Mutations in exon 11 (11.1 and 11.2) of the *BRCA1* gene and risk factors for breast cancer in Burkina Faso

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Abstract

Breast cancer is the leading cause of death among women in both developed and developing countries. It is multifactorial, including genetic predispositions such as oncogenic mutations on *BRCA1* and 2 genes. The objectives of the present study were to identify oncogenic mutations in exon 11 of the *BRCA1* gene and to determine the risk factors for breast cancer among women population in Burkina Faso.

This study involved 100 women, including 50 cases of breast cancer and 50 controls (no clinical signs and no family history of breast cancer or other cancers). Mutations in the *BRCA1* gene were detected by PCR using sequence primers specific for exon 11 fragments (11.1 and 11.2).

In our study population, age (OR=22.40; CI: 4.33-115.82; p<0.001) and obesity (OR=4.23; CI: 1.64-10.92; p=0.003) were risk factors while multiparity was a protective factor for breast cancer (OR=0.35; CI: 0.15-0.81; p=0.02). A mutation was found on both fragments 11.1 and 11.2 of the *BRCA1* gene exon 11 in 04/50 (8.0 %) of patients. No mutations were observed in controls.

The present study revealed high frequency of oncogenic mutations in exon 11 fragments (11.1 and 11.2) of the *BRCA1* gene. These mutations on exon 11 are and involved in the occurrence of breast cancer in our population. Age and obesity were also risk factors for breast cancer among women population in Burkina Faso.

Introduction

Breast cancer is the leading cancer in women in both developed and developing countries.[1] It is the most frequently diagnosed heterogeneous disease and the leading cause of death in women through the world.[2] According to GLOBOCAN, the global cancer burden is now estimated at 19.3 million new cases and 10.0 million deaths in 2020.[3] In West Africa, especially in Burkina Faso, few studies related to breast cancer have been carried out. Cancer in general and breast cancer remain a public health problem in the world and in Burkina Faso. Breast cancer is the most common cause of cancer death among women in Burkina Faso.[4]

Several factors including environmental, hormonal and viral factors appear to be important in the mechanism of risk factors.[2] However, no factor could be directly involved in the etiopathogenesis of breast cancer, with the exception of the hereditary transmission of some predisposition genes such as the *BRCA1* genes (Breast Cancer gene 1), *BRCA2* (Breast Cancer gene 2), *CHEK2*, *TP53*, *ATM* and *PTEN*.[5]

Between 5 and 10% of breast cancers are hereditary and attributable to a genetic mutation.[6] Being a carrier of a mutation in one of your genes does not always mean the onset of cancer, but increases the risk of developing cancer, this is called a genetic predisposition.[7] Breast cancer usually affects women regardless ages and can rarely affect men. Research has identified numerous genetic mutations that promote the development of breast cancer. Most often, these relate to genes called *BRCA1* (Breast Cancer 1 corresponding to gene 1 for breast cancer) and *BRCA2* (Breast Cancer 2: gene 2 for breast cancer) which are involved in the maintenance of breast cancer genome integrity.[7,8] The *BRCA1* gene is a large gene located on the long arm

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Contributions: ITK, AAZ, FIZ, JS conceived and designed the study. ITK, FIZ, AAZ, AKO, JA, ATY, NZ, AHB, AYS, were involved in data generation, collection, and assembly. ITK, AAZ, AKO, FIZ, JA, BB, JS were involved in data extraction, analysis, and interpretation. ITK, AAZ, FIZ, AKO, MNLO, JA, ATY, BB, NZ, AHB, AYS, TMZ, DOY, JS were involved with drafting or revising the manuscript. ATY and JS provided administrative, technical, and material support. Supervision of the study was made by JS. All authors critically revised and approved the final version of this publication.

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(q) of chromosome 17 at band 21, between base pairs 38,449,843 and 38,530,933 (locus: 17q21.31), encoding 1683 amino acids. More than 500 mutations or sequence variations have already been described, and most often a mutation seems to be unique for each family.

