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ORIGINAL ARTICLE

Involvement of *ERCC1* (*rs3212986*) and *ERCC2* (*rs1799793*, *rs13181*) polymorphisms of DNA repair genes in breast cancer occurrence in Burkina Faso

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Abstract

Background: Genetic alterations can result in DNA repair defects, increasing susceptibility to breast cancer. The aim of this study was to evaluate the involvement of two DNA repair genes, *ERCC1* (*rs3212986,* GenBank NC_000073.9) and *ERCC2* (*rs1799793, rs13181*, GenBank: NC_000019.10*)* in the occurrence of breast cancer in Burkina Faso.

Methods: This case–control study enrolled 128 participants including 64 patients and 64 healthy controls. Genotyping of polymorphisms were performed by real-time PCR and PCR-RFLP.

Results: The heterozygous AC genotype of the *ERCC2rs13181* polymorphism was associated with the occurrence of breast cancer when the mutant allele is inherited under the dominant pattern (CC/AC vs AA; OR = 2.74, 95% IC (1.09–6.87); $p = .028$), but this association became insignificant after the Bonferroni correction ($p = .156$). No association was observed between *ERCC1*rs3212986 and *ERCC2rs1799793* polymorphisms and breast cancer risk.

Conclusion: This study showed that the heterozygous genotype (CA) of the *ERCC2rs13181* polymorphism may be associated with a risk of breast cancer.

KEYWORDS
breast cancer, Burkina Faso, *ERCC1*, *ERCC2*, polymorphism

1 | INTRODUCTION

Breast cancer is a major public health concern, affecting both developed and developing countries. Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women worldwide. It was estimated 2,261,419 new cases and 684,996 deaths in 2020 worldwide (Sung et al., 2021). Breast cancer mortality rates are higher in developing countries than in developed countries (15 and 12.8 per 100,000, respectively). They are higher in Melanesia, West Africa, Micronesia/Polynesia, and the Caribbean (Sung et al., 2021).

In Burkina Faso, breast cancer is the leading cause of cancer mortality. In 2020, the country recorded 1927 (24.9%) new cases and 1142 (21%) deaths (Ferlay et al., 2020). Breast cancer is on the rise and is taking on alarming epidemic proportions (Sung et al., 2021).

Breast cancer is a heterogeneous and multifactorial pathology arising from the escape of mammary epithelial cells from proliferation control mechanisms. There are familial and sporadic forms of breast cancer (Noorani, McGahan, & Office canadien de coordination de l'évaluation des technologies de la santé, 2000; Viassolo et al., 2016). Familial forms are hereditary and are due to a genetic predisposition while sporadic forms are the result of an association between both genetic and environmental factors. The genes considered to have a significant involvement in the development of breast cancer are the oncogenes (HER2) (Slamon et al., 1987), anti-oncogenes (BRCA1, BRCA2) (Evans et al., 2006), xenobiotic metabolism genes (GSTT1 and GSTP1) (Hussain et al., 2018) and DNA repair genes (ERCC and XRCC) (Goode et al., 2002). Genetic mutations involved in the occurrence of breast cancer can be grouped into three categories: high penetrance mutations, moderate risk mutations, and low penetrance mutations: mutations in the BRCA1 and BRCA2 genes are the major breast cancer predisposition genes. These high-penetrance genes (BRCA1 and BRCA2) are responsible for approximately 25% of incident familial breast cancer cases (Shiovitz & Korde, 2015; Walsh et al., 2006). Then, moderate penetrance mutations are associated with a two- to fourfold risk of breast cancer. Moderately penetrant genes include ATM, BRIP1, CHEK2, NBS1, PALB2, and RAD50 (Walsh & King, 2007). Finally, common low-penetrance susceptibility alleles that have been identified by genome-wide association studies (GWAS) as many genetic regions (loci) associated with breast cancer risk (Ghoussaini et al., 2013; Milne et al., 2017). The majority of SNPs (single nucleotide polymorphisms) are located in genes involved in DNA repair, cell cycle control, apoptosis, cell growth, and cell division. Once DNA is damaged, the organism triggers a set of mechanisms that detect DNA damage, signal its presence, and promote subsequent repair in order to safeguard the integrity of its genome and ensure its survival: Base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ) are active at different stages of the cell cycle, enabling cells to repair DNA damage (Aravind, 2000; Cromie et al., 2001; Iliakis, 2009; Kurz & Lees-Miller, 2004; Pardo et al., 2009). DNA repair genes play a crucial role in the stability and maintenance of genome integrity. Allelic variants of these genes are involved in the initiation of the carcinogenic process and may be associated with an increased risk of breast cancer. Among these polymorphisms, those characterizing the repair genes *ERCC1* (excision repair cross-complementation group 1, endonuclease non-catalytic subunit) and *ERCC2* (excision repair cross-complementation group 2) have been particularly studied because of the importance of their respective functions. The *ERCC1* (OMIM:126380, HUGO HGNC: 3433) and *ERCC2* (OMIM:126340, HUGO HGNC: 3434) genes are part of the nucleotide excision repair (NER) pathway. The *ERCC1* gene is located on the long arm of chromosome 19 at 19q13.32. This gene is 15 kb in size and consists of 13 exons. It is transcribed into a 1.1 kb messenger RNA and encodes the *ERCC1* protein (van Duin et al., 1987). Several studies have demonstrated the involvement of the *ERCC1* gene through these polymorphisms in the occurrence of cancer in certain countries. Thus, the rs3212986 variant (HGVS: c.*197G>T; SNP n.8092C>A), a polymorphism located in the 3′ non-coding region, has been reported to be associated with an increased risk of developing several types of cancer such as lung cancer (Yu et al., 2018), colorectal cancer (Zhang et al., 2018), pancreatic cancer, and breast cancer (Xie et al., 2020).

