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Expression of CYT4Z1 in Breast Carcinoma; Correlating with Clinic Pathological Parameters

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Abstract

Background: Breast cancer is a common malignancy with great heterogeneity in clinical behavior and a major cause of cancer-related deaths. CYP4Z1 is a fatty acid hydroxylase that is involved in steroid metabolism and has hypothesized role in breast cancer, so it could promote or suppress tumor that is sensitive to estrogen hormones level through its influence on hormonal control.

Methods: This study has characterized the IHC expression of CYP4Z1 using monoclonal antibodies on 120 mastectomy specimen of breast carcinoma cases with collected clinicopathological parameters.

Results: CYP4Z1 expression showed a strong significant association with malignant tumor in contrast with benign tumor, invasive ductal carcinoma (NOS) and those with history of malignancies in families (P=0.0001, P=0.0001, P=0.008) and it revealed that there is a non-significant difference in expression of CYP4Z1 with other clinicopathological parameters. (Patient age, tumor stage, tumor size, lymph node involvement, tumor grade).

Conclusions: There is significant association of IHC expression of CYP4Z1 and some prognostic clinicopathological factors that reflect a high expression of CYP4Z1 as indicative of a worse prognosis

Keywords: Biomarker; Breast Cancer; Cytochrome 4Z1; Clinicopathological Prognostic Parameters

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Abbreviation: CYP4Z1: Cytochrome 4Z1; 20-HETE: 20-hydroxyeicosatetraenoic Acid; SPSS-25: Statistical Packages for Social Sciences-version 25; CYPp450: Cytochrome P450.

Introduction

Breast carcinoma is the most worrisome cancer, the commonly diagnosed and leading cause of cancer death in women worldwide with great heterogeneity in clinical behavior and it is related to 14% of tumor mortality [1,2].

In Iraq, according to the data from the Cancer Registry of Iraq 2016, breast carcinoma is the most common malignancy affecting Iraqi women representing 19.5 % of all registered tumors with a trend for increase in incidence rate and propensity to affect younger generation, tendency to be diagnosed at advanced stages and likelihood prevalence of aggressive tumor behavioral forms and cancer mortality [3-7].

In Arab countries including Iraq, it is the first malignancy among cancers diagnosed in women, present in earlier stages and in more advanced stages, but studies in western Iraq are limited [8]. P450 cytochrome (CYPs) are superfamily of membrane-bound enzymes which are found in high level in liver where it plays important roles in endogenous compounds biosynthesis and metabolism in addition to oxidative metabolism and detoxification of various exogenous compounds. In this aspect it can bioactivate endogenous substrate to active metabolites, so it can facilitate cancer development by activation of compounds consumed in food, converting procarcinogens to carcinogens thus it has various potentially significant role in tumor biology, thus it has various potentially vital role in tumor biology, progression and prognostic significance [9,10]. Recently, a variety of CYPs have been found to expressed in increasing number of cancer tissue and normal tissues [11]. CYP4Z1 is a fatty acid hydroxylase that is involved in steroid metabolism and it is a type of CYP4 which is the least well characterized and specifically expressed in mammary tissue and hypothesized role in breast cancer through formation of the signaling molecule 20-Hydroxyeicostatetraenoic acid (20-HETE) so it could promote or suppress tumor that is sensitive to estrogen hormones level through its influence on hormonal control. CYP4Z1 have genetic variability with polymorphism that influence on this process [12-14].

An expanded understanding cancer biology has led to support the possible influence of CYP4Z1 which contributes to malignancy

in many organs and potentiate the violent biological behavior and poor clinical prognosis [15-17]. Originally, CYP4Z1 was identified in mammary tissue and up regulated in breast carcinoma. It is the least well described type of the CYP4 enzymes, so the local unique expression of CYP4Z1 appears to be very significant because it provides the basis for the development of new novel diagnostic and therapeutic strategies since expression of CYPs in cancers may be involved in activation and/or inactivation of anticancer drugs in addition to its possible related prognostic influence [18]. In addition, the stable CYP4Z1 overexpression in breast cancer cells has been stated to stimulate angiogenesis and growth of tumor in mice with attendant increase in cellular 20-HETE [19].

