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Chitinase-3-Like Protein1 (YKL-40) as Biomarker in Serum of Egyptian Breast Cancer Females

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Abstract

Background: YKL-40 is a recently discovered human glycoprotein which is related in amino acid sequence to the chitinase protein family, but has no chitinase activity, its expression was shown to be highly expressed in breast cancer

Aim: we aim to detect level of YKL-40 in metastatic and non-metastatic breast cancer patients and comparing the results with fibroadenoma patients and normal females.

Methods and materials: 116 female patients were enrolled in this study and they are divided into 37 patients with fibroadenoma, 43 non-metastatic & 36 metastatic patient. Thirty healthy females were also included and served as control. YKL-40 level is detected in serum of studied groups using ELISA kit provided from Quantikine R&D systems, Minneapolis, USA.

Results: There is statistical significant difference regarding YKL-40 level between the control group versus non-metastatic group as well as metastatic group, and between fibroadenoma group and non-metastatic as well as metastatic breast cancer group (P<.001 each). Also there is high statistical significant difference between N1, N2 and N3 in non-metastatic group as well as between N2 and N3 in metastatic group (each<.001).

Conclusion: We concluded that there is significantly elevated serum YKL-40 level in breast carcinoma compared to women with benign breast tumors and healthy controls.

Keywords: YKL-40; Biomarker; Breast cancer

Introduction

Breast cancer is the top cancer in women both in the developed and the developing world. Despite being the most common cancer, 5-year relative survival rate of breast carcinoma is still over 80% when they are detected in early phase [1]. The incidence of breast cancer varies greatly around the world, being comparatively lower in less-developed countries than in the more-developed ones [2].

Like other carcinomas, breast cancer occurs based on an interaction between genetic heterogeneity and the environment. It has been reported that an accumulation of genetic variants is involved in the process of breast carcinogenesis [3]. Among these genetic variants, many of them play roles in apoptosis or cellular proliferation, since the balance between the two decides which direction to go; normal mammary development or carcinogenesis of the mammary gland [4].

YKL-40 is a new biomarker, which represents a heparin-binding and chitin- binding glycoprotein. It belongs to a group of mammalian proteins with an amino acid sequence similar to that of 18 glucosyl hydrolases, a group of bacterial chitinases [5]. Although YKL-40 does not have a chitinase activity, It is possible that YKL-40 has a role in the process of angiogenesis, stimulating the endothelial cells, and contributes to the formation of branching tubules, It is also well established that YKL-40 is a potent growth factor inducing the proliferation of chondrocytes and fibroblasts [6].

YKL-40 may have a role in the proliferation and differentiation of malignant cells; may protect tumor cells from apoptosis, stimulates angiogenesis; participates in the extracellular tissue remodeling; stimulates fibroblasts around the tumor; but this hypothesis still has to be confirmed in vivo [7].

Aim of the Work

In this study we aim to detect the level of YKL-40 in metastatic and non-metastatic breast cancer patients and compare the results with fibroadenoma patients and normal females. Also to compare YKL-40 level at different T stages, N stages in breast cancer group.

Subjects and Methods

The present study included 116 Egyptian women with age ranged from (20-65 years). They were recruited from National Cancer Institute in the period from August 2011 to February 2012. Patients were classified into fibroadenoma or breast carcinoma according to history taking, clinical examination and confirmed by mammography and surgical biopsies. Thirty healthy controls recruited during routine

checkup, who were proven to be healthy with no family history of breast cancer. The studied subjects were divided into three groups as follows:

Group I: (n=30) healthy females as a control group. Group II: (n=37) patients with fibroadenoma. Group III: (n=43) patients with non-metastatic breast carcinoma, they are classified according to TNM grading system into 24 cases with T2 and 19 cases with T3, also 5 cases with N1, 24 with N2 and 14 with N3. Group IV: (n=36) patients with metastatic breast carcinoma, they are classified according to TNM grading system into 28 cases with T2 and 8 cases with T3, also, 20 with N2 and 16 with N3.

Inclusion criteria: Adult females, age ranged from (20-65) years with no previous treatment with chemotherapy.