The *ERCC2* DNA repair gene, also known as XPD, is located in the q13.3 region of the long arm of chromosome 19 and comprises 25 exons spanning at least 54,000 bp. It codes for a 2.3 kb messenger RNA

(Weber et al., 1988). Several polymorphisms of the *ERCC2* gene have been identified, among which two missense mutations have been well studied namely: ERCC2rs1799793 (HGVS: c.934G>A (p.Asp312Asn); SNP c.23591G>A) at exon 10 and ERCC2rs13181(HGVS: c.2251A>C (p.Lys751Gln); SNP c.2251A>C) at exon 23 resulting in an amino acid change (D312N and K751Q, respectively) (Benhamou, 2002).

These two polymorphisms are associated with an elevated risk of several types of cancer including breast cancer (Gómez-Díaz et al., 2015; Hu et al., 2004; Shao et al., 2007). The rs1799793 is a polymorphism causing an exchange of aspartic acid (Asp) to asparagine (Asn) at codon 312 in the ERCC2 gene. The rs13181 polymorphism causes a substitution of lysine (Lys) for glutamine (Gln) at codon 751. The involvement of these polymorphisms in the occurrence of breast cancer seems to have contradictory effects depending on the populations and even the ethnic groups studied (Brandt-Rauf et al., 2009).

In Africa, only a few countries in North Africa have conducted studies on the involvement of these polymorphisms in breast cancer. In sub-Saharan Africa, particularly in Burkina Faso, to our knowledge, the *ERCC1* and *ERCC2* DNA repair genes have not yet been studied either in relation to breast cancer or to other cancers. Thus, our study aims to explore the rs3212986 polymorphism of the *ERCC1* gene and the rs1799793 and rs13181 polymorphisms of the *ERCC2* gene in Burkina Faso.

2 | MATERIALS AND METHODS

2.1 | Study setting and population

This is a matched case–control study that took place between March and October 2021, in Burkina-Faso, in the city of Ouagadougou. The sample consisted of 128 Burkinabe participants, including 64 females (histologically confirmed as having breast cancer) and 64 female healthy controls (not patients) who came for consultation in two University Hospital Centers: Yalgado OUEDRAOGO (CHU-YO) and Bogodogo (CHU-B) and two medical centers: Schiphra and Paul VI. Biomolecular analyses were performed at the Laboratory of Molecular Biology and Genetics (LABIOGENE), and at the Pietro Annigoni Biomolecular Research Center (CERBA).

In this study, all patients with a histologically confirmed diagnosis of breast cancer and followed by an oncologist were considered as "cases".

The controls were constituted by women without a history of breast cancer, followed by a gynecologist for other pathologies than cancer. These women share the same socio-demographic framework as the cases included in this study.

2.2 | Data collection and sampling

After obtaining the participants' consent, a questionnaire was administered to collect their socio-demographic data. Subsequently, 5 ml of venous blood samples were collected from each participant and placed in an EDTA (ethylenediaminetetraacetic acid) tube. After centrifugation at 3500 rpm for 15 min, the plasma and pellet were separated and stored at −20°C with individual codes.

2.3 | DNA extraction and quantification

The genomic DNA of the participants was extracted from the plasmas by the kit QIAamp®DSP DNA Blood Mini (Qiagen) according to the manufacturer's protocol. Biodrop was used to quantify and verify the purity of the extracted DNA.

2.4 | Genotyping of the ERCC1rs3212986, ERCC2rs1799793, and ERCC2rs13181 polymorphisms

The genotyping of the *ERCC2rs13181* polymorphism and the *ERCC1rs3212986* and *ERCC2rs1799793* polymorphisms were performed by RFLP-PCR and TaqMan allelic discrimination (real-time PCR), respectively.

2.4.1 | ERCC1rs3212986 and ERCC2rs1799793 polymorphisms

For each mutation (*ERCC1rs3212986* and *ERCC2rs1799793*), genotyping of each sample was performed in a 20 µl reaction medium containing 5 µl of pure water (molecular biology grade), 10 µl of Taqman® 2X Universal PCR Master Mix (Applied Biosystems™, ThermoFisher), 0.5 µl of each 1/3 diluted primer [0.83 µM] and probe [2.5 µM] and 3 µl of DNA [10 ng/µl]. The sequences of the primer pairs and probes used are listed in Table 1 (Mitra et al., 2009). The following program: initial denaturation at 95°C, 10 min, denaturation at 92°C, 15 s followed by 50 cycles of amplification (hybridization and elongation at 60°C, 1 min) was used for each polymorphism using the QuantStudio™ 5 Real-Time instrument (Applied Biosystems™, ThermoFisher).