Almost 90 % of families with autosomal dominant inheritance breast or ovarian cancer have a chromosomal abnormality in this region.[9] As for the *BRCA2* gene, isolated in 1995, it is located on chromosome 13q12-13 and has no homology with the *BRCA1* gene. More than 100 different mutations have been counted with few common mutations into different families.[10]

The exon 11 is the largest of the all the 22 exons of the BRCA1 gene and represents about 60% of the coding sequences (El Khachibi *et al*., 2015).

In line with such data and according to the high frequency of breast cancer in Burkina Faso, the present study was aimed at the investigation of mutations in exon 11 of *BRCA1* gene and determination of the breast cancer risk factors to improve the prevention strategy for this pathology in Burkina Faso.

Materials and Methods

Ethical considerations

Our study obtained the approval of the Ethics Committee for Health Research of Burkina Faso (CERS) (Deliberation n° 2019-5-067 of May 15, 2019). All participants or guardians of participants have given their free and informed consent. Respect for the confidentiality and anonymity of the information provided was essential. An information and consent form were given to each participant before the sample was taken.

Study population and sample collection

This cross-sectional case-control study was conducted between October 2019 and November 2020. One hundred (100) women were enrolled including 50 breast cancer patients and 50 healthy women (controls) seen at medical examination in University Hospital Center Yalgado Ouedraogo (CHU-YO) and Bogodogo (CHU-B) and medical centers such as Paul VI and Schiphra. Was considered as cases women with histologically confirmed breast cancer while controls were designated as women without breast pathology and no familial history of breast cancer seen at gynecological department, with normal mammograms and clinically declared healthy for breast cancer.

After obtaining the free and informed consent of the patients and guardians, a questionnaire was administered to collect the socio-demographic (age, ethic, profession, marital status, parity, abortion, contraception), anthropometric (BMI) data of the participants. Venous blood was collected from 2 mL EDTA (Ethylene-Diamine-Tetra-Acetic) tubes. After centrifugation at 1500 rpm for 15 minutes, the plasma and the pellet were separated and stored at -20°C at the Pietro Annigoni Biomolecular Research Center (CERBA).

Patients were recruited from among those under medical care in the cancer department and controls were recruited from among women attending the gynecology department.

The sample size was limited to 100 participants, given that the participants freely consented to the study and met the inclusion criteria, and that at the end of the collection period all the patients under medical care were interviewed.

Extraction of genomic DNA and characterization of mutations by classic PCR

Genomic DNA was extracted from the pellet using the "Rapid Salting Out" technique as described by Miller *et al*.[11] and store at -20°C until molecular analyses.

For the detection of mutations PCR was performed using the method described by Bashir, *et al*.[12] with GeneAmp® PCR System 9700 device (Applied Biosystem, USA). The total reaction volume was 50 µL including 30 µL of nuclease-free water, 10 µL of Green Buffer 5X (Promega Go Taq® G2 Flexi DNA polymerase REF: M7805, 1 µL of each forward and reverse primer (Table 1), 1 µL of 20 nM dNTPs (Promega REF: U1420), 0.25 µL of Go Taq 5X (Promega REF: M7805), 4µL of 25 mM Mgcl2 (Promega REF: M7805) and 2.75 µL of 80 µg/ml of DNA. Primers sequences were described elsewhere.[13] The amplification program of exon 11.1 and exon 11.2 of the BRCA1 gene consisted of an activation step at 94°C for 5 minutes, followed by 35 cycles of denaturation at 94°C for 60 seconds, hybridization at 57°C for 60 seconds, and extension at 72°C for 60 seconds. Final extension was performed at 72°C for 7 minutes. The PCR products were electrophoresed on a 2% agarose gel and visualized under UV light at 312 nm using the GeneFlash revealing device.

Statistical analyzes

Study data was entered into Excel 2013 and processed with Statistical Package for the Social Sciences (SPSS) version 21. Results were considered statistically significant at $p \leq 0.05$, using Fisher's exact test. The Odd Ratio (OR) and 95 % confidence intervals (CI) were calculated to estimate associations between cases and controls using Epi Info version 7.1.

Results

Amplification of β-globin gene (the internal control) was required for PCR validation and the results were invalid in the absence of the β-globin band (268 bp). The presence of band corresponding to *BRCA1* gene (239 and/or 278 bp) stand for wild-type sample while its absence defined a mutant sample (Figure 1).

