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Patients' characteristics, Cytochrome P4501A1 genetic polymorphisms and breast cancer risk in Sudanese women

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Background: The CYP1A1 catalyses polycyclic aromatic hydrocarbons activation to reactive metabolites, causing deoxyribonucleic acid (DNA) damage and cancer. It is highly polymorphic and displays ethnic differences in various populations.

Aim: To evaluate the association of three polymorphic variants in the CYP1A1 gene with breast cancer in Sudanese women.

Setting: This is a case-control study.

Methods: After consenting, the participants completed questionnaires consisting of sociodemographic data, gynaecological status, and breast cancer history. We recorded clinical data, weight, and height for each woman and drew blood for PCR and RFLP analyses for CYP1A1 genotyping.

Results: The CYP1A1 M1 and CYP1A1 M3 genotypes and homozygous CYP1A1 M1 (C/C) and CYP1A1 M3 (C/C) genotypes are not associated with breast cancer risk and menopausal status in women. The homozygous CYP1A1 M2 (A/A) genotype had a significant association with a risk reduction of breast cancer in premenopausal women. In contrast, the heterozygous CYP1A1 M2 (A/G) and the homozygous (G/G) are associated with significant breast cancer risk.

Conclusion: Despite the limitations encountered in this study that included the small sample size and availability of age-matched controls, the results suggest that the CYP1A1 M2 polymorphism, educational level, and family history of breast cancer may have an association with the risk of developing breast cancer amongst Sudanese women and warrant confirmation in more extensive studies.

Keywords: breast cancer; CYP1A1 gene; polymorphisms; genotype; premenopausal; postmenopausal; Sudan; risk factors; education.

Introduction

Breast cancer is the leading cause of cancer death in women worldwide, accounting for 23% (1.38 million) of the total new cancer cases and 14% (458 400) of the total cancer deaths in 2008.[1] The incidence rates are higher in developed countries.[2] In Africa, breast cancer has overtaken cervical cancer as the most common malignancy affecting women, and the incidence rates appear to be rising.[3] Although accurate figures regarding the incidence of cancer in Sudan are not available, cancer has emerged as one of the significant health problems.[4] Breast cancer is the most common hospital treated malignancy, accounting for about one-fifth of all cancers in females. In the Radiation and Isotope Center in Khartoum and the Institute of Nuclear Medicine, Molecular Biology and Oncology (INMO) at Gezira University located in Wad-Madani in Al-Gezira State, 17% (2395/13 924) breast cancer patients from all oncology patients and 21% (732/3547) of breast cancer, respectively, were seen in each institution.[5,6,7] In Sudan, as in the other developing countries, the primary breast cancer risk factors are those associated with urbanisation and economic development, such as earlier menarche, later childbearing, having fewer children, and obesity.[8] However, the exposure to environmental carcinogens may vary according to social, ethnic, geographic, and occupational factors and may play a role in breast cancer risk in Sudan.

Cytochrome P-4501A1 (CYP1A1) is one of the three-cytochrome P450 family members. It is the critical enzyme in phase I bio-activation of xenobiotics.[9,10] It catalyses many reactions,

including cholesterol, drugs, oestrogen and environmental pollutants. In addition, it metabolises several pro-carcinogens into active carcinogens.[11] Cytochrome P-4501A1 catalyses catechol oestrogen oxidation to oestrogen semiquinones and quinones. These metabolites are carcinogenic and increase breast cancer risk. These oestrogen metabolites can bind to DNA and result in damage that directly causes genetic alterations and effect tumour initiation.[12,13,14]

The CYP1A1 gene has three polymorphisms, which are M1, M2, and M3. Polymorphism M1 is a threonine to cysteine substitution in the 3′ noncoding region. Polymorphism M2 is isoleucine to valine in codon 462 in exon 7. Polymorphism M3 is an A–T to G–C transition mutation in the 3′ noncoding region 300 base pairs from the polyadenylation site. These polymorphisms have been associated with breast cancer risk and have undergone extensive scrutiny.[15]

Published data regarding the association of CYP1A1 polymorphism and breast cancer risk reported mixed results.[16,17,18,19,20,21,22,23] The regions where women live and the environmental exposures to various polyaromatic hydrocarbons and others play a significant role and influence the association between breast cancer risk and CYP1A1 polymorphisms.