TABLE 1 Sequence of primers and nucleotide probes

Polymorphisms	Primers and nucleotide probes	
ERCC1rs3212986 [*C8092A*]	**F:** 5′-GCTTTCTTTAGTTCCTCAGTTTCCC-3′; **R:** 5′-CAGTGCCCCAAGAGGAGATG-3′. **Probes:** 5′-FAM-TGC TGC TGCTGCTTCCGCTTCMGB-3′; 5′-VIC-CTGCTGCTGCTTCTTCCG CTT CTT-MGB-3′	
ERCC2rs1799793 [*G23591A*]	**F:** 5′-CCGCAGGATCAAAG AGACAGA-3′. **R:** 5′-CCTCTGCGAGGAGACGCTAT-3′. **Probes:** 5′-FAM-CCGTGCTGCCCGACGAAGTMGBNFQ-3′. 5′-VIC-CGT GCT GCC CAA CGA AGT GC-MGB NFQ-3′	
Polymorphism	**Primers**	**Amplicon size (bp)**
ERCC2rs13181 [A18911C]	**F:** 5′-CCCCCTCTCCCTTTCCTCTGTTC-3′ **R:** 5′-GGACCTGAGCCCCCACT AACG-3′	413

2.4.2 | *ERCC2rs13181* [a 2251C] polymorphism

Each well of a PCR plate contained a total reaction volume of 20 µl consisting of 4 µl of 5X FIREPOL®Master Mix (Solis BioDyne), 0.5 µl of each primer diluted to the 10th [0.5 µM], 10 µl of sterile water and 5 µl of extracted nucleic acids [10 ng/µl]. The master mix (5X) contained PCR enzyme (Taq polymerase), optimized buffer containing MgCl2, dNTPs, gel loading dye (green), and density reagent. The sequences of the primer pairs used are listed in Table 1 (Lu et al., 2013).

The following program: initial denaturation at 95°C, 5 min followed by 50 cycles (*ERCC1rs3212986* and *ERCC2rs1799793*) of amplification followed by 35 cycles (*ERCC2rs13181*) of amplification (denaturation at 95°C, 30 s, hybridization at 63°C, 1 min and elongation at 72°C, 1 min) and a final elongation at 72°C, 5 min using the Gene Amp®PCR System 9700 (Applied Biosystems).

PCR products were digested with PstI enzyme at 37°C for two hours in the Gene®AmpPCR system 9700 thermal cyclers, according to the manufacturer's recommendations. Then, the digestion products were subjected to electrophoresis on a 3% agarose gel. Visualization of the DNA bands was done under UV light at 132 nm using the Gene Flash Revelation (Synengege Bio Imaging, USA).

2.5 | Statistical analysis

Data were entered using Excel 2016 software. Data were analyzed using R software and Epi Info version 7. The chi-square test was used for frequency comparisons. Odds ratios and 95% confidence intervals were calculated to assess risk. Results are considered statistically significant for a $p < .05$. Bonferroni correction was performed to adjust the *p*-values. Logistic regression analyses were also performed to calculate the odds ratio associating the different genotypes of the polymorphisms and some parameters of our study population.

TABLE 2 Sociodemographic characteristics of the study population

	Cases	Controls
	***N* = 64 (%)**	***N* = 64 (%)**
Age (years)		
≤40	16 (25.00)	43 (67.18)
˃ 40	**48 (75.00)**	**21 (32.82)**
Residence		
Rural	4 (6.24)	00 (0.0)
Urbain	60 (93.76)	64 (100)
Profession		
Women farmers	1 (1.56)	1 (1.56)
Students	**3 (4.69)**	**16 (25)**
Households	**26 (40.62)**	**12 (18.76)**
Public employee	24 (37.5)	27 (42.18)
Others	10 (15.63)	8 (12.50)
Marital status		
Married	48 (75.00)	45 (70.32)
Singles	12 (18.76)	17 (26.56)
Widows	4 (6.24)	2 (3.12)

Sigificance *p* value is in bold.

3 | RESULTS

3.1 | Sociodemographic characteristics

Our study population consisted of 128 women, 64 of whom were patients and 64 controls. Their ages ranged from 19 to 65 years with a mean of 40.89 ± 10.71 years. About 75% of the breast cancer patients were older than 40 years. The

mean age of the cases was higher than that of the controls (45.60 ± 8.48 years in cases versus 36.19 ± 10.69 years in controls). A higher risk of breast cancer was observed for the age range above 40 years in patients compared to controls ($p < .001$).

Both groups (cases and controls) consisted of participants, most of whom resided in urban areas (93.76% for cases and 100% for controls).

Regarding the occupation of the participants, civil servants, and housewives were the most represented among the cases with the same proportion (39.06%) while the control group was dominated by civil servants (42.18%). Female students represented 25% of controls and 4,69% of cases. Thus, housewives had an increased risk of breast cancer while students had a decreased risk of breast cancer. The distribution by marital status shows that the proportion of married women was higher and almost identical between cases (75%) and controls (70.32%), followed by single women (Table 2).

3.2 | Polymorphisms (ERCC1rs3212986 and ERCC2rs1799793)

Figure 1 identifies both polymorphisms *ERCC1rs3212986* and *ERCC2rs1799793*.

3.2.1 | *ERCC1rs3212986* [C8092A] polymorphisms

The genotypic frequencies of this polymorphism were consistent with Hardy–Weinberg equilibrium (HWE) in both groups (cases: $\chi^2 = 0.256$, $p = .610$ and controls: $\chi^2 = 1.662$, $p = .197$). The genotypic frequencies of homozygous (CC), heterozygous (CA), and homozygous mutated (AA) were 17.2%; 45.3% and 37.5% in cases and 25%; 48.4% and 26.6% in controls, respectively. No significant association was found between the variants of this polymorphism and breast cancer ((CA): OR = 1.36, 95% IC (0.54–3.41), $p = .511$; (AA): OR = 2.05, 95% IC (0.76–5.51), $p = .151$). In addition, the frequency of the [A] (mutant) allele was 60.2% in cases and 50.8% in controls. This difference was not statistically significant (OR = 1.46, 95% IC (0.89–2.40), $p = .131$) (Table 3).

