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Impact of residence on the association between benzo[*a*]pyrene-DNA adduct levels and CYP1B1 gene polymorphisms in breast cancer patients

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Abstract

Globally, breast cancer is the primary cause of cancer-related death, and rising incidence rates are anticipated. Improving illness prevention and treatment strategies requires a better understanding of the interactions occurring between genetic variables, environmental exposures, and disease pathogenesis. This study investigated the impact of residence on the association between benzo[*a*]pyrene-DNA adduct levels and CYP1B1 gene polymorphisms in breast cancer patients. In brief, 58 female breast cancer patients in Babylon, Iraq were recruited as subjects of this cross-sectional study. We gathered clinical information (including residency, age, age at diagnosis, and haematological markers), and by using molecular and biochemical methods, the *CYP1B1* polymorphisms and the benzo[*a*]pyrene-DNA adduct levels were assessed. Among the different types of breast cancer, there was no apparent association between the residence and *CYP1B1* polymorphisms. However, the amounts of benzo[*a*]pyrene-DNA adduct varied according to where a patient lived, with urban residents showing higher concentrations than rural residents. Benzo[*a*]pyrene-DNA adduct levels were shown to be correlated with specific polymorphisms in the CYP1B1 gene. Our study highlights the intricate connections between environmental exposures, genetic variables, and place of residency in the aetiology of breast cancer. Variations in quantities of benzo[*a*]pyrene-DNA adducts imply possible functions for environmental carcinogens, although no substantial correlation was found between genetic polymorphisms and the place of residence.

KEYWORDS

CYP1B1 gene polymorphisms, breast cancer, benzo[*a*]pyrene-DNA adduct concentrations, genetic susceptibility, residence

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1. INTRODUCTION

Breast cancer (BC) accounts for about one-third of cancers occurring in women that have been re-

ported to the Iraqi Cancer Registry, and represents the commonest cause of cancer-related fatalities worldwide (surpassing both prostate and lung cancers). It is anticipated that the incidence rates will rise globally [1,2]. New lifestyle and fertility patterns, particularly in less developed countries, impact this rise in addition to improved detection. In developed nations, the incidence of BC is notably higher. Significant differences in screening, treatment access, and supportive care still exist between nations, despite advances in medical care [1]. Genes such as *XRCC1*, *OGG1*, *CYP1A1*, and *MTHFR* have been associated with increased risk of developing BC; however, their mutation frequency in established BC risk genes is insignificant [3].

Cytochrome P450 enzymatic activity may be impacted by *CYP1B1* polymorphisms, especially in exons 2 and 3, that could alter sensitivity to environmental carcinogens [4]. Nevertheless, conflicting findings have been reported concerning the connection between *CYP1B1* polymorphisms and BC [5]. Taking residency status and genotype-allele frequency connections into account, this study aimed to examine the relationship between *CYP1B1* polymorphisms and BC in Babylon, Iraq.

2. PATIENTS AND METHODS

A cross-sectional study was carried out in 2023, and included 58 female BC patients, aged 25 to 60 years, mostly from the Marjan Hospital in Babylon. Medical history, clinical data, and participant demographics were gathered. According to accepted practices, the oncologist identified, managed, and tracked these patients. Various types and stages of BC were represented in the cohort. Those who were smoking, drinking alcohol, nursing a baby, or had a severe disease were among the excluded patients.

In order to extract DNA and to genotype *CYP1B1* polymorphisms, venous blood samples were obtained. An hematology analyzer and a human benzo[*a*]pyrene-DNA adduct detection kit for ELISA were used in our analyses. For the molecular genotyping of *CYP1B1*, 500 µL of frozen blood were subjected to DNA extraction. The polymerase chain reaction - restriction fragment length polymorphisms (PCR-RFLP) approach was employed in order to genotype rs1800440 polymorphisms of the CYP1B1 gene. PCR primers' design and restriction enzyme selection were carried out by the aid of NCBI-primer BLAST and Wat Cut online software, respectively. The selected primers (forward: 5-TCATTTTCGCAGGCTCATTTGG-3; reverse: 5-AGTGGCCTAACCCGGAGAA-3) were used to amplify 213 bp around the targeted polymorphisms. The PCR conditions were first optimized by gradient annealing temperature (55°C–65°C), and 10 µL of PCR product were subjected to overnight restriction analysis by 5 units of the BstMW I enzyme (SibEnzyme, Russia). The PCR product and the restriction reaction product were then resolved on 2% agarose and stained by ethidium bromide. The CC genotype produced 155- and 58-bp restriction fragments, the TC genotype produced 213-, 155-, and 58-bp restriction fragments, while the TT genotype produced the original amplicon of 213-bp fragments [6].

The statistical calculations for this study were carried out by using the IBM 2017 SPSS program (version 21.0). The data were displayed as mean ± standard error, and a statistically significant *P*-value was defined as being 0.05 or less. In order to determine whether there were any significant differences, the Student's *t*-test was employed.

The principles outlined in the Helsinki Declaration were strictly adhered to, and before beginning the study and after, patients were fully informed about it, and every participant provided verbal consent for her participation. Both the Marjan Hospital (Babylon Health Directorate) and the College of Pharmacy (University of Babylon) Institutional Review Board have authorized the study's protocol.