Exclusion criteria: Age below 20 and above 65 and any condition known to increase the YKL-40 serum level. Written consent forms were signed by all participants in this study including controls. All cases were subjected to estimation of YKL-40 level in serum. The Fibro adenoma and carcinoma biopsies were examined histopathologically.

Methods

Detailed history was taken. The following information was particularly stressed upon: Course of illness, age of onset of the disease, mode of presentation, positive family history. Routine preoperative investigations were done including: CBC, FBG, liver function tests (ALT & AST), kidney function tests (urea and creatinine) and PT & PC.

Quantitation of Chitinase 3-like 1(YKL-40) by using ELISA kit provided from Quantikine R&D systems, Minneapolis, USA (Catalog Number DC3L10) was done on all sera. This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for YKL-40 has been pre-coated onto a microplate. Standards and samples are pipetted into the wells and any YKL-40 present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for YKL-40 is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of YKL-40 bound in the initial step. The color development is stopped and the intensity of the color is measured.

Statistical analysis

Analysis of data was performed using SPSS 17 (Statistical Package for Scientific Studies) for Windows. Description of variables was presented as follows: Description of quantitative variables was in the form of mean, Standard Deviation (SD). Description of qualitative variables was in the form of numbers (No.) and percent's (%). Data were explored for normality using Kolmogorov-Smirnov test of normality. The results of Kolmogorov-Smirnov test indicated that data was not normally distributed (non-parametric data) so non-parametric tests were used for comparisons. Comparison between non parametric quantitative variables was carried out by Mann–Whitney U. kruskal-wallis test was used when comparing between more than two groups of independent variables. Results were expressed in the form of P-values. Binary correlation was carried out by Spearman correlation test. Results were expressed in the form of correlation coefficient (R) and P-values.

Results

The present study was conducted on 146 female subjects. They were classified into 4 groups: **Group 1:** 30 healthy control females with no family history of breast cancer. **Group 2:** Fibroadenoma patients; 37 females **Group 3:** Non metastatic breast cancer patients with nodal affection but without distal metastasis (bone, liver, brain, and lung); 43 female patients **Group 4:** Metastatic breast cancer patients with nodal affection and distal metastasis (bone, liver, brain. lung); 36 female patients.

As regards the age of the studied groups, it was 26.1 ± 4.48 years in control group and 31.53 ± 14.04 in fibroadenoma patients group, 53.72 ± 7.33 and 50.61 ± 10.22 in non metastatic breast cancer and metastatic breast cancer respectively. There was no statistical significant difference between the control group versus fibroadenoma (P=0.706) and non metastatic breast cancer versus metastatic breast cancer cases (P=0.292). On the other hand, there is statistical significant difference between the control group versus non-metastatic group as well as metastatic group, and between fibroadenoma group and non-metastatic as well as metastatic breast cancer group (P<.001 each) (Table 1).

	Controls (30)	Fibroadenoma (37)	Non metastatic breast cancer (43)	Metastatic breast cancer (36)	P value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age (year)	26.1 ± 4.48	31.53 ± 14.04	53.72 ± 7.33	50.61 ± 10.22	<.001**
Family History					
Yes	0 (0%)	6 (16.2%)	26 (60.55)	22(61%)	< .001**
No	10 (100)	31 (83.8%)	17 (39.5)	14(39%)	

Table 1: The age distribution and family history of all studied groups

Table 1 also shows that number of fibroadenoma patients with positive family history was 6 (16.2%) and the rest has no family history. Meanwhile, the non-metastatic breast cancer patients and metastatic breast cancer patients show high increase in the number of patients with positive family history 26 out of 43 (60.55) and 22 out of 36 (61%) respectively. We found statistical significant difference between Fibroadenoma group and both non-metastatic as well as metastatic breast cancer (p<.001).

In non-metastatic group, patients (43 females) were either Invasive duct carcinoma (ii, iii) 74.4%, 18.6%, respectively or Invasive lobular carcinoma (ii, iii) 4.7% and 2.3% respectively (Table 2). Regarding the grades of the tumor in non-metastatic group, 24/43 (55.8%) were grade T2 and 19/43 (44.2%) were grade T3 (Table 2). Regarding the nodal affection distribution among the patient group, it was 11.6%, 55.8% and 32.6% in N1, N2, and N3 respectively (Table 2).