3.2.2 | *ERCC2rs1799793* [G23591A] polymorphism

Genotype frequencies were consistent with Hardy–Weinberg equilibrium (HWE) only in the healthy controls group (cases: $\chi^2 = 3.008$, $p = .08$ and controls: $\chi^2 = 8.374$, $p = .003$). The mutant A allele of this polymorphism was represented in cases with a frequency of 38.3%, whereas it was 35.2% in the control group. This difference was not statistically significant (OR = 1.141, 95% IC (0.69–1.90), $p = .604$).

The genotypic frequencies of homozygous (GG), heterozygous (GA), and homozygous mutated (AA) were 32.8%; 57.8% and 9.4% in cases and 34.4%; 60.9% and 4.7% in controls, respectively. No significant association was found between the variants of this polymorphism and breast cancer ((GA): OR = 0.99, 95% IC (0.47–2.10), $p = .987$. (AA): OR = 2.10, 95% IC (0.46–9.48), $p = .544$) (Table 3).

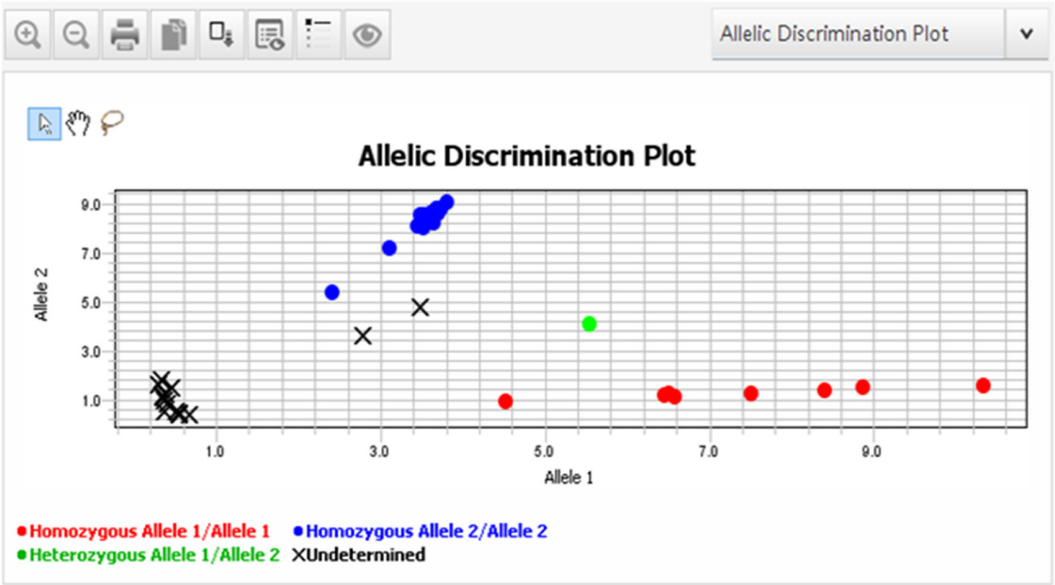

FIGURE 1 Allelic discrimination profile of rs3212986 and rs1799793. Wild-type homozygotes (blue), heterozygotes (green), and mutant homozygotes (red) of both polymorphisms (ERCC1rs3212986 and ERCC2rs1799793).

TABLE 3 Distribution of genotype and allele frequencies of the ERCC1rs3212986, ERCC2rs1799793, and ERCC2rs1318 polymorphism

	Cases *N* = 64 (%)	Controls *N* = 64 (%)	OR (95% IC)	*p* value	Bonferroni correction
ERCC1rs3212986					
Genotypes					
CC	11 (17.2)	16 (25.0)	–	Reference	Reference
CA	29 (45.3)	31 (48.4)	1.36 [0.54–3.41]	0.511	0.671
AA	24 (37.5)	17 (26.6)	2.05 [0.76–5.51]	0.151	0.368
Alleles					
C	51(0.398)	63 (0.492)	–	Reference	
A	77 (0.602)	65 (0.508)	1.46 [0.89–2.40]	0.131	
ERCC2rs1799793					
Genotypes					
GG	21 (32.8)	22 (34.4)	–	Reference	Reference
GA	37 (57.8)	39 (60.9)	0.99 [0.47–2.10]	0.987	0.861
AA	6 (9.4)	3 (4.7)	2.10 [0.46–9.48]	0.544	0.483
Alleles					
G	79 (0.617)	83 (0.648)	–	Reference	
A	49 (0.383)	45 (0.352)	1.14 [0.69–1.90]	0.604	
ERCC2rs13181					
Genotypes					
AA	46 (71.9)	56 (87.5)	–	Reference	–
AC	18 (28.1)	8 (12.5)	**2.74 [1.09–6.87]**	**0.028**	0.156
CC	0 (0.0)	0 (0.0)	NA	NA	NA
Alleles					
A	110 (0.859)	120 (0.938)	–	Reference	
C	18 (0.141)	8 (0.062)	**2.45 [1.03–5.87]**	**0.039**	

Sigificance *p* value is in bold.

Abbreviations: CI, Confidence interval; NA, Not applicable; OR, Odds ratio; *p*, Statistical significance.

