified a haplotype of about 400 kb containing the variant in hereditary breast cancer patients and not in any of the healthy controls. This Senegalese haplotype is shorter compared with the one identified in the US, which spanned 700 kb, as well as the one associated with the Jewish mutation c.66_67delAG. This suggested that the Senegalese haplotype would be older than the African-American haplotype which was estimated to be 200 years old. Age estimation of the Senegalese haplotype suggested that the variant c.815_824dup10 arose around 1400 years ago. Then we supposed that the variant appeared first in Senegal and was spread throughout the world by population migration, especially by slave trade. Senegal by its geographical position in West Africa was one of the major ports during the

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**Table 3.** Haplotypes of ten probands with the *BRCA1 c.815_824dup10* mutation and 15 healthy controls.

| Patient | D17S1793 | D17S1320 | D17S855 | D17S1323 | D17S1325 | D17S951 | D17S1183 |
|---------|----------|----------|---------|----------|----------|---------|----------|
| Index cases |
| AB1 | 193 | 195 | 186 | 188 | **144** | **146** | **156** | **156** | 171 | **173** | 170 | 178 | 129 | 146 |
| AT | 193 | 195 | 188 | 190 | **144** | **144** | **156** | **158** | 157 | **173** | 172 | 174 | 135 | 146 |
| FDF | 193 | 193 | 195 | 195 | **144** | **152** | **150** | **156** | **173** | 175 | 168 | 172 | 120 | 120 |
| FW | 193 | 195 | 186 | 186 | **144** | **152** | **154** | **156** | **171** | **173** | 170 | 172 | 146 | 150 |
| FY1 | 193 | 193 | 224 | 224 | **144** | **152** | **156** | **158** | 173 | 175 | 172 | 174 | 129 | 148 |
| ML1 | 193 | 193 | 213 | 224 | **144** | **148** | **150** | **156** | **173** | 173 | 172 | 172 | 124 | 139 |
| NA | 195 | 195 | 195 | 195 | **144** | **150** | **154** | **156** | **175** | 179 | 170 | 178 | 124 | 124 |
| SM | 193 | 193 | 190 | 190 | **144** | **144** | **156** | **162** | 169 | **173** | 168 | 170 | 124 | 146 |
| SN | 193 | 193 | 192 | 192 | **144** | **148** | **156** | **173** | 175 | 174 | 176 | 124 | 124 |
| WM | 193 | 197 | 203 | 224 | 140 | **144** | **156** | 158 | 167 | 171 | 170 | 172 | 120 | 129 |
| Healthy controls |
| T33 | 192 | 200 | 193 | 196 | 152 | 152 | 150 | 154 | 171 | 177 | 168 | 172 | 121 | 121 |
| T37 | 193 | 195 | 187 | 193 | 152 | 152 | 152 | 154 | 169 | 169 | 170 | 174 | 121 | 121 |
| T38 | 192 | 193 | 191 | 193 | 152 | 155 | 152 | 154 | 171 | **173** | 168 | 172 | 121 | 129 |
| T41 | 192 | 195 | 185 | 189 | **144** | 154 | **156** | 159 | 157 | 171 | 170 | 174 | 121 | 121 |
| T42 | 193 | 195 | 203 | 205 | 150 | 159 | 152 | 154 | 175 | 175 | 174 | 176 | 121 | 124 |
| T49 | 193 | 193 | 187 | 191 | 147 | 154 | 152 | **156** | 157 | 175 | 170 | 174 | 121 | 121 |
| T52 | 193 | 193 | 187 | 189 | **144** | 149 | 154 | 154 | 175 | 175 | 174 | 176 | 121 | 124 |
| T53 | 189 | 193 | 189 | 191 | **144** | 150 | 154 | 154 | 167 | 175 | 174 | 174 | 121 | 121 |
| T55 | 191 | 193 | 188 | 191 | 152 | 152 | 154 | 159 | 157 | **173** | 176 | 176 | 121 | 128 |
| T56 | 193 | 193 | 188 | 193 | **144** | 152 | 154 | **156** | 168 | 171 | 168 | 174 | 121 | 121 |
| T61 | 193 | 193 | 189 | 193 | 148 | 152 | 154 | 152 | 171 | 171 | 170 | 176 | 121 | 124 |
| T63 | 193 | 193 | 185 | 193 | 150 | 152 | 154 | 159 | 171 | 175 | 170 | 180 | 121 | 124 |
| T67 | 191 | 193 | 191 | 203 | 150 | 152 | 150 | 152 | 171 | 175 | 168 | 172 | 121 | 124 |
| T70 | 189 | 197 | 185 | 191 | 150 | 152 | 152 | 154 | 167 | 169 | 174 | 174 | 121 | 121 |
| T83 | 193 | 195 | 189 | 191 | 152 | 154 | 154 | 157 | 168 | 171 | 168 | 170 | 121 | 129 |

Bold are genotypes of the haplotype segregating with *BRCA1 c.815_824dup10* mutation.
trans-Atlantic slave trade toward the European and the US continents.47 But it would be of interest to screen for this mutation in other West African countries. Studies conducted in Nigeria and Burkina Faso have not reported it.12,13

While the allelic frequency of c.815_824dup10 in our study is high (27.7%), it is necessary to recruit more index cases and more controls in order to estimate the exact allelic frequency of this variant in Senegalese population.

