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Research Article

GENETIC POLYMORPHISMS IN CYTOCHROME P450 ENZYMES AND CHEMOTHERAPY RESPONSE IN BREAST CANCER

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ABSTRACT

This investigation aimed to elucidate the influence of genetic polymorphisms within cytochrome P450 enzymes, namely CYP3A4, CYP3A5, CYP2B6, CYP2C8, CYP2C9, and CYP2C19, on the clinical response to neoadjuvant chemotherapy in 198 breast cancer patients. Utilizing RLFP analysis, functionally significant variants were identified. Results demonstrated a significant correlation between the CYP2C92 polymorphism and chemotherapy resistance (OR = 4.64; 95% CI = 1.01 – 20.91). Notably, CYP2C92 heterozygotes displayed heightened resistance, particularly in women with nodal forms of breast cancer and a hereditary cancer burden (OR = 15.50; 95% CI = 1.08 – 826.12), suggesting potential combined effects. However, no significant associations were observed between chemotherapy resistance and other examined genotypes, as well as combined clinical and tumor-related parameters. In conclusion, the presence of the CYP2C9*2 polymorphism strongly correlates with neoadjuvant chemotherapy resistance within this study's breast cancer patient population.

Key words:-. Breast, Cancer, Women, Cytochrome P450, Gene, Neo-adjuvant.

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INTRODUCTION

Breast cancer treatment is notably characterized by variability in drug efficacy and toxicity [1, 2]. The variability of treatment can lead to ineffective treatment and adverse reactions in clinical practice [3]. These variations are influenced by a variety of factors, including demographics, dietary habits, drug pharmacokinetics, and pharmacodynamics. There is however a high degree of importance to polymorphisms in genes encoding drug-metabolizing enzymes, drug transporters, and drug targets among these factors [4]. Clinical outcomes can be significantly influenced by polymorphisms within these genes, making them crucial factors in predicting drug availability and response [5].

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Optimising therapeutic efficacy while minimizing adverse effects requires an understanding of the functional significance of these genetic variations. In personalized medicine approaches, particularly when it comes to treating breast cancer, it is imperative to elucidate how genetic polymorphisms influence drug metabolism and response [6, 7].

Genes coding for drug transporters and metabolizing enzymes can have a significant impact on drug efficacy and toxicity. A significant proportion of these genes are polymorphic, such as CYP2C8 and CYP2C9 [8]. Many of the CYP2C9 variants are known to reduce enzyme activity. CYP2C8 and 2C9 activity are reduced when polymorphic alleles of CYP2C8 and 2C9, which are present among Caucasians, result in non-synonymous mutations [9]. A wide range of anticancer agents such as cyclophosphamide, ifosfamide, paclitaxel,

tamoxifen, and tegafur must be metabolized by these enzymes [10].

Drug metabolism is also influenced by CYP2C19, which has approximately 28 variant alleles. Cyclophosphamide, ifosfamide, tamoxifen, and thalidomide are metabolized differently when these mutations occur in exon 5 or exon 4, respectively [11, 12]. Similarly, CYP2B6, with around 29 polymorphisms, includes functionally significant variants like CYP2B6*5 and CYP2B6*7, which decrease enzymatic activity and affect drugs like cyclophosphamide and ifosfamide [13]. There is a wide variety of substrate specificity and genetic variability among CYP3A enzymes, especially CYP3A4 and CYP3A5. CYP3A4*2 and CYP3A5*3 are two alleles associated with decreased activity, affecting cyclophosphamide, ifosfamide, docetaxel and paclitaxel metabolism among others [14]. Studying functionally significant variants in CYP3A4, CYP3A5, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 were examined in breast cancer patients before and after neoadjuvant chemotherapy [15].