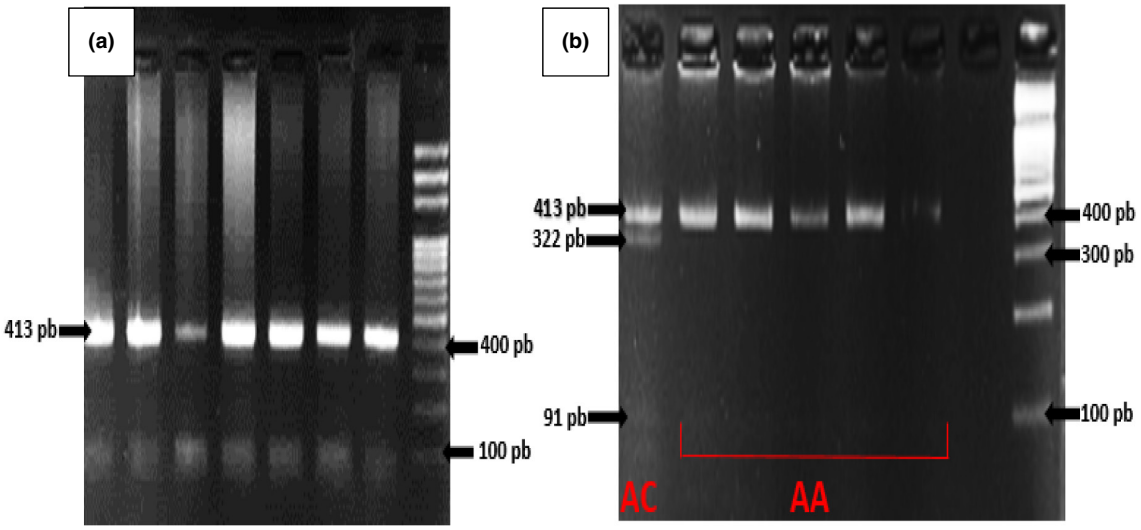

FIGURE 2 Electrophoretic profile. (a) Electrophoretic profile of the ERCC2rs13181 polymorphism amplification products. (b) Electrophoretic profile representing the RLFP results of the ERCC2rs13181 polymorphism

3.3 | *ERCC2rs13181* polymorphism and risk of breast cancer

After conventional PCR amplification of a fragment of exon 23 of the ERCC2 gene, an amplicon of size 413 bp was obtained (Figure 2a). The restriction enzyme PstI was used to identify the A18911C substitution creating a cut site. If mutated, the digest produces two fragments of 322 bp and 91 bp and, therefore, can be distinguished from wild-type homozygotes that yield one band at 413 bp, whereas heterozygotes carry three distinct bands of 413 bp, 322 bp, and 91 bp. In our study, genotyping under the action of PstI yielded homozygous wild-type (AA) and heterozygous (AC) individuals (Figure 2b).

Genotype frequencies were consistent with Hardy–Weinberg equilibrium (HWE) in both groups (cases: $\chi^2 = 1.532$, $p = .215$ and controls: $\chi^2 = 0.392$, $p = .53$). The genotypic frequencies of homozygous (AA), heterozygous (AC), and homozygous mutated (CC) were 71.9%; 28.1%, and 00% in breast cancer patients and 87.5%; 12.5%, and 00% in controls, respectively. The frequency of the [C] allele (mutant) was 14.1% in cases and 6.2% in controls. For the risk of developing breast cancer, the homozygous wild-type (AA) genotype and the A allele were taken as reference. These data suggest that the heterozygous genotype (AC) significantly increased the risk of breast cancer compared to the wild type (AA) (OR = 2.74, 95% IC (1.09–6.87), $p = .028$), but this association became insignificant after the Bonferroni correction ($p = .156$).

3.4 | Association between selected parameters and the genotypes of the three polymorphisms using multivariate logistic analysis

The expression of the different genotypes of the polymorphisms was correlated with three parameters characteristic of the population (menopausal status, family history, and age at diagnosis). No risk was found between the expression of the polymorphism genotypes (*ERCC1rs3212986* and *ERCC2rs1799793*) and these parameters ($p > .05$) (Table 4).

3.5 | Combined genotypes of polymorphisms and the risk of breast cancer occurrence

To assess the combined effect of polymorphisms on breast cancer risk, several combined genotypes were constructed. Statistical analyses of our data revealed no statistically significant association between breast cancer and the different combined genotypes (Table 5). No significant association was found between the combined genotypes of the polymorphisms and breast cancer.

4 | DISCUSSION

4.1 | Sociodemographic characteristics

In our study population, the mean age of cases was 45.60 ± 8.48 years. This mean is close to that found in Cameroon (46.4 ± 15.87 years) (Ndamba et al., 2015) in Burkina Faso (47,4 ± 1,11 years) (Zoure et al., 2018), and in Mali (47,4 ± 13,6 years) (Togo et al., 2010). However, our results are inconsistent with those found in the developed countries of Europe and North America, where breast cancer generally occurs in older women (between 55 and 75 years) (Key et al., 2001). This difference could be explained by the fact that Burkina Faso's population is characterized by its youth, with nearly 80% of the population under the age of 35, according to a study published in 2020 by the National Institute of Statistics and Demography (Institut national de la statistique et de la démographie, 2020).

The distribution by origin clearly shows that the majority of women in our study population came from urban areas. These results could be explained not only by the fact that in urban areas there is more exposure to breast cancer risk factors than in rural areas, but also by the fact that our data collection was carried out in an urban area (Ouagadougou). The results of our study also showed that the majority of cases were housewives with a proportion of 40% compared to 18% in the controls. This result is similar to that of other study in 2017 in Burkina Faso (Bambara et al., 2017), and in Ivory Coast in 2021 (Aka et al., 2021). This could be explained by the regular use of carcinogens and endocrine disruptors by these housewives in their various tasks (cooking, cleaning, etc.).