Aim

The study aims to evaluate the immunohistochemical CYP4Z1 expression in breast carcinoma and correlate its score with other conventional clinicopathological parameters.

Patients and Methods

This is a descriptive study carried out on archived tissue specimens which were surgically obtained from 128 patients (120 of invasive ductal carcinoma and 8 patient of benign tumor) during 3 years work in Anbar province, west of Iraq, examined with respect to immunohistochemistry CYP4Z1 expression.

All personal facts from samples have been won from the regional oncological centers. The learn about used to be exact authorized by using the ethics committee, College of medicine, University of Anbar. Paraffin embedded blocks of breast carcinoma for affected person underwent modified radical mastectomy with axillary clearance were processed for CYP4Z1 assessment. Then assigning IHC score used to be performed on the invasive carcinoma component only.

All slices had been evaluated except scientific result knowledge. For each staining run, high quality control slides were prepared. The results of CYP4Z1 staining scores had been recorded accordance to the gadget hooked up by Allred DC, et al. (1998) [19,20]. The standards of fantastic response for CYP4Z1 had been assessed by way of scoring the proportion and intensity in one hundred malignant cells carried out at X 40 goal in 25 malignant fields on carcinoma.

The scoring for the share of membrane staining sample of malignant cells and the depth of staining have been taken in account and the staining being graded on the basis of a four point scoring systems which are ranged from 0-3. The intensity of CYP4Z1 staining used to be described through a visual scale from zero to 3 (grade 0=no staining, grade I=weak, grade 2=moderate, grade 3=intense staining).

For CYT4Z1-expression, cells have been regarded fantastic if they established clear membranous and/or cytoplasmic immunolabeling. The scoring result were calculated as opposed to the energy of staining in character cells. The scoring outcome of each immunolabeling of particular phone kinds had been introduced as non (0), weak (1), moderate (2) and intense (3).

The sections were 'weak' CYP4Z1 rating when much less than 33% of cells had an expression. A rating of 'moderate' was used to cells which had an expression on 33% to 66% of the area while the rating 'high' denoted sections had an expression on extra than 67% of the cells. Scores 0 and 1had been grouped collectively as negative-weak expression while scores 2 and 3 were grouped as medium - high expression.

The resulting slides were considered ana analyzed through the usage of a Leica BMRM microscope (Leica DMRB, Wetzler, Germany) with images digitally captured and processed using a Leica MPS52 Camera (Q imaging, Germany) and Ac Quis imaging capture system (Synoptics, Cambridge, UK) respectively. Statistical analysis of data was carried out using the available statistical package of SPSS-25 (Statistical Packages for Social Sciences- version 25). Data were presented in simple measures of frequency & percentage.

The importance of difference of one kind percentages (qualitative data) was once examined using Pearson Chi-square test take a look at (2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the P value was equal or less than 0.05.

Results

All the demographic and pathological data for study cases are shown in Tables 1 and 2.

CYP4Z1 expression: The staining was predominately localized to cell membrane/ cytoplasm without any significant nuclear staining and the staining was uniform across all sections with varying degree of staining intensity (Figure 1).

The results showed frank difference in CYP4Z1 expression in malignant samples in contrast to benign samples, where 85 cases (70.8%) of malignant samples showed a moderate-intense expression which

Table 1: Correlation of clinicopathological parameters and CYP4Z1 expression.