Sociodemographic and clinical characteristics of the study population

Tables 2 and 3 show the socio-demographic and clinical distribution of the study population. The study population consisted of 100 women, including 50 cases with breast cancer and 50 controls without breast cancer. The mean age in cases and controls was 49.44 ± 11.40 years and 36.34 ± 10.77 years, respectively ranging from 24 to 73 years for cases and 21 to 65 for controls. The predominant age group among cases was over 45 (64%) *versus* 30 to 45 (52%) among controls. In terms of age there was a significant difference between cases and controls ($p<0.001$) and 18% of patients had at least one abortion. The age of onset of menarche, less than 15 years, was observed in 30%. In addition, 5% of cases were postmenopausal. Like obesity, age was also risk factors for breast cancer (OR=22, 40, CI: 4.33-115, 82, $p<0.001$) in the present study.

Table 1. Specific primers for amplification of BRCA1 gene (Mills *et al.*, 2012).

Exon	DNA sequences	Amplicon sizes (base pair)
Exon 11.1	F: AGAGGCATCCAGAAAAGTATCAGG R1: GGGAGTCCGCCTATCATTACAT	239
Exon 11.2	F: ACAGCCTGGCTTAGCAAGGAG R2: CCCCATCATGTGAGTCATCAGA	278
β-Globin	F: CAACTTCATCCACGTTCACC R: GAAGAGCCAAGGACAGGTAC	268

Treatments received by patients

Among the 50 cases, the right breast cancer accounted for 52%. No cases of bilateral cancer have been reported. Of the cases, 38 or 76% received chemotherapy, 20 or 40% radiotherapy, 19 or 38% received both treatments (chemotherapy and radiotherapy) and 11 patients or 22% received no treatment. Also, breast surgery was performed in 94% of cases.

Family history of breast and other cancers

In the present study, a family history of cancer was found in 32% of the cases, including 14% with breast cancer, 14% with other types of cancer (cancers of the cervix, bladder, vulva, colon, liver, prostate), and 4% with breast and other types of cancers as presented in Figure 2.

Genetic characteristics of the study population

In this study, no mutations were found in the exon 11 locus (11.1 and 11.2) in 46/50 (92.0 %) of patients. In contrast, four (04) patients had (8.0%) mutations at exon 11 (11.1 and 11.2). Furthermore, no mutation of the fragments of exon 11 (11.1 and 11.2) was detected in the controls.

Association between multiparity and other risk factors in cases

Multiparity (≥ 2 childbirth) is considered as protective factor for breast cancer (Zouré *et al.*, 2016). In the present study population, the multiparous women accounted for 74 % of cases against 26 % of non-multiparous.

Epidemiological characteristics of multiparous cases (37) and non-multiparous cases (13)

In our study 91.43% of multiparous cases and 42.86% of non-multiparous cases were over 40 years of age at the time of diagnosis with a significant difference (OR: 14.2, CI (2.90-69.58,) p<0.001).

The mean age in multiparous and non-multiparous cases was 52.23 ± 10.26 years and 41.76 ± 11.35 years respectively with age ranging from 28 to 73 years for multiparous and 24 to 66 for non-multiparous women. The majority age group among the multiparous was over 45 years (75.70%) while it was 30 to 45 years in non-multiparous (61.50%).

Married women were estimated at 94.60 % among multiparous and 23.10% among non-multiparous with a significant difference (OR=58.33; CI: 8.53-398.80; p<0.001). In addition, 89.20% of multiparous cases and 100% of non-multiparous

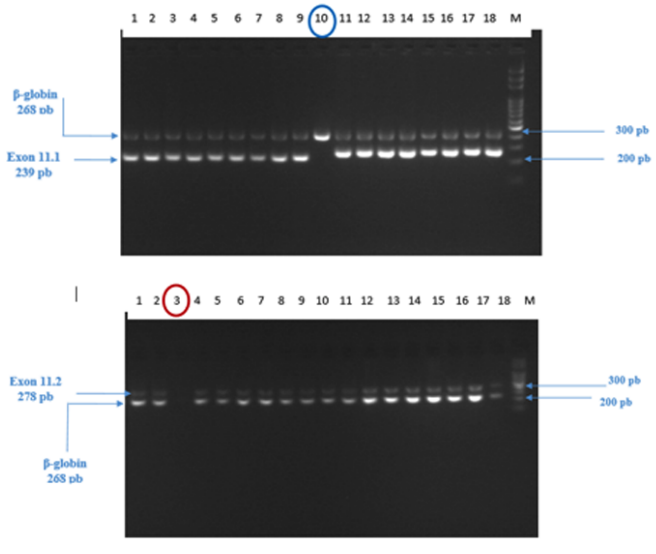
Table 2. Sociodemographic characteristics of the study population.