Family history of breast cancer was not associated with the occurrence of breast cancer in our study. This finding is inconsistent with several studies that have found an association between family history of breast cancer and the occurrence of breast cancer (Antoniou et al., 2003; Economopoulou et al., 2015). This may be due to the relatively small size of our sample and also to information bias due to participants' information.

4.2 | *ERCC1rs3212986, ERCC2rs1799793, ERCC2rs13181* polymorphisms, and breast cancer risk factors

Genetic analysis of the study population showed first that the different genotypes and alleles in the sample were in

TABLE 4 Association between menopausal status, family history of patients/age at diagnosis and the genotypes of the three polymorphisms using multivariable logistic regression

	Pre-menopausal			
Genotypes	**Cases (%)**	**Controls (%)**	**OR (95% IC)**	***p* value**
ERCC1rs3212986				
CC	5 (18.52)	10 (19.61)	–	Reference
CA	13 (48.15)	27 (52.94)	0.99 [0.90–1.10]	0.980
AA	9 (33.33)	14 (27.45)	0.98 [0.88–1.08]	0.731
ERCC2rs1799793				
GG	10 (30.04)	17 (33.33)	–	Reference
GA	17 (62.96)	31 (60.78)	0.98 [0.91–1.06]	0.787
AA	0 (0.00)	3 (5.89)	NA	NA
ERCC2rs13181				
AA	19 (70.37)	46 (90.20)	–	Reference
AC	8 (29.63)	5 (9.80)	1.69 [0.53–5.39]	0.374
CC	0 (0.00)	0 (0.00)	NA	NA
Post-menopausal				
ERCC1rs3212986				
CC	6 (16.22)	6 (46.15)	–	Reference
CA	16 (43.24)	4 (30.77)	1.40 (0.82–2.32)	0.738
AA	15 (40.54)	3 (23.08)	0.15 (0.88–1.09)	0.749
ERCC2rs1799793				
GG	11 (29.73)	5 (38.46)	–	Reference
GA	20 (54.05)	8 (61.54)	1.13 (0.29–4.33)	0.876
AA	6 (16.22)	0 (00.00)	NA	NA
ERCC2rs13181				
AA	27 (72.97)	10 (76.92)	–	Reference
AC	10 (27.03)	3 (23.08)	0.59 (0.18–1.88)	0.373
CC	0 (0.00)	0 (0.00)	NA	NA
	Family history			
Genotypes	**Yes (%)**	**No (%)**	**OR (95% IC)**	***p* value**
ERCC1rs3212986				
CC	8 (38.10)	19 (17.75)	–	Reference
CA	10 (47.62)	50 (46.72)	0.47 (0.16–1.38)	0.172
AA	3 (14.28)	38 (35.51)	2.53 (0.65–1.09)	0.180
ERCC2rs1799793				
GG	9 (42.86)	34 (31.78)	–	Reference
GA	12 (57.14)	64 (59.81)	0.70 (0.27–1.72)	0.480
AA	0 (0.00)	9 (8.41)	NA	NA
ERCC2rs13181				
AA	17 (80.95)	85 (79.44)	–	Reference
AC	4 (19.05)	22 (20.56)	0.90 (0.27–2.97)	0.909
CC	(0.00)	0 (0.00)	NA	NA

TABLE 4 (Continued)

Genotypes	Age at diagnostic (years)		OR (95% IC)	*p* value
	Before 40 years	After 40 years		
ERCC1rs3212986				
CC	4 (19.05)	7 (16.28)	–	Reference
CA	11 (52.38)	18 (41.86)	0.94 (0.22–3.94)	0.927
AA	6 (28.57)	18 (41.86)	1.72 (0.36–7.97)	0.492
ERCC2rs1799793				
GG	7 (33.33)	14 (32.56)	–	Reference
GA	14 (66.67)	23 (53.49)	0 0.82 (0.27–2.53)	0.732
AA	0 (0.00)	6 (13.95)	NA	NA
ERCC2rs13181				
AA	17 (80.95)	29 (67.44)	–	Reference
AC	4 (19.05)	14 (32.56)	2.05 (0.58–7.25)	0.264
CC	0 (0.00)	0 (0.00)	NA	NA

Abbreviations: CI, Confidence interval; NA, Not applicable; OR, Odds ratio; *p*, Statistical significance.

TABLE 5 Analysis of combined genotypes

	ERCC2rs13181											
	AA				**AC**				**CC**			
	C	**T**			**C**	**T**			**C**	**T**		
ERCC1 rs3212986	**n**	**N**	**OR (95% IC)**	***p***	**n**	**n**	**OR (95% IC)**	***p***	**n**	**n**	**OR (95% IC)**	***p***
CC	6	13	–	Ref	5	3	3.61(0.64–20.32)	0.135	0	0	NA	NA
CA	21	29	1.57 (0.51–4.80)	0.428	8	2	2.4 (0.29–19.78)	0.608	0	0	NA	NA
AA	19	14	2.94 (0.90–9.65)	0.071	5	3	1.0 (0.13–7.57)	1.00	0	0	NA	NA
	ERCC2rs1799793											
	GG				**GA**				**AA**			
	C	**T**			**C**	**T**			**C**	**T**		
	n	**N**	**OR (95% IC)**	***p***	**n**	**n**	**OR (95% IC)**	***p***	**n**	**n**	**OR (95% IC)**	***p***
ERCC1 rs3212986												
CC	8	4	–	Ref	5	8	0.31 (0.06–1.61)	0.158	2	0	NA	NA
CA	9	10	2.22 (0.50–9.96)	0.293	18	21	1.37 (0.38–4.94)	0.629	1	1	0.5 (0.02–10.25)	1.00
AA	5	7	2.80 (0.53–14.74)	0.219	14	10	2.24 (0.56–8.91)	0.313	3	2	0.75 (0.08–6.64	0.895
ERCC2 rs13181												
AA	15	18	–	Ref	56	35	1.92 (0.85–4.29)	0.106	3	5	0.72 (0.14–3.51)	0.684
AC	6	4	1.80 (0.43–7.59)	0.656	11	4	1.72 (0.51–5.82)	0.380	0	1	NA	NA
CC	0	0	NA	NA	0	0	NA	NA	0	0	NA	NA

Abbreviations: C, Cases; CI, Confidence interval; *n*, Number; NA, Not applicable; OR, Odds ratio; *p*, Statistical significance; Ref, Reference; T, Controls.