		Z1 Cytochrome4z1			P value
		Total	0---1	2---3	
		No (%)	No (%)	No (%)	
Type	Malignant	120 (93.7)	35 (29.2)	85 (70.8)	0.0001*
	Benign	8 (6.3)	8 (100)	-	
Histopathology	Invasive ductal CA	86 (67.2)	17 (19.8)	69 (80.2)	0.0001*
	Intra ductal CA	12 (9.4)	4 (33.3)	8 (66.7)	
	Invasive lobular CA	8 (6.3)	6 (75.0)	2 (25.0)	
	Invasive papillary CA	2 (1.6)	1 (50.0)	1 (50.0)	
	Mucinous adeno CA	6 (4.7)	3 (50.0)	3 (50.0)	
	Lobular CA insitu	2 (1.6)	1 (50.0)	1 (50.0)	
	Metaplastic CA	1 (0.8)	1 (100)	-	
	Medullary CA	1 (0.8)	1 (100)	-	
	Paget's disease	1 (0.8)	-	1 (100)	
	Undifferentiated CA	1 (0.8)	1 (100)	-	
IDC *others;	Yes	99 (82.5)	21 (21.2)	78 (78.8)	0.0001*
	No	21 (17.5)	14 (66.7)	7 (33.3)	
Age (years)	<30y	6 (4.7)	5 (83.3)	1 (16.7)	0.038*
	30---39	30 (23.4)	7 (23.3)	23 (76.7)	
	40---49	33 (25.8)	15 (45.5)	18 (54.5)	
	50---59	36 (28.1)	11 (30.6)	25 (69.4)	
	60---69	14 (10.9)	3 (21.4)	11 (78.6)	
	=>70y	9 (7.0)	2 (22.2)	7 (77.8)	
	Mean±SD	48.3±13.0	46.3±13.0	49.3±12.9	
Age (years)	<50y	69 (53.9)	27 (39.1)	42 (60.9)	0.152
	=>50y	59 (46.1)	16 (27.1)	43 (72.9)	
Grade	[I]	11 (9.2)	4 (36.4)	7 (63.6)	
	[II]	47 (39.2)	8 (17.0)	39 (83.0)	
	[III]	54 (45.0)	19 (35.2)	35 (64.8)	
	Not	8 (6.7)	4 (50.0)	4 (50.0)	0.1
Family history	Yes	34 (28.3)	4 (11.8)	30 (88.2)	0.008*
	No	86 (71.7)	31 (36.0)	55 (64.0)	

*Significant difference between proportions using Pearson Chi-square test at 0.05level.

Table 2: Correlation of cancer stage and CYP4Z1 expression.

		Cytochrome 4Z1			P value
		Total	0---1	2---3	
		No (%)	No (%)	No (%)	
TNM Staging	T1N0M0	16 (13.3)	7 (43.8)	9 (56.3)	0.708
	T1N1M0	2 (1.7)	-	2 (100)	
	T2N0M0	44 (36.7)	13 (29.5)	31 (70.5)	
	T2N1M0	16 (13.3)	4 (25.0)	12 (75.0)	
	T2N2M0	2 (1.7)	-	2 (100)	
	T2N3M0	1 (0.8)	-	1 (100)	
	T3N0M0	7 (5.8)	2 (28.6)	5 (71.4)	
	T3N1M0	8 (6.7)	1 (12.5)	7 (87.5)	
	T4N0M0	5 (4.2)	1 (20.0)	4 (80.0)	
	T4N1M0	2 (1.7)	-	2 (100)	
	T4N2M0	1 (0.8)	1 (100)	-	
	TisN0M0	13 (10.8)	5 (38.5)	8 (61.5)	
	TisN1M0	3 (2.5)	1 (33.3)	2 (66.7)	
Tumor size	T1	18 (15.0)	7 (38.9)	11 (61.1)	0.702
	T2	63 (52.5)	17 (27.0)	46 (73.0)	
	T3	15 (12.5)	3 (20.0)	12 (80.0)	
	T4	8 (6.7)	2 (25.0)	6 (75.0)	
	Tis	16 (13.3)	6 (37.5)	10 (62.5)	
LN involvement	Yes	35 (29.2)	7 (20.0)	28 (80.0)	0.156
	No	85 (70.8)	28 (32.9)	57 (67.1)	
LN involvement	LN0	85 (70.8)	28 (32.9)	57 (67.1)	0.356
	LN1	31 (25.8)	6 (19.4)	25 (80.6)	
	LN2	4 (3.3)	1 (25.0)	3 (75.0)	

*Significant difference between proportions using Pearson Chi-square test at 0.05 level.