METHODS

The Cancer observed 198 women with morphologically confirmed stages T1-4N0-3M0 breast cancer. In addition to CMF and CMXeloda (Cyclophosphamide, Methotrexate, and either Fluorouracil or Xeloda), 261 patients were treated with neoadjuvant chemotherapy. Among the medications used were FAC (Fluorouracil, Adreamicin, Cyclophosphamide) and CAF (Fluorouracil, Adreamicin, and either Fluorouracil or Xeloda). According to the World Health Organization criteria, the chemotherapeutic effect was estimated after two to four chemotherapy courses. The patients with complete remission (CR) had no tumor; those with partial remission (PR) had a reduction in tumour area of 50-100%; and those with stable disease (SD) had a reduction in tumour area of 0–50; patients with progressive disease (PD) had an increase in tumour area or new lesions were detected [16]. Three percent of the patients achieved complete remission, 47 percent achieved partial remission, 46 percent achieved stable disease, and four percent progressed. CR, PR, and SD patients exhibited positive chemotherapy response, whereas patients with PD showed negative chemotherapy response. In light of the results of neoadjuvant therapy, the patients were divided into two groups [17].

Table 1: To genotype CYP450 polymorphisms using primers and restriction endonucleases.

Polymorphism	Amplicone	Restriction products, b.p.*
*CYP3A5*3* (intron 3)	294	147 126 21
*CYP3A4*1B* (5'-NTR)	112	112
*CYP3A4*2* (exon 6)	123	97 27
*CYP2C9*2* (exon 3)	373	178 118 73
*CYP2C9*3* (exon 7)	129	129
*CYP2C19*2* (exon 5)	229	107 122
*CYP2C19*3* (exon 4)	146	127 18
*CYB2B6*5* (exon 9)	119	104 15
*CYP2C8*2* (exon 5)	166	68 64 32
*CYP2C8*3* (exon 3/8)	466	309 109 45

Table 2: Cancer patients' genotypes and allele frequencies for CYP P450 genes

Nomenclature	WT	HT	VT	p	q
*CYP2C8*2*	98.19	0.76	0.00	98.99	0.41
*CYP2C8*3*	82.79	14.63	0.49	90.87	7.99
*CYP2C9*2*	78.52	19.18	0.24	88.66	9.29
*CYP2C9*3*	80.19	18.11	1.03	91.12	9.889
*CYP2C19*2*	57.51	35.17	2.31	79.12	20.86
*CYP2C19*3*	98.93	2.04	0.00	97.96	1.04
*CYP3A4*1B*	93.84	5.13	0.00	96.39	2.49
*CYP3A4*2*	100.00	0.00	0.00	100.00	0.00
*CYP3A5*3*	0.24	10.98	86.94	6.27	92.95
*CYP2B6*5*	84.62	13.58	1.81	92.01	8.06

Table 3: CYP2 genotype distributions and risk of breast cancer patients developing neoadjuvant chemotherapy resistance

Genotype	Positive neoadjuvant chemotherapy response		Negative neoadjuvant chemotherapy response		OR	CI (95%)	p
	n	%	n	%			
CC	204	83.64	9	90.00	1.89	0.25 - 84.64	0.99
CT	38	14.93	1	10.00	1.13	0.54 - 2.40	0.99
TT	7	2.39	0	0.00	0.63	0.01 - 4.82	0.99
TT	247	98.61	10	100.00	0.04	0.01 - 3.55	0.08
TA	1	0.39	0	0.00	24.30	0.28 - 1914.18	0.08
AA	0	0.00	0	0.00	*		
GG	204	83.01	6	60.00	0.33	0.07 - 1.64	0.09
GA	45	18.01	4	40.00	3.08	0.61 - 13.53	0.09
AA	0	0.00	0	0.00	*		
CC	205	83.28	5	50.00	0.22	0.05 - 0.99	0.02
CT	45	16.89	5	50.00	4.64	1.01 - 20.91	0.02
TT	0	0.00	0	0.00	*		
AA	212	83.42	8	80.00	0.74	0.14 - 7.41	0.66
AC	37	13.38	1	10.00	0.66	0.01 - 5.03	0.99
CC	4	1.21	1	10.00	9.15	0.16 - 124.95	0.15
GG	137	53.59	8	66.67	3.32	0.64 - 32.61	0.19
GA	110	42.79	2	16.67	0.32	0.03 - 1.66	0.20
AA	5	1.59	2	16.67	6.13	0.11 - 69.01	0.20
GG	242	98.87	10	100.00	0.21	0.02 - 10.78	0.23
GA	6	2.04	0	0.00	4.82	0.09 - 48.97	0.23
AA	0	0.00	0	0.00	*		