In the light of the mixed published reports concerning CYP1A1 polymorphisms and their association with breast cancer risk that vary with region and ethnic groups, we aimed to assess the association of CYP1A1 genetic polymorphisms with breast cancer in women of Afro-Arabian descent from Sudan. Our study is unique as it is the first to be conducted on women of this type of ethnicity.

Materials and methods

Subject selection and characteristics

This study was a case-control study consisting of women with breast cancer and cancer-free controls (100 each cohort) who visited Wad Madani Teaching Hospital, Central Sudan, between January 2012 and December 2014. The patients consisted of females with histopathologically confirmed breast cancer recruited from the inpatient surgical clinic. Eligible participants included women diagnosed with breast cancer by histological examination, free from other malignancies, and not previously treated for any cancer. Exclusion criteria included women with other malignancies or women with breast cancer who received previous cancer treatment of any kind. In comparison, control subjects were women who were free of breast disease or any other malignancies and had no past history of breast disease. All study participants provided written informed consent.

The participants completed a verbal questionnaire designed to collect sociodemographic characteristics and gynaecological variables. The sociodemographic characteristics included age, educational level, and occupation. The gynaecological variables included age at menarche, age at first full-term pregnancy, and age at menopause, lactation, and history of abortions. At the end of the verbal interview, the interviewer measured the woman's height and weight, and determined body mass index (BMI). Whole blood was collected from each participant in Ethylenediaminetetraacetic acid (EDTA) vacutainer tubes (Greiner Bio-One BMbH, Germany) on the day of their surgery at the surgery department in Wad Medani Teaching Hospital and immediately processed to obtain the buffy coats and stored at –80 °C.

DNA extraction, polymerase chain reaction and single nucleotide polymorphisms (SNP) genotyping

We extracted the deoxyribonucleic acid (DNA) from the buffy coats using the QIAamp DNA Mini Kit and protocol (Qiagen, Germantown, MD, United Stated [US]), which we then amplified by polymerase chain reaction (PCR) and used for restriction fragment length polymorphism (RFLP) analysis.[24] We performed the PCR amplification and restriction endonuclease digest for each of the three CYP1A1 variants (CYP1A1 M1, M2, and M3). Cytochrome P-4501A1 M1 variant (348 base pair [bp] fragment), CYP1A1 M2 polymorphism (a 377 bp fragment), and the CYP1A1 M3 polymorphism (a 400 bp fragment), and amplified each variant using previously published primers.[23] We confirmed the PCR fragment products on a 1% agarose (Vivantis, Malaysia). Restriction enzymes for the three variants of the CYP1A1 gene were MspI (CYP1A1 M1), BsrDI (CYP1A1 M2), and MspI (CYP1A1 M3) (New England Biolabs, UK). Digestion for the CYP1A1 M1 MspI variants was carried out at 37 °C overnight for 16 h and revealed a 348 bp band for the CYP1A1 M1 (T) allele and two bands of 230 bp and 118 bp for the CYP1A1 M1 (C) allele. BsrDI digestion for the CYP1A1 M2 polymorphism which was carried out for 16h overnight at 65 °C resulted in a 377 bp fragment for the G allele and two bands of 237 bp and 140 bp for the A allele. For the CYP1A1 M3 variant, a 400 bp fragment for the T allele and two fragments of 330 bp and 70 bp for the C allele were detected following a 16 h digestion at 37 °C and separated on a 3% agarose gel electrophoresis (Bio-Rad Laboratories, Hercules, CA, US) stained with ethidium bromide (New England Biolabs, United Kingdom [UK]).

Statistical analysis

We performed the data analysis with the aid of SPSS program. We performed a multivariate analysis using logistic regression to obtain the odds ratio (OR) with a 95% confidence interval (CI) and assessed the association between the CYP1A1 variants between breast cancer patients and controls. Covariates included age, BMI, menopausal status, and breast cancer family history. For all statistical tests, the level of significance was two-sided at a $p < 0.05$.