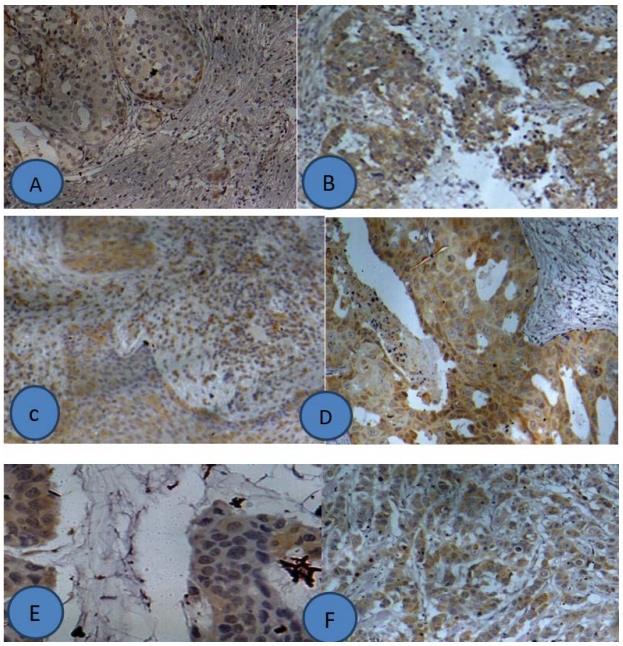

Figure 1: CYP4Z1 Expression in breast carcinoma. Tumors were classified on the bases of histological subtypes. A-Invasive ductal carcinoma (Score 3), B-Invasive lobular carcinoma (Score 2), C-Ductal carcinoma insitu (Score 3), D-Paget's disease (Score 2), E-Invasive papillary carcinoma (Score 3), F-Mucinous carcinoma (Score 1).

is considered as high score over expression, 35 (29.2%) of malignant samples showed no or weak CYP4Z1 expression, while no benign case showed moderate-intense expression. The infiltrative ductal carcinoma showed moderate-strong expression in 69 cases (80.2%) out of 86 studied samples in contrast to other subtype of mammary carcinoma which were lower than in other carcinoma subtypes with statistic significant difference (P=000.1). In our study, patients were classified into two main age groups, the first which were younger than 50 years old were 69/128 (53.9%), 27 (39.1%) of them were with weak or negative score and 42(60.9%) were with high score of CYP4Z1 expression. The other 59 (46%) of studied cases were older than 50 years, 16 (27%) of them were with weak or negative expression and 43 (72.9%) were with high CYP4Z1 expression.

Among 43 negative cases, 27 cases (62.8%) were younger than 50 years old and the 16 cases (37.2%) were older than 50 years. Among 85 positive cases, 42 cases (49.4%) were younger than 50-year-old and 43 cases (50.6%) were older than 50 years old with no statistic significant difference (P=0.152). Family history were documented in 34 cases of those with breast carcinoma (28.3%) with strong CYP4Z1 expression seen in 30 cases of them (88.2%) with significant statistic difference (P=0.008). In our study the mean patients were age 47.5 years, 53.9% of them were younger than 50 year, 60% of them show CYP4Z1 overexpression. The peak age frequency of 50-59 year was reported in our study which included 28.1% of breast carcinoma patients, 69.4% show moderate-intense expression. The mean age for breast carcinoma patients with CYP4Z1 overexpression was 49 years, 54.5% of them show moderate-intense expression and 78% of those over 60 year old and we find a statistic significant association between the age and the tumor expression of CYP4Z1 which reflects gradual increase of CYP4Z1 expression of with age (P=0.038) (Table 1). In our study, the most common histological subtypes were invasive ductal carcinoma -not otherwise specified (67.2%), followed by intraductal carcinoma (9.4%), invasive lobular carcinoma (6.3%) and mucinous carcinoma (4.7%) (Table 1). The CYP4Z1 overexpression was high in carcinoma of grade II (83%), lower in grade I (63.6%) and intermediate in those of grade III cases with no statistic significant difference (P=0.100) (Table 1). Regarding TNM stage of breast carcinoma, the tumor size ranged from 0.9 cm to 6.3 cm with mean size of 2.8 cm and CYP4Z1 expression show no statistic significant difference regarding TNM stage and lymph nodes involvements (P=0.708) in spite of expression was more frequently seen in T3(80%). The majority of carcinoma cases seen in T2 stage 63(52.5%) with no statistic clinical significance between tumor size and CYT4Z1 were expression (P=0.702). Among patients with tumor size more than 5 cm (T3), 80% had overexpression of CYP4Z1, compared to 73% for those of T2 and 61% for those tumors smaller than 2 cm (T1), i.e. CYP4Z1 expression increases intensity gradually with tumor size with no statistic significant difference (P=0.702). Lymph node status was evaluated for patients with mastectomy and axillary clearance,85 cases(70.8%) were with no lymph node involvements, only 35(29.2%) have lymph nodes metastasis, 80% of them (28/35) cases show moderate-intense CYP4Z1 overexpression in contrast to 67.1% (57/85) of studied samples showing no lymph nodes involvements with no statistical significance difference (P=0.156).