Hardy–Weinberg equilibrium in both cases and controls ($p > .05$) for all three polymorphisms except the control group for the *ERCC2rs1799793* polymorphism. Indeed, the Hardy–Weinberg principle states that within a population, allelic, and genotypic frequencies remain constant from one generation to the next (Hartl & Clark, 2017). Thus, it is possible to believe that the genotypic and allelic distribution of the three polymorphisms of the study within our sample represents that of the population of Burkina Faso.

In the present study, the results of the association analysis indicated that the *ERCC1rs3212986* (C8092A)

polymorphism was not associated with breast cancer risk in the study population ($p > .05$). The same result was reported in the Taiwanese population in 2018 (Tsai et al., 2018), Chinese in 2013 (Yang et al., 2013), and American in 2006 (Shen et al., 2006). In contrast, a case–control study (872 cases and 671 controls) conducted by Lee et al. in the Korean population indicated that the AA mutant genotype of the polymorphism is associated with a risk of breast cancer (Lee et al., 2005). In addition, Crew et al. reported an association between the CA genotype of the polymorphism and breast cancer in the U.S. population (OR = 1.09, 95% IC (0.92–1.30), $p < .05$) after a study of 1053 cases and 1102 controls in the U.S. (Crew et al., 2007). All of these results suggest that ethnicity, patient selection, and/or sample size should be considered.

In addition, the *ERCC2rs1799793* (Asp312Asn) polymorphism showed no association between the Asp312Asn polymorphism of the *ERCC2* gene and the risk of CRC occurrence in the study population. These results are corroborated by previous studies in various populations: Portuguese (Costa et al., 2007), Chinese (Wang et al., 2014), and Australian (Dębniak et al., 2006). However, the results were not unanimous because other studies reported a significant association between the mutated A allele of this polymorphism and the occurrence of breast cancer, notably those conducted on the Russian population (OR = 1.43, 95% IC (1.02–2.0), $p = .04$) (Shadrina et al., 2016), Mexican (OR = 9, 00, 95% IC (1.10–73.50), $p = .04$) (Gómez-Díaz et al., 2015), and Egyptian (OR = 3.5, 95% IC (1.5–8.3), $p = .003$) (Hussien et al., 2012). Paradoxically, a meta-analysis of 9010 breast cancer cases and 9873 controls reported a protective effect of genotype (AA) in the Asian population under the recessive model (OR = 0.53, 95% IC (0.32–0.90), $p = .02$) (Jiang et al., 2010). These results suggest, once again, a possible role of environment, ethnic differences, and variable genetic background in the development of breast cancer.

Finally, concerning the *ERCC2rs13181* (Lys751Gln) polymorphism of the *ERCC2* gene, several studies have been carried out regarding its possible involvement in the susceptibility to develop several cancers including breast cancer. It is in this perspective that we have researched the involvement or not of this polymorphism in the appearance of breast cancer in the population of Burkina Faso. Thus, after association analysis, our results revealed that the AC genotype of the rs13181 (Lys751Gln) polymorphism was associated with the occurrence of breast cancer (OR = 2.74, 95% IC (1.09–6.87), $p = .028$), but this association became insignificant after Bonferroni correction ($p = .156$). Our results are similar to those obtained by Pabalan et al. (2010) in this meta-analysis, which found that the AC heterozygote was involved in the development of breast cancer in the African-American population, when the mutant allele was under the dominant pattern (CC/AC vs AA, OR = 1.25, 95% IC (1.03–1.53), $p = .003$) (Pabalan et al., 2010). In 2014, another meta-analysis by Yan et al. reached the same conclusion in the Caucasian population (CC/AC vs. AA, OR = 1.07, 95% IC (1.02–1.12), $p = .005$) (Yan et al., 2014). Also, a statistically significant association was observed between this polymorphism and the occurrence of breast cancer in Polish populations (OR = 3.72, 95% IC (2.44–5.68), $p < .005$) (Smolarz et al., 2019). On the contrary, other studies reported no evidence of association between Portuguese (Costa et al., 2007), Brazilian (Dufloth et al., 2005), Chinese (Zhao & Ying, 2016), and Moroccan populations (Hardi et al., 2018). In the same vein, a Case/Control study (464 cases and 450 controls) conducted by Rajagopal et al. (2020) on the Indian population showed no association between the ERCC2rs13181 (Lys751Gln) polymorphism and breast cancer risk. Furthermore, according to the study, the AA genotype conferred a significant protective effect against the development of triple-negative tumors (OR = 0.49, 95% IC (0.26–0.92), $p = .026$) (Rajagopal et al., 2020). All of these studies suggest that ethnicity, sample characteristics, and environmental factors that interact with this variant should be considered in the analysis of outcomes.