Characteristics	Cases n = 50		Controls n = 50	
	n	%	n	%
Age, year				
<30	2	4	14	28
30-45	16	32	26	52
>45	32	64	10	20
Ethnic group				
Mossi	28	56	43	86
Others	22	44	7	14
Profession				
Pupils/Students	3	6	12	24
Civil servant	25	50	20	40
Housewife/informal sector	22	44	18	36
Marital status				
Single	12	24	17	34
Married	33	66	32	64
Widow	5	10	1	2
Residence				
Rural	4	8	2	4
Urban	46	92	48	96

Table 3. Anthropometric and other characteristics of the study population.

Characteristics	Cases n=50 (%)	Controls n=50 (%)	OR	p-value
BMI (kg/m²)				
< 25	17 (34)	30 (60)	Ref	-
25 ≤ IMC ≤ 29.9	9 (18)	10 (20)	1.55 (0.53 - 4.67)	0.4
≥30	24 (48)	10 (20)	4.23 (1.64 - 10.92)	0.003
Parity				
Multiparous	37 (74)	25 (50)	Ref	-
Non multiparous	13 (26)	25 (50)	0.35 (0.15 - 0.81)	0.02
Contraception				
Yes	33 (66)	37 (74)	Ref	-
No	17 (34)	13 (26)	1.42(0.61 - 3.46)	0.51

OR: Odds ratio; CI: Confidence Interval; p: p- value; Ref: Reference.



M = Molecular weight marker 100 - 1000 pb.
: No amplification of exon 11.1 (mutant gene)
: Absence of amplification of β-globin and exon 11.2 (invalid result)
1-9, 11-18: Presence of exons 11.1 amplification wild-type gene)
1-2, 4-18: Presence of exons 11.2 amplification (wild-type gene)

Figure 1. Electrophoresis gel under UV showing exons.

cases lived in urban areas. Obesity was noted in 54.10% of multiparous cases and 30.80% of non-multiparous cases.

No statistically significant difference was found (OR=0.36; CI: 0.08-1.58; p=0.26). Contraception was observed in 38.00% of multiparous cases and 23.00% in non-multiparous women. No statistically significant difference was found (p=0.49).

Abortion was noted in 21.6% of multiparous cases and 7.7% of non-multiparous cases. No significant difference was observed (OR=0.30; CI: 0.03-2.68; p=0.41). Age at menarche before 15 years was noted in 24.3% of multiparous cases and 46.1% of non-multiparous cases. The results of these observations thus noted are shown in Table 4.

Family history of multiparous and non-multiparous cases

Among the multiparous cases, those with a family history of breast cancer were 3 patients or 8.1 % and other cancers accounted for 21.62%. In non-multiparous cases 04 patients (30.8%) had a family history of breast cancer.

Discussion

The objective of this study was to characterize mutations in the *BRCA1* gene of breast cancer in Burkinabe women. Once considered as disease of older women, breast cancer is increasingly occurring in young women.[14] Our study population is marked by its youth with 58% of women less than 45 years. Thus, we recruited 100 women aged between 21 and 73 years with an average of 49.44 years and 36.34 years respectively for the cases and the controls. The average age of the cases is comparable to that found in 2018 in Burkina Faso, *i.e.* 48.20 ± 12.4 years,[15] proving once again that breast cancer is increasingly affecting the young population. It is well known that age is a risk factor for breast cancer.[16] In the present study 64 % of cases were over 45 years old.