In metastatic breast cancer, 77.8% had Invasive duct carcinoma (iii) and 22.2% had Invasive lobular (iii) (Table 3). Regarding the grades of the tumor in metastatic group, 28/38 (77.8%) were grade T2 and 8/36 (22.2%) were grade T3 (Table 3). Meanwhile, the nodal affection distribution among the group was 55.5% and 44.5% in N2 and N3 respectively (Table 3).

Pathology	Non metastatic breast cancer (43)	
	N.	%
Invasive duct		
ii	32	74.4
iii	8	18.6
Invasive lobular		
ii	2	4.7
iii	1	2.3
Grades		
T2	24	55.8
T3	19	44.2
Nodal affection		
N1	5	11.6
N2	24	55.8
N3	14	32.6

Table 2: Pathological classification, grading and nodal affection of non-metastatic breast cancer

Pathology	Metastatic breast cancer (36)	
	N.	%
Invasive duct		
ii	-	-
iii	28	77.8
Invasive lobular		
ii	-	-
iii	8	22.2
Grades		
T2	28	77.8
T3	8	22.2
Nodal affection		
N1	-	-
N2	20	55.5
N3	18	44.5

Table 3: Pathological classification, grading and nodal affection of metastatic breast cancer

Table 4 shows that the level of YKL-40 was progressively increased in level from control to breast cancer; it was 26.77 ± 10.8 in controls, 51.44 ± 48.04 in fibroadenoma; 136.50 ± 88.87 in non-metastatic breast cancer and 137.78 ± 80.86 in metastatic breast cancer. No statistical significant difference was found between the control group and fibroadenoma cases (P=0.269) and non-metastatic breast cancer versus metastatic breast cancer cases (P=0.899). On the other hand, there is statistical significant difference between the control group versus non-metastatic group as well as metastatic group, and between fibroadenoma group and non-metastatic as well as metastatic breast cancer group (P<.001 each) (Table 4).

	Controls (30)	Fibroadenoma (37)	Non metastatic breast cancer (43)	Metastatic breast cancer (36)	P value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ±SD	
YKL40(ng/mL)	26.77 ± 10.8	51.44 ± 48.04	136.5 ± 88.87	137.78 ± 80.36	<.001**

Table 4: The serum level distribution of YKL-40 in all studied groups

On comparing the results of the levels of YKL-40 at different tumor stages among non-metastatic and metastatic groups, there is no statistical difference between T2 and T3 in non-metastatic as well as metastatic group (Table 5).

Meanwhile, when comparing the results of the levels of YKL-40 at different nodal affection among non-metastatic and metastatic groups, there is high statistical significant difference between N1, N2 and N3 in non-metastatic group as well as between N2 and N3 in metastatic group (each<.001) (Table 6).

	Non metastatic group			Metastatic group		
	T2 (24)	T3 (19)	P value	T2 (28)	T3 (8)	P value
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
	126.39 ± 79.83	145.01 ± 100.98	0.575		148.79 ± 86.52	0.288
YKL-40 (ng/mL)				99.25 ± 45.52		

Table 5: Levels of YKL-40 at different tumor stages among non-metastatic and metastatic groups

	Non metastatic group				Metastatic group		
	N1 (5)	N2 (24)	N3 (14)	P value	N2 (20)	N3 (16)	P value
	Mean ± SD	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
YKL-40 (ng/mL)	62.75 ± 38.79	100.38 ± 72.9	224.77 ± 52.51	<.001	103.34 ± 79.73	143.34 ± 79.73	<.001

Table 6: Levels of YKL-40 at different nodal affection among non-metastatic and metastatic groups

YKL-40 was correlated to other variables among the whole groups with age (r=.472), with Nodal affection (r=0.527). There was statistical significance between YKL-40 and these 2 parameters (Table 7). Table 7 shows that the only 2 variants that can be used as predictors for cancer cancer in our study are the age and nodal affection.