RESULTS AND DISCUSSION

Table 2 presents the distribution of cytochrome P450 genotypes based on genotypes and allele frequencies among the breast cancer patients studied. For the majority of polymorphisms, the genotype frequencies align with expected values, indicating consistency. However, significant deviations from Hardy-Weinberg equilibrium were observed for CYP2C19*2 ($p = 0.003$) and CYP2B6*5 ($p = 0.0008$) variants. This deviation suggests non-equilibrium conditions at these loci, implying potential functional significance. In our cohort of breast cancer patients, the frequencies of CYP2C8*2 and CYP2C8*3 mutant alleles were 0.39% and 8.33%, respectively. Literature suggests that the CYP2C8*2 allele is exclusive to African Americans, with a frequency of 18%, while the CYP2C8*3 mutant allele is predominantly found in Caucasians at a frequency of 13%. Notably, neither allele has been identified in Asians thus far. These findings underscore the ethnic variability in the distribution of cytochrome P450 polymorphisms and their potential implications for drug metabolism and response in breast cancer treatment

In this group of breast cancer patients, the frequency of the CYP2C9*2 and CYP2C9*3 mutant alleles was 10.36% and 9.90%, which was not significantly different from the number found in the literature for Caucasians, i.e., 8-19% and 0–8.5% for CYP2C9*2 and CYP2C9*3, respectively. The prevalence is higher in Caucasians, where the alleles are found at 1% and 0.5%, respectively. The CYP2C9*2 allele has not been detected in a Chinese population, and the frequency of the CYP2C9*3 allele was 2–2.6%. The CYP2C19*2 mutant allele was found to be present in 21.9% of the population.

There were no significant differences in the distribution of genotypes between subjects with breast cancer, except for CYP2B6*5 ($p = 0.0198$) and CYP19*2 ($p = 0.0003$). This situation may be caused by the population possessing its own pool of alleles, resulting in a different frequency of unfavorable alleles in this group. The impaired efficacy of neoadjuvant chemotherapy in patients containing the CYP2C9*2 mutant allele might result from the impaired enzymatic activity of CYP2C9, which is responsible for the chain reaction that converts the cyclophpsphamide prodrug into an active metabolite. Furthermore, the CYP2C9*3 (OR = 9.15) and CYP2C19*2 (OR = 6.13) mutant type genotypes and heterozygotic CYP2C19*3 (OR = 4.82) genotypes are associated with a low efficacy of neoadjuvant chemotherapy; however, this association was not statistically significant ($p > 0.05$). In this study, it appears that CYP2B6*5, CYP2C8*2, CYP2C8*3, CYP2C9*3, CYP2C19*2 and CYP2C19*3 mutant alleles are not associated with improved response to neoadjuvant chemotherapy.

CONCLUSION

During this study, cytochrome genetic polymorphisms were analyzed to determine how they relate to the effectiveness of neoadjuvant chemotherapy for breast cancer patients with a hereditary cancer burden, a clinical form of cancer, a degree of malignancy, and a histological type of tumor. The risk of neoadjuvant chemotherapy resistance in heterozygotes who have a high hereditary load was 7.6-fold higher than in homozygotes (OR = 7.6, p = 0.04). Patients with nodal breast cancer also showed a similar association. Cancer heterozygotes with BRAF V600E mutations and a cancer hereditary load were 15.5-fold more likely to develop resistance to chemotherapy than those with the wild type genotype. There was no statistically significant association between neoadjuvant chemotherapy efficacy and other clinical characteristics and genetic variants of the investigated cytochromes.

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