Ethical considerations

This research was approved by the Ethics and Research Committees of the Institute of Endemic Diseases, University

of Khartoum. Wad Madani Teaching Hospital also permitted to conduct the study (protocol number 2009-014; project research number: 014).

Results

Patients' demographic characteristics and breast cancer risk

The age range of selected participants was 19–86 years. The patients' mean age was (47.0 ± 12.2), and that of the controls was (43.1 ± 12.2). Table 1 shows the breast cancer risk by demographic variable. Full-term pregnancy had a negative relationship with the risk of breast cancer ($p = 0.067$) in this study. Age at menarche, lifetime duration of lactation, age at first full-term pregnancy, and miscarriage have no significant effect on breast cancer risk in this study. In addition, working full-time or part-time had an insignificant reduction in breast cancer risk in this study. Uneducated women and a family history of breast cancer had a highly significant impact on breast cancer risk. Our data also showed a high association between raised BMI and an increased risk of breast cancer.

Cytochrome P-4501A1 M1 polymorphism and breast cancer risk

There were no significant alterations in allelic and genotypic frequencies for M1 comparing patients to controls. Table 2 shows the M1 genotypes and allele frequency percentages.

Cytochrome P-4501A1 M2 polymorphism and breast cancer risk

Table 3 displays the relationship between CYP1A1 M2 polymorphism with breast cancer risk. Allele frequency percentages for the CYP1A1 M2 (A) were 77.0% for the patients and 89.5% for controls. There was a significant difference between the two groups. Similarly, there was a significant difference between patients and controls in the (G) allele's prevalence. The homozygous CYP1A1 M2 (A/A) genotype had a significant risk reduction of breast cancer, whilst we found that the heterozygous CYP1A1 M2 (A/G) was associated with a significantly increased breast cancer risk.

Furthermore, homozygosity for the CYP1A1 M2 (G/G) allele presented a significantly increased risk of breast cancer in the

TABLE 1: Selected characteristics of breast cancer patients and the control group among Sudanese women.

Variable	Patient			Control			OR	95% CI	*p*
	n	%	± s.d.	*n*	%	± s.d.			
Mean age (year)	-	-	47.0 ± 12.2	-	-	43.1 ± 12.2	-	-	0.025
Mean age (year) at menarche	-	-	13.6 ± 1.4	-	-	13.7 ± 1.6	-	-	0.738
Menopausal status									
Premenopausal	41	41	-	45	45	-	Ref	-	-
Postmenopausal	58	59	-	55	55	-	1.16	0.66–2.03	0.610
The lifetime duration of lactation	-	-	-	-	-	-	-	-	0.947
0 year	-	-	-	-	-	-	Ref	-	-
≤ 1 year	-	-	-	-	-	-	0.89	0.22–3.58	0.871
> 1 year	-	-	-	-	-	-	1.07	0.60–1.94	0.811
Full-term pregnancy									
Yes	52	55	-	65	68	-	Ref	-	-
No	43	45	-	31	32	-	1.73	0.96–3.12	0.067
Age (year) at first full-term pregnancy									
< 22	23	44	-	31	48	-	Ref	-	-
≥ 22	29	56	-	34	52	-	1.15	0.55–2.39	0.709
Miscarriage									
Yes	28	33	-	33	33	-	1.0	0.54–1.85	0.993
No	57	67	-	67	67	-	Ref	-	-
Education level	-	-	-	-	-	-	-	-	0.008
Not educated	26	28	-	11	11	-	4.73	1.68–13.32	0.003
< High school	58	62	-	69	69	-	1.68	0.73–3.88	0.223
≥ High school	10	11	-	20	20	-	Ref	-	-
Family history of Breast Cancer a first-degree relative	-	-	-	-	-	-	-	-	< 0.001
Yes	21	24	-	0	0	-	NA	-	-
No	65	76	-	100	100	-	Ref	-	-
Body Mass Index (kg/m²)	-	-	-	-	-	-	-	-	0.103
≤ 25	38	45	-	44	48	-	Ref	-	-
25–30	23	27	-	33	36	-	0.81	0.41–1.60	0.541
> 30	24	28	-	14	15	-	2.0	0.90–4.37	0.089
Career status									
Work full/part-time	26	26	-	36	36	-	Ref	-	-
Not work	73	74	-	64	64	-	1.58	0.86–2.90	0.139

OR, odds ratio; s.d., standard deviation; CI, confidence interval; Ref, reference level; NA, not applicable.