In this study we identified a founder pathogenic variant involved in predisposition to inherited breast cancer in Senegalese women. Screening of the variant in women at risk in Senegal and involved in predisposition to inherited breast cancer in Senegalese women. Screening of the variant in women at risk in Senegal and other West African countries (Mali, Gambia, Ivory Coast, Ghana, and Benin) will be of interest for breast cancer prevention strategies. It will also lead the ground for onco genetic counselling in Senegal.

METHODS

Patients

Female index cases with biopsy-proven breast cancer and family history of breast or ovarian cancer, followed up at the Joliot Curie Institute and the Senology department of Aristide le Dantec Hospital in Dakar were recruited. After free written informed consent all participants were interviewed to collect demographic data and medical history. Twenty-seven unrelated female index cases were included in this study. Pedigrees were drawn with Progeny software and 5 ml blood sample was collected from each participant. Characteristics of each index cases and pedigrees are available upon request. From the 27 index cases recruited a first group of 15 was screened for mutations in all exons of the BRCA1 and BRCA2 genes. After identification of a recurrent mutation in this first group, the twelve (12) consecutives index patients were screened for this recurrent mutation by PCR genotyping. For index cases with the BRCA1 pathogenic variant, healthy relatives were further recruited for genetic testing after written informed consent.

We have also recruited a control population including 90 healthy women without known cancer who came for routine check-up at the Laboratory of Biology of Le Dantec Hospital and 80 women with sporadic breast cancer and without family history from the Joliot Curie Institute. This study was approved by the ethics committee of Cheikh Anta DIOP University under Protocol 014/2014/CER/UCAD. All participants gave their informed consent before participation in the study.

Molecular analysis

DNA extraction and Sanger sequencing. Genomic DNA was extracted from whole blood with a QiAmp® DNA blood purification kit (Qiagen). BRCA1 and BRCA2 exons were amplified by PCR with specific primers located in intron/exon boundaries. Twenty-eight fragments covering the 22 coding exons of BRCA1 and 32 fragments covering the 26 coding exons of BRCA2 gene were amplified.48 The large exons 10 and 11 of BRCA2 were amplified as two and nine fragments, respectively, while exon 11 of BRCA1 was amplified as seven fragments (Supplementary Table 1). PCRs were carried out with initial denaturation at 95 °C for 10 min followed by 40 cycles of 95 °C for 30 s, 55 °C for 30 s, and 72 °C for 30 s with a GeneAmp® PCR System 9700 (Applied Biosystems) as described previously.48 The PCR products were purified with a MinElute 96 UF kit and sequenced using a Big Dye terminator V3.1 sequencing kit on a 3730 Genetic Analyzer. Obtained sequences were compared with the GenBank reference sequence (NM_007294.3) with Alamut Software. This study was approved by the ethics committee of Cheikh Anta DIOP University under Protocol 014/2014/CER/UCAD. All participants gave their informed consent before participation in the study.

PCR genotyping of c.815_824dup10 recurrent pathogenic variant of BRCA1. For the following 12 patients and healthy relatives recruited, the recurrent pathogenic variant identified in the first group was genotyped by PCR with primers 5′-TGGCTTGGATAATTTTCTGACAGG-3′ and 5′-TGAAGCTCTGGCAA TTCTGCT-3′ using standard PCR conditions, followed by a 4% agarose gel migration during 4 h at 100 V. Individuals with the pathogenic variant showed two fragments at 422 and 412 bp (Supplementary Fig. 2).

Haplotype analysis. We selected ten index cases with the pathogenic variant and 15 unrelated healthy controls for haplotype analysis. Seven microsatellite markers flanking the BRCA1 gene located in 2.30 Mb were genotyped by PCR (locus order: cen-D17S1793-D17S1320-D17S855-D17S1323-D17S1325-D17S951-D17S1183-tel) with fluorescent labelled primers (Supplementary Table 2). The PCR products were analysed in automated sequencer ABI Prim 310 using Genscan 3.1.2 software (Applied Biosystems). Allele sizes are given as size of the PCR amplicons containing the microsatellites. Genotyping was performed by Inqaba Biotec.49

Age estimation of the founder mutation. The age of c.815_824dup10 pathogenic variant in generations (G) was calculated using the following equation: \( G = \log(\log(1 - \delta)) \). Linkage disequilibrium (\( \delta \); delta) between the mutation and each of the closest recombinant microsatellite markers D17S855 and D17S1325 was calculated as \( \delta = (Pd - Pn)/(|Pd - Pn|) \), with Pd being the frequency of the ancestral microsatellite marker allele among the current generation carrying the mutated BRCA1 and Pn being the frequency of that microsatellite allele on chromosomes not carrying the mutation. The symbol \( \theta \) (Teta) represents the recombination fraction between a marker and the gene.49 The genetic distances were inferred from Ensembl database (https://www.ensembl.org/index.html).

Reporting summary

Further information on experimental design is available in the Nature Research Reporting Summary linked to this paper.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Accession codes for novel BRCA2 mutations c.5219T>C, c.6051T>G and c.7842A>G are available from European Nucleotide Archive (ENA) under the accession codes MT0132011, MT0132012 and MT0132013, respectively.

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AUTHOR CONTRIBUTIONS

R.N. conceived and designed the experiments. J.P.D.D. and V.B-H. performed the experiments and analyzed the data. R.N., J.P.D.D. wrote the manuscript. A.De., D.D., P.L.S., S.M.K.G., A.C., P.A.D., H.S. and A.Di. gave advise in manuscript drafting. All authors have read and approved the final version.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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