4.3 | Association between selected population characteristics and gene expression of polymorphisms (*ERCC1rs3212986, ERCC2rs1799793, ERCC2rs13181*)

Our results suggest that no association was recorded between the different genotypes of the polymorphisms and menopausal status, family history, and age at diagnosis in our study population after multivariable logistic analysis.

Several studies had shown that menopausal status (pre-menopausal and post-menopausal) was associated with these polymorphisms in the occurrence of breast cancer. In a study conducted in the Indian population in 2010, Samson et al. had shown that the ERCC2rs13181 polymorphism was significantly associated with an increased risk of breast cancer (OR = 1.75 95% CI = 1.02–2.80), especially in premenopausal patients (OR = 2.6 95% CI = 1.33–4.79) (Samson et al., 2011). The likely hypothesis is that this category of patients is constantly exposed to steroid hormones and carcinogens acting on the breast cells. This exposure can initiate tumorigenesis by causing DNA damage. This damage can alter DNA repair genes, thereby reducing the quality of repair mechanisms, thereby increasing the risk of breast cancer. Also, in a case–control study (872 cases and 671 controls) conducted

by Lee et al. in the Korean population, the AA mutant genotype of the *ERCC1*rs3212986 polymorphism was associated with a risk of breast cancer in premenopausal women (Lee et al., 2005).

Regarding the family history of breast cancer and the age at diagnosis of patients, our results agree with those of a study performed by Hardi et al. (2018) in the Moroccan population. In this case–control study (151 cases/156 controls), no relationship was found between polymorphisms (*ERCC2rs1799793*, *ERCC2rs13181*) and age at diagnosis and family history of breast cancer (Hardi et al., 2018).

4.4 | Combined effects of genotypes and breast cancer risk

Generally, although the effect of a single SNP is small to implicate a pathology, it is thought that the genetic effect of combination of relevant functioning SNPs may contribute additively or synergistically to the risk of developing a pathology. Thus, in our study, we investigated the combination of different genotypes of the three polymorphisms. No significant association was found between these combined genotypes and the risk of breast cancer. With regard to the association between the genotypes of the *ERCC2rs1799793/ERCC2rs13181* polymorphisms and breast cancer, our results do not agree with those found by Dabniak et al. Indeed, in their study, the association of the *ERCC2rs1799793* (AA) and *ERCC2rs13181* (CC) genotypes was involved in the occurrence of breast cancer (OR = 1.5 and $p = .016$) (Dębniak et al., 2006). To our knowledge, there are no previous studies available regarding the association between the *ERCC1rs3212986/ERCC2rs1799793* and *ERCC1rs3212986/ERCC2rs13181* polymorphisms in breast cancer. The lack of association between the combined genotypes of the polymorphisms may be justified by the relatively small sample size that influences the statistical power. Indeed, the larger the sample size, the greater the power of the study, which allows the detection of the effects of rarer risk genotypes.

4.5 | Limitations of our study

The limitations of our study were not only the small size of our sample but also and above all, the information bias that occurred during the collection of information. Thus, it would be necessary to conduct another study with a larger sample size in order to accurately assess the impact of these repair genes on the development of breast cancer in Burkina Faso.

5 | CONCLUSION

Our study is the first to investigate the likely links between DNA repair genes and breast cancer in Burkina Faso. It assessed the possible involvement of polymorphisms of the DNA repair genes *ERCC1* (*rs3212986*) and *ERCC2* (*rs1799793, rs13181*) in the occurrence of breast cancer in our population. The mutant AC genotype of the *ERCC2rs13181* polymorphism was associated with the occurrence of breast cancer when the mutation was under the dominant genetic pattern, especially in premenopausal women but this association was insignificant after Bonferroni's correction.

AUTHOR CONTRIBUTIONS

Abdou Azaque Zouré was involved in the study design, data analysis, and manuscript drafting. Marc Donald Wilfried Adico was involved in the study design, data collection, manipulation, and drafting and revising the manuscript for intellectual content. Hermann Karim Sombié was involved in the statistical analysis and revising the manuscript for intellectual content. Touwendpoulimdé Isabelle KIENDREBEOGO was involved in the data collection and analysis of the data and revising the manuscript for intellectual content. Soayebo Dabré was involved in data analysis and drafting and revising the manuscript. Lanyo Jospin Amegnona was involved in data collection, the manipulation, and revising the manuscript. Bélélé Siméon Bakyono was involved in data collection, the manipulation, and revising the manuscript. Lassina Traoré was involved in data collection and revising the manuscript. Teega-Wendé Clarisse Ouedraogo was involved in the manipulation and revising the manuscript. Rogomenoma Alice Ouedraogo was involved in the manipulation and revising the manuscript. Théodora M. Zohoncon was involved in the supervision of the data and samples collection and revising the manuscript. Albert Théophane Yonli was involved in the supervision manipulation and revising the manuscript. Bagora Bayala was involved in the supervision in the manipulation and revising the manuscript. Aboubacar Hierrhum Bambara was involved in the supervision of samples collection and revising the manuscript. Florencia W. DJIGMA was involved in the supervision of the statistical analysis and revising the manuscript. Jacques SIMPORE was involved in the supervision of all aspects of this study and revising the manuscript. All authors have read, edited, and approved the final manuscript.

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CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data of this study are available on request from the corresponding author.

ETHICS STATEMENT

Our study obtained approval from the Health Research Ethics Committee (CERS) of Burkina Faso (Deliberation No. 2019-5-067 of May 15, 2019).

INFORMED CONSENT

The participants gave their free and informed consent. Every effort was made to preserve not only the privacy but also the confidentiality, dignity, and honor of the patients.

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