TABLE 2: Allelic and Genotypic frequencies of Cytochrome P-4501A1 M1 allele for Sudanese female breast cancer patients and control group with menopausal ages.

Variable	Patients		Control		OR	95% CI	*p*
	n	%	*n*	%			
Total women (*N*)	100	-	100	-	-	-	-
Allele frequency (total number of alleles)							
M1(T)	92	96.0	95	97.5	1.63	0.52–5.06	0.398
M1(C)	8	4.0	5	2.5	-	-	-
Genotypic frequency (total number of genotypes)							
M1(T/T)	92	92.0	95	95.0	-	-	-
M1(T/C)	8	8.0	5	5.0	1.65	0.52–5.24	0.390
M1(C/C)	-	-	-	-	-	-	-
Total premenopausal women <45 (*N*)	58	-	69	-	-	-	-
Allele frequency (total number of alleles)							
M1(T)	96	96.5	97	97.9	1.61	0.45–7.33	0.537
M1(C)	4	3.5	3	2.1	-	-	-
Genotypic frequency (total number of genotypes)							
M1(T/T)	54	93.1	66	95.7	1.63	−0.35–7.59	0.531
M1(T/C)	4	6.9	3	4.3	-	-	-
M1(C/C)	-	-	-	-	-	-	-
Total postmenopausal women ≥ 45 (*N*)	42	-	31	-	-	-	-
Allele frequency (total number of alleles)							
M1(T)	80	95.2	60	96.7	1.50	0.27–8.46	0.644
M1(C)	4	4.8	2	3.3	-	-	-
Genotypic frequency (total number of genotypes)							
M1(T/T)	38	90.5	29	93.5	1.53	0.26–8.92	0.637
M1(T/C)	4	9.5	2	6.5	-	-	-
M1(C/C)	-	-	-	-	-	-	-

OR, odds ratio; CI, confidence interval.

TABLE 3: Allelic and Genotypic frequencies of Cytochrome P-4501A1 M2 allele for Sudanese female breast cancer patients and control group with menopausal ages.

Variable	Patients		Control		OR	95% CI	*p*
	n	%	*n*	%			
Total women (*N*)	100	-	100	-	-	-	-
Allele frequency (total number of alleles)							
M2(A)	154	77.0	179	89.5	2.55	1.46–4.45	0.001
M2(G)	46	23.0	21	10.5	-	-	-
Genotypic frequency (total number of genotypes)							
M2(A/A)	70	70.0	87	87.0	-	-	0.012
M2(A/G)	14	14.0	5	5.0	-	-	-
M2(G/G)	16	15.5	8	7.9	-	-	-
Total premenopausal women (*N*)	58	-	69	-	-	-	-
Allele frequency (total number of alleles)							
M2(A)	89	76.7	125	90.6	2.92	1.43–5.97	0.003
M2(G)	27	23.3	13	9.4	-	-	-
Genotypic frequency (total number of genotypes)							
M2(A/A)	41	70.7	61	88.4	-	-	0.043
M2(A/G)	7	12.1	3	4.3	-	-	-
M2(G/G)	10	17.2	5	7.2	-	-	-
Total postmenopausal women (*N*)	42	-	31	-	-	-	-
Allele frequency (total number of alleles)							
M2(A)	65	77.4	54	87.1	1.97	0.80–4.86	0.135
M2(G)	19	22.6	8	12.9	-	-	-
Genotypic frequency (total number of genotypes)							
M2(A/A)	29	69.0	26	83.9	-	-	0.311
M2(A/G)	7	16.7	2	6.5	-	-	-
M2(G/G)	6	14.3	3	9.7	-	-	-

OR, odds ratio; CI, confidence interval.

final model. The distribution of the CYP1A1 M2 (A) allele in premenopausal breast cancer patients and control groups were associated with a significant reduction in the risk of breast cancer, whilst the (G) allele was associated with increased risk (p = 0.003). However, homozygous (G/G) premenopausal women had a significantly increased risk. The homozygosity for the CYP1A1 M2 (A) allele (CYP1A1 M2 (A/A) conferred a significant reduction of risk in postmenopausal women. Heterozygosity for the CYP1A1 M2 (CYP1A1 M2 [A/G]) and CYP1A1 M2 (G/G) variants has no

TABLE 4: Allelic and genotypic frequencies of Cytochrome P-4501A1 M3 allele for Sudanese female breast cancer patients and control group with menopausal ages.