Rural and urban settings

Environmental factors play a very important role in influencing the onset of breast cancer such as geographic region and type of activity. This could be explained by the westernized way of life and the level of exposure to the environment, that urban areas are increasingly polluted compared to rural ones. The type of activity performed by women, such as the use of a toxic carcinogen, for example, could play a role in the occurrence of breast cancer. An association was found between professional activity and the occurrence of breast cancer in our study. A study on women at risk shows that professionally active women are the most exposed.[17] The highest frequency of breast cancer was found in patients living in urban areas, *i.e.*, 92%, probably because the samples were collected in Ouagadougou, an urban area.

Parity

Age at menarche, age at first pregnancy, parity, time elapsed between the age of first menstruation and first pregnancy in young women have been studied.[18]

Indeed, the early onset of the first period and advanced age at the first pregnancy induce a risk of breast cancer in women under 40 years of age.[18] In our study we noted an average age at menarche of 15 years. Our results are in agreement with those of other countries with a mean age of 12.8 years in France and 13.7 years in Morocco,[19] all ≤ 15 years.

This factor is believed to be associated with the duration of exposure to estrogen in women.[20] However, no association has been found in our population. Furthermore, multiparous cases were in the majority compared to non-multiparous cases in our study and a significant association was found

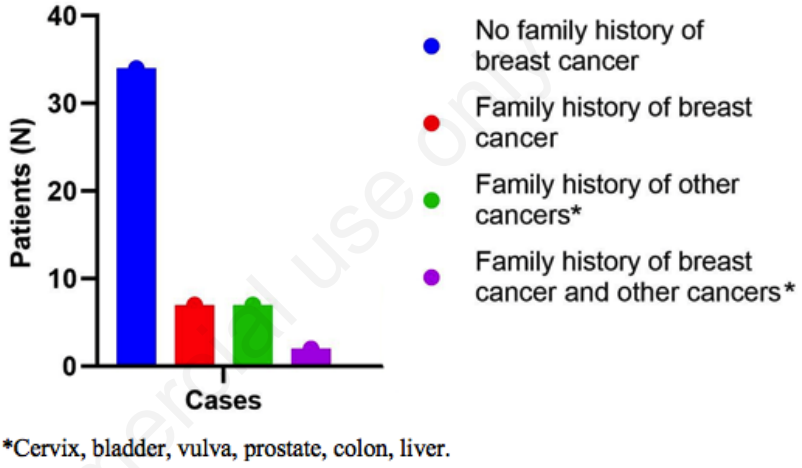


Figure 2. Family history of breast cancer in cases.

Table 4. Epidemiological characteristics of multiparous and non-multiparous cases.

Characteristics n = 37 (%)	Multiparous n = 13 (%)	Non multiparous	OR	p-value
Age, year				
< 30	1(2.7)	1(7.7)	Ref	-
30 - 45	8 (21.6)	8 (61.5)	1 (0.05-18.91)	1
> 45	28 (75.7)	4 (30.8)	0.14 (0.007-2.76)	0.27
BMI (kg/m²)				
< 25	11(29.7)	6 (46.1)	Ref	-
25 ≤ BMI ≤ 29.9	6 (16.2)	3 (23.1)	0.91 (0.16-5.04)	1
≥ 30	20 (54.1)	4 (30.8)	0.36 (0.08-1.58)	0.26
Abortion				
Non	29 (78.4)	12 (92.3)	Ref	-
Yes	8 (21.6)	1(7.7)	0.30 (0.03-2.68)	0.41
Contraception				
Non	23 (62)	10 (77)	Ref	-
Yes	14 (38)	3 (23)	0.49 (0.11-2.10)	0.49
Social status				
Single	2 (5.4)	10 (76.9)	58.33 (8.53-398.80)	< 0.001
Married	35 (94.6)	3 (23.1)	Ref	-
Residence				
Rural	4 (10.8)	0 (0)	Ref	-
Urban	33 (89.2)	13 (100)	-	-

OR: Odd ratio; CI: Confidence interval; p: p- value; Ref: Reference.

(OR=0.35, CI: 0.15-0.8, p=0.02). Multiparity is considered a protective effect by some authors,[21] and this protective effect seems to increase in proportion to the number of deliveries.

In fact, women who have had seven or more deliveries have a reduced risk of about 30%, compared to those who have had fewer.[18,22] Unfortunately this protective effect is zero after menopause thus leading to an increased risk of breast cancer.[21] In our population women with seven or more children represented 4%. Other factors come into play in the occurrence of breast and that multiparity alone is not enough to protect women against this scourge.