3. RESULTS

The characteristics and the benzo[*a*]pyrene-DNA adduct levels in female BC patients are presented in Table 1, according to their *CYP1B1* genotype and their place of residence (rural *versus* urban). White blood cells' count, platelets' count, packed cell volume percentage, haemoglobin levels, the concentration of benzo[*a*]pyrene-DNA adduct (ng/mL), and the age at diagnosis are among the variables assessed. Although statistical significance varied, there seem to be some overall differences in these variables across different categories. As an example, the concentration of benzo[*a*]pyrene-DNA adduct was found to be significantly higher in urban areas than in rural ones (2.7 ng/mL *versus* 1.9 ng/mL; *P*=0.015). Similarly, although statistical significance was not reached, the platelet count was found to be much greater in patients from urban than those from rural locations (283.8×10^9/L *versus* 250.4×10^9/L).

4. DISCUSSION

This study aimed at examining the relationship between benzo[*a*]pyrene-DNA adduct levels in BC patients and particular genetic polymorphisms in the CYP1B1 gene, after taking into account the residential location (rural *versus* urban) of the patients in order to understand the interaction be-

tween genetics, residency, and benzo[*a*]pyrene-DNA adduct levels in BC. The findings indicate that there is no significant relationship between residence and *CYP1B1* polymorphisms; however, urban residents exhibited greater quantities of benzo[*a*]pyrene-DNA adduct.

Table 1. Differences in benzo[*a*]pyrene-DNA adduct levels and other variables of clinical importance in Iraqi women with breast cancer according to their residence and *CYP1B1* genotype.

Variables	Residence / *CYP1B1* genotype	N	Mean	Standard error	*P*-value
Concentration of benzo[*a*]pyrene-DNA adduct (ng/mL)	Rural	21	1.9	0.03	0.015
	Urban	37	2.7	0.31	
	CC	27	2.5	0.4	>0.05
	CT	25	2.3	0.2	
	TT	6	2.3	0.2	
Haemoglobin (g/dL)	Rural	21	11.0	0.4	>0.05
	Urban	37	11.1	0.2	
	CC	27	10.9	0.2	>0.05
	CT	25	11.1	0.3	
	TT	6	11.6	0.6	
Packed cell volume (%)	Rural	21	33.2	0.9	>0.05
	Urban	37	34.3	0.6	
	CC	27	33.6	0.7	>0.05
	CT	25	34.1	0.9	
	TT	6	34.3	1.8	
White blood cells ($\times 10^9$/L)	Rural	21	6.3	0.7	>0.05
	Urban	37	6.9	0.5	
	CC	27	6.5	0.5	>0.05
	CT	25	6.9	0.7	
	TT	6	6.7	0.8	
Platelets ($\times 10^9$/L)	Rural	21	250.4	25.2	>0.05
	Urban	37	283.8	17.0	
	CC	27	247.1	17.8	>0.05
	CT	25	276.1	21.9	
	TT	6	364.2	54.7	
Age at diagnosis (years)	Rural	21	49.5	1.6	>0.05
	Urban	37	47.9	1.5	
	CC	27	46.9	1.9	>0.05
	CT	25	49.3	1.5	
	TT	6	52.8	3.0	

Elevated benzo[*a*]pyrene-DNA adduct levels have been associated with specific CYP1B1 gene variations, suggesting a possible genetic susceptibility to environmental carcinogens [3]. The cytochrome P450 superfamily, which includes CYP1B1, metabolizes a variety of drugs and affects the course of the development and of the chemotherapy of cancer [7]. For example, the metabolism of oestrogen by CYP1B1 increases the risk of BC [8].

Tumorigenesis is associated with dysregulated cellular proliferation, specifically in BC, which is caused by an overexpression of CDC20 [9]. Variations in disease susceptibility are influenced by genetic variants of *CYP1B1*, with varying outcomes noted in various groups and geographical areas [10]. Research indicates that in order to improve precision medicine and customize treatment plans, more research is required into the molecular mechanisms and epidemiological aspects of *CYP1B1* polymorphisms in BC [5]. Recognizing this function could increase the effectiveness of treatment and reduce side-effects, thereby highlighting the significance of tailored therapeutic approaches in the treatment of BC.

5. CONCLUSION

No considerable correlation between *CYP1B1* pol-

ymorphisms and place of residence (rural *versus* urban) was identified, despite examining a heterogeneous sample. On the other hand, the amounts of benzo[*a*]pyrene-DNA adduct varied according to where a person lived, with urban residents showing higher concentrations than rural ones. Moreover, benzo[*a*]pyrene-DNA adduct levels were correlated with specific polymorphisms in the CYP1B1 gene. These results highlight the intricate interactions that exist between environmental exposures, genetic variables, and the pathophysiology of BC. In order to clarify the underlying causes and consequences of customized treatment approaches, more research is necessary. However, our findings align with recent data from *in vitro* and animal studies suggesting that CYP1B1 may play a significant role in the pathogenesis of BC.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

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