Variable	Patients		Control		OR	95% CI	*p*
	n	%	*n*	%			
Total women (*N*)	100		100				
Allele frequency (total number of alleles)							
M3(T)	98	99.0	99	99.5	2.01	0.18–22.35	0.562
M3(C)	2	1.0	1	0.5	-	-	-
Genotypic frequency (total number of genotypes)							
M3(T/T)	98	98.0	99	99.0	2.02	0.18–22.65	0.561
M3(T/C)	2	2.0	1	1.0	-	-	-
M1(C/C)	-	-	-	-	-	-	-
Total premenopausal women (*N*)	58		69				
Allele frequency (total number of alleles)							
M3(T)	15	99.1	38	100.0	-	-	0.270
M3(C)	1	0.9	-	-	-	-	-
Genotypic frequency (total number of genotypes)							
M3(T/T)	59	98.3	69	100.0	-	-	0.27
M3(T/C)	1	1.7	-	-	-	-	-
M3(C/C)							
Total postmenopausal women (*N*)	42		31				
Allele frequency (total number of alleles)							
M3(T)	83	98.8	61	98.4	0.74	0.05–11.98	0.828
M3(C)	1	1.2	1	1.6	-	-	-
Genotypic frequency (total number of genotypes)							
M3(T/T)	41	97.6	30	96.8	0.73	0.04–12.17	0.827
M3(T/C)	1	2.4	1	3.2	-	-	-
M3(C/C)	-	-	-	-	-	-	-

OR, odds ratio; CI, confidence interval.

significant association with increased breast cancer risk in postmenopausal women.

Cytochrome P-4501A1 M3 polymorphism and breast cancer risk

Table 4 shows the M3 genotype and allele frequencies. There was no significant alteration in allelic and genotypic frequency percentages for M3 comparing patients with controls. In addition, menopausal status was not found to be associated with alterations in the M3 allelic polymorphisms as a breast cancer risk factor.

Discussion

The study investigated the association of three polymorphic variants of the CYP1A1 gene in Sudanese women with breast cancer and other socio-economic and demographic factors that included menarche, education levels, family history of breast cancer, menopause, and BMI.

Cytochrome P-4501A1 M1 and CYP1A1 M3 genotypes showed no relationship to increased breast cancer risk in premenopausal or postmenopausal ages. African American women carrying the CYP1A1 M1 variant have a significantly higher risk of breast cancer, whilst Nigerian women carrying the CYP1A1 M1 variant had a reduced risk of breast cancer.[21] There was a non-significant 6% increased risk of postmenopausal women developing breast cancer for carriers of the CYP1A1 M3 (T/C) genotype.[23] In addition there is a significant correlation between M1, M3 and M4 polymorphisms with breast cancer risk in Indian women.[25]

Our results suggest that CYP1A1 M2 polymorphisms are significantly associated with breast cancer risk in Sudanese women (Table 3). Allele frequency percentages for the CYP1A1 M2 (A) and (G) alleles between patients and the control group were found to be significantly different. The A allele and AA genotype were associated with a reduced risk in the premenopausal group. Furthermore, the G allele and GG genotype were associated with increased risk in this group. We did not observe a similar association in postmenopausal women. Singh et al reported no significant alterations of allelic and genotypic frequencies for M2 when comparing patients with controls based on menopausal state.[25] However, we observed a significant protective effect for this allele in postmenopausal women ($p < 0.05$). Heterozygosity in the CYP1A1 M2 allele had a significant breast cancer-protective effect (OR: 0.33; CI: 0.12–0.89; *p*-value 0.03) in postmenopausal women. Miyoshi and Noguchi et al investigated the association of two CYP1A1 polymorphisms, that is, 3′ noncoding region (6235(T/C) and codon 462 (Ile/Val), with breast cancer risk in Japanese women.[26] Variant allele 6235C carriers at the 3′ noncoding region polymorphism showed a significantly reduced breast cancer risk compared with non-carriers. Variant allele 462Val carriers at the codon 462 polymorphism showed a significantly reduced risk compared with non-carriers. However, CYP1A1 M2 and CYP1A1 M4 are rare in Nigerian women.[23] The differences between Nigerian women and Sudanese women may be related to geographic distribution – Nigerian women are from West Africa, whilst Sudanese women are from East Africa. Sudanese women are of Afro-Arabian descent and may have different genetic make-up and other cancer sustainability genes. A more