Contraception

Oral contraception is now standard practice in the way of life of women around the world.[19] In our study, we have 34% of cases who have already used oral contraceptives, which is less than in the controls. A study in Burkina Faso found 36.27% who used oral contraceptives.[21] No association was found between taking oral contraception and the occurrence of breast in our study.

Menopause

An advanced age at menopause has often been described as increasing the risk of breast cancer.[23] In general, menopause is observed between 45 and 55 years old.

Women with menopause after age 55 have a 50% risk of developing breast cancer, conversely, women with menopause aged 45 or before have a 30% lower risk of breast cancer.[23] In our study, 2.8 of the cases had menopause before age 50 and 24% after age 50. No association was found between the menopausal situation and breast.

This could be explained by the youth of our study population, the majority of whom were not postmenopausal.

Obesity

In our study 64% of the cases were obese, *i.e.,* more than in the controls (20%). Among the obese cases 26% were of menopausal age. Obesity (body mass index $\geq$ 30 kg/m^2) is believed to be a protective factor in pre-menopausal women, it increases the risk in post-menopausal women.[24]

In some pre-menopausal women, excess fatty tissue is thought to cause ovulation to malfunction and thus reduce the rate of estrogen circulation in the blood. On the other hand, in postmenopausal women, the increased risk is explained by a continuous circulation of the level of estrogen in the blood.[24] In our study, an association was found between obesity and breast cancer (OR=4, 23, CI: 1.64-10, 92, p=0.003). Interestingly, 64% of cases were over 45 years, mean age for menopause in women.

Family history and genetic characteristics

Family history is consistently associated with an increased risk of breast cancer.[25] The relative risk for any form of parentage is approximately 1.9 and the risk is greater in younger women and when the disease has developed in a close relative (mother, daughter or sister), before age 50 years old.[18] In Western countries, about 13% of breast cancer patients have a family history of kinship.[25]

In our study, 32% of cases have at least one member of their family already affected by breast cancer or another type of cancer. In addition, certain genetic mutations can increase the risk of breast cancer. Two genes, *BRCA1* and *BCRA2*, seem to be the most involved.[5]

Compared to the general population, women with mutations in these genes have an increased risk of breast cancer.[18] In our study, the *BRCA1* gene was analyzed for the presence of mutations at exon 11 (exon 11.1 and 11.2). A mutation to exon 11 (11.1 and 11.2) was noted in 8% of cases. Thus, to determine the type of mutation, sequencing will be necessary. Our results are comparable to those found in a Sudanese population of 03 patients or 18.7% of their population who carried a *BRCA1* mutation located at exon 1 (11.1).[13] Another study carried out in Morocco found in its population respectively 07 (32.6 %) young patients (age $\leq$ 45 years) of which 6 had a family history of breast cancer and 01 sporadic case, all carriers of the *BRCA1* mutation located at the level exon 11.[26] In the study conducted by Zouré *et al* (2018) in Burkina Faso on the c.68_69delAG (exon2), c.181T> G (exon5), c.798_799delTT and 943ins10 (exon11) mutations of the BRCA1 gene, no carrier has been found. Our results will be more appreciable with a larger sample size in Burkina Faso.

Study's limitation

One limitation of our study is the small size of our study population. For this point, it should be emphasized that it was very difficult to collect the cases because the participants freely consented and that at the end of the collection period all the patients under medical care were interviewed. The other is that, we did not perform sequencing to confirm and classify pathogenic mutations. This is due to the lack of financial resources in a developing country context.

Conclusions

This study has shown the involvement of genetic factors including mutations of exon 11 (11.1 and 11.2) of the *BRCA1* gene in the occurrence of breast cancer in Burkina Faso. Age and obesity were found to be a factor that increase the risk of developing breast cancer in the study population. However, it has been found that multiparity is a protective factor. This PCR screening technique, used in this study, makes it possible to make an early diagnosis of cancer as part of the prevention and effective monitoring of carriers of these oncogenic mutations. Combining this PCR technique with further DNA sequencing could be useful for early diagnosis of breast cancer in Burkina Faso.

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