Discussion

Breast carcinoma is a disease with a great heterogeneity in its clinical behavior and its prognosis is related to a large variety of clinical and pathological factors. Despite the growing evidence for the contribution of CYP4Z1 to tumor malignancy, there were limited studies looking for CYP4Z1 expression in breast carcinoma and no study looking for CYP4Z1 in metastatic breast carcinoma [18].

While the CYP4Z1 substrate is unknown, CYP4Z1 mRNA was detected in normal mammary gland tissue and breast carcinoma tissue, whereas only minimal expression was found in all other tissues

[9]. In the present study, CYP4Z1 overexpression was seen in 70.8% of Iraqi female patients' breast carcinoma with more predominant in T3(80%). This reflects the correlation between CYP4Z1 expression and development of tumor in contrast to benign tumors that show no CYP41 expression. This CYP4Z1 overexpression is associated with high stage and it correlates with poor prognosis.

These results came in accordance with preceding study concerned with CYP4Z1 expression in breast carcinoma [20]. This overexpression is verified by other studies which show that CYP4Z1 overexpression is concomitant with increased production of 20-hydroxyeicosatetraenoic acid (20-HETE) in breast carcinoma, and it has been assumed that CYP4Z1 metabolizes arachidonic acid to 20-HETE resulting in enhanced growth and spread of breast cancer cells [15,16].

The current study which includes 120 patients with breast carcinoma of various types and stages proved that CYP4Z1 is expressed to various extent in breast carcinoma and that 70.8% exhibit an overexpression and this expression was heterogeneous in the tumor as there were areas with stronger staining and other areas with weaker staining within the same tumor slice.

IHC scoring is a semi quantitative method, which represents a weakness of our study and we tried to standardize the analysis by grading the slide using the most strongly stained area, exceeding 5% of the tumor area on each slide. Numerous evidences indicates the importance of CYP4Z1 expression in breast carcinoma where it is increasingly recognized as a potential marker or a target for advance of new tumor therapy [17]. In the present study, we present convincing evidence of IHC CYP4Z1 expression in breast carcinoma and we demonstrate generally absent or weak expression in benign breast lesions.

As the sample size of our study was to small, strong statistically significant correlation between CYP4Z1 expression and some of clinicopathologic features were not possible. However, some clear significant statistic correlation, particularly with prognostic factors of carcinoma (Age, family history and carcinoma subtypes) is documented and this reflects a difference in correlation of CYPp450 in certain families and role of family history in women who have a first degree relative with breast carcinoma which show a statistically significant difference with CYP4Z1 expression that supports the previous data that verify the polymorphism of CYP4Z1 in populations that reflected in susceptibility of them for various types of malignancies and so our result data suggest that CYP4Z1 may be associated with the breast cancer health disparity among the societies.