recent study by Zhang et al reported a significant increase in breast cancer risk in women with the CYP1A1 M2 variant genotype, especially postmenopausal women when compared with women who had the homozygous wild-type CYP1A1 M2 genotype with those harbouring the variant M2 genotype.[27] The women with at least one CYP1A1 M2 variant allele had a two-fold increased risk of breast cancer compared with those with homozygous wild-type CYP1A1 M2. The risk became greater amongst postmenopausal women. In women living in Iran, the heterozygote genotype frequency (A/G) significantly increased in patients compared with controls. (A/A) genotype showed a significantly decreased risk of breast cancer. A higher frequency of heterozygotes was mainly observed amongst premenopausal breast cancer patients.[27,28]

The present study showed that the education levels, family history of breast cancer, and raised BMI had significant associations with breast cancer risk in Sudanese women. Our findings agree with previously published reports from Sudan and other countries.[29,30,31,32] Recently, several studies reported the association of many reproductive factors, including early age at menarche and late age at menopause, with a high breast cancer risk.[33,34,35,36,37,38]

In this study, the education level had a significant effect; educated women have a decreased risk of developing cancer. A positive association between the level of education and breast cancer risk is consistent with most but not all previously published studies.[39] A family history of breast cancer in a first-degree relative (Table 1) had a significant relationship with the increased risk of breast cancer in Sudanese women. Many studies support that women with a family history of breast cancer run a higher risk of breast cancer than women without a family history.[40,41,42]

Patients with BMI ≥ 30 (kg/m^2) (BMI: 19 kg/m^2 – 24.9 kg/m^2 is considered an ideal weight) comprised about 30% of the patient group, which was significantly higher than that in the controls. On the one hand, several studies support the hypothesis that a higher BMI level may be associated with a decrease in premenopausal breast cancer risk. The results from several case-control and cohort studies supported this hypothesis.[43,44,45,46] On the other hand, a few studies did not observe a statistically significant association when comparing the highest versus lowest levels of BMI.[47,48]

There were several limitations to our study; the first concern was the sample size. Studies of this type have not been performed before in Sudan. In addition to the limited studies conducted in Africa, which consisted of a small size, it was challenging to calculate the sample size with reliable power. Therefore, a study with a larger sample size and reliable power may provide more reliable results if conducted in the future. The second limitation is that all the women in the study are from central Sudan and thus do not represent Sudan as a whole. Sudan is a vast country with various ethnic and demographic people, and, therefore, a sample size that includes women from all parts of Sudan is warranted to provide generalisable results. The third limitation of this study is that Sudan is comprised of different environments spanning from the desert in the north to the tropical savanna climate in the south and ranging from developing to under developing populations. Therefore gene-gene and gene-environment interaction may play a critical role in breast cancer development and should be considered when drawing conclusions. Our study did not address ovarian cancer history and radiation exposure because we have examined many other risk factors. Future studies will address other risk factors which were not covered in this study.

In conclusion, our study suggested that the CYP1A1 M2 polymorphism is associated with the risk of developing breast cancer amongst Sudanese patients. The CYP1A1 polymorphism may serve as a potential marker for the diagnosis of breast cancer in Sudan. Despite the limited research capacity and availability of funding to support research in Sudan, we believe our study provides a scientific base and opens the door for genetic polymorphism research for breast cancer in Sudan.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

F.H., S.I.M., A.R.O.M. and D.O.A.A. contributed equally to the design and implementation of the research, analysis of the results, and writing of the article.

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Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Disclaimer

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