The result confirms the suggested progressive effect of CYP4Z1 with age specially in invasive ductal carcinoma subtype of carcinoma and all the metastatic carcinoma expression CYP4Z1 which had unfavorable disease prognosis markers so that further sample size may be better delineate the relationships. The statistic significant association between the age and the tumor expression of CYP4Z1 which reflects an expression of CYP4Z1 increases gradually with age and plays an essential role in promoting carcinogenesis, angiogenesis and tumor aggressiveness.

Although the accurate role of CYP4Z1 in tumor progression is unclear, these data indicate that CYP4Z1 has been involved in the pathogenesis of tumor progression. The low number of analyzed lymph nodes that were identified by axillary dissection may cause underestimation of the number of stage III tumors. Many clinical studies have established that alteration in CYP4Z1 expression predicts poor prognosis for breast cancer and it is associated with features of tumor aggressiveness and also a predictive marker of responsiveness to selected forms of therapy [17].

Additionally, it was described that expression of CYP4Z1 gene is up regulated by activated glucocorticoid and progesterone receptors [21]. In our study, all benign breast lesion demonstrated negative or weak CYP4Z1 expression and this may be attributed to low protein expression of CYP4Z1, protein conformational changes, or protein degradation and these results agree with those reported in previous studies [20].

Our study showed a propensity of CYP4Z1 indicate larger tumor size (Table 2). Although this difference was not statistically significant but the portion of tumors larger than 5cm have higher rate of CYP4Z1 overexpression than those smaller than 5cm in size (80% in T3 versus 61% in T1). This result may reflect CYP4Z1 role in enhancing progressive proliferation of malignant cells that result in increase in tumor mass size, significant increase of tumor weight and micro vessel density with CYP4Z1 overexpression by 2.6-fold and 1.9-fold in human tumor xenograft models, respectively [17]. The highest CYP4Z1 expression was seen in invasive ductal carcinoma, NOS (80%), which is known to have an aggressive clinical course, very often resulting in early recurrence and death. This difference is significant statistically 66.7% of intraductal carcinoma show overexpression of CYP4Z1, while 25% of those of infiltrative lobular carcinoma. This lower CYP4Z1 expression may reflect the lower aggressiveness of infiltrative lobular carcinoma in contrast to invasive ductal carcinoma.

This supports the view that CYP4Z1 overexpression is correlated with tumor aggressiveness, tumor progression and statistical significance that seen in other literatures in spite of some limitations that should be considered when interpreting our results which are limited by relatively small number of the non-ductal subtype of mammary carcinoma [15].

Our study has correlating CYP4Z1 overexpression with grade (83% in grade II, 63% in grade I and 64% in grade III) with no statistically significant difference in contrast breast carcinoma with no grade classification (mucinous carcinoma, metaplastic carcinoma, medullary carcinoma) that has lower CYP4Z1 expression in 50%. This verifies the correlation between the tumor aggressiveness and CYP4Z1 expression. This is in concordance with a previous study that showed CYP4Z1 overexpression which was specifically associated with increasing tumor grade of breast cancer as well as inferior patient outcome in mammary and ovarian cancer [2,6,20].

The prognostic importance of CYP4Z1 has also been investigated in the context of patients with or without lymph nodes involvements, where overexpression was seen in 67% for those with no lymph nodes involvements(N0) and more with N1(80%) and N2(75%). Although there is no significant statistic difference, it still reflects the correlation of higher expression of CYP4Z1 with higher tumor stages including lymph nodes involvement and so aggressiveness of tumor.

Conclusion

This study has defined the expression profile of CYP4Z1 in mammary cancer and it may offer the potential application as biomarkers to distinguish between benign and malignant breast disease growths and be a prognostic biomarker for malignant progression in these tumors. The underlying mechanism at the cellular level remains unclear, but it seems to play an important role in controlling the functions of other molecules enhancing tumor development and metastasis, Therefore, the impact of CYP4Z1 expression on other molecules functions is interesting to be investigated.

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