	Correlation Coefficient	P value
	r	
AGE	.472**	0
T “all cancer cases”	0.049	0.71
N “all cancer cases”	.527**	0

Table 7: Correlation between YKL-40 and other variables among the whole group

Discussion

According to the Centers for Disease Control, 1 in every 4 deaths in the United States is due to cancer. Many of these deaths could be averted by improved early cancer detection, since existing therapies, especially surgery, are much more effective in early cancer stages as compared to later stages [8].

Breast cancer is the commonest cancer among women, contributing for 30% of all female cancers. It affects one in 14 women during their life time, almost one every three affected women will die of the disease. Breast cancer constitutes 33% of all female cancers at the National Cancer Institute, Cairo University [9].

The present study demonstrated that the age of fibroadenoma patients was 31.53 ± 14.04 years and 53.72 ± 7.33 and 50.61 ± 10.22 years in non-metastatic breast cancer and metastatic breast cancer respectively. We found statistical significant difference between fibroadenoma group and non-metastatic as well as metastatic breast cancer group (P<.001 each). These results are coincided with [10] who concluded that the incidence of breast cancer increases with age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically. At the same time [11], confirmed that the risk of getting breast cancer increases with age. A woman is more than 100 times more likely to develop breast cancer in her 60s than in her 20s. More recently, [12] stated that the strongest risk factor for breast cancer (after gender) is age: the older the woman, the higher her risk. These data are coincided with our results.

Family history of breast cancer is an important established risk factor of the disease. In the present study, fibroadenoma patients with positive family history were only 6 (16.2 % of all fibroadenoma patients), meanwhile it was 26 (60.55%) in the non-metastatic breast cancer patients and 22 (61%) in metastatic breast cancer patients. These data show statistical significant difference between Fibroadenoma group and both non-metastatic as well as metastatic breast cancer (p<.001). Most previous studies done by [13] confirmed our results as they found that a positive family history of breast cancer seems to increase risk similarly for ER+ and ER− tumors and similarly for all ER/PR subtypes.

The pathological classification of our non-metastatic breast cancer patients, were either Invasive duct carcinoma (ii,iii) 74.4%, 18.6%, respectively or Invasive lobular carcinoma (ii,iii) 4.7% and 2.3% respectively, and our metastatic breast cancer patients, were either Invasive duct carcinoma (iii) 77.8% or Invasive lobular carcinoma (iii) 22.2%. These results are in agreement with [14] who stated that the most common tumor for breast cancer in Egypt was invasive duct carcinoma (83.4%). They stated that carcinoma of the breast is the most prevalent cancer among Egyptian women and constitutes 29% of National Cancer Institute cases. Median age at diagnosis is one decade younger than in countries of Europe and North America and most patients are premenopausal. Tumors are relatively advanced at presentation. The majority of tumors are invasive duct subtype and the profile of hormone receptors is positive for estrogen receptors and/or progesterone receptors in less than half of cases.

The present study demonstrated that the grades of the tumor in non-metastatic group was (55.8%) of grade T2 and (44.2%) of grade T3. These results coincided with that of king et al. [15] who studied 346 patients with invasive breast cancer. They found the majority of the patients (58.3%) had T2 and (28.5%) had T3.

The biological function of YKL-40 in cancer is not yet known. It has been suggested that YKL-40 may play a role in the proliferation and

differentiation of malignant cells. It protects the cancer cells form undergoing apoptosis, stimulates angiogenesis, has an effect on extracellular tissue remodeling. It stimulates fibroblasts surrounding the tumor, although in vivo proof of these hypotheses are yet to be obtained [16].

It could not be excluded that YKL-40 might act as a growth factor for cancer cells, too. Another possibility is that YKL-40 protects cancer cells from undergoing apoptosis. It is also called "breast regression protein" (Brp), because it induces mammary involution in mice a few days after weaning. YKL-40 facilitates cell attachment and migration of vascular endothelial cells, which is an indication that the protein may function in angiogenesis [17].

The present work showed that the level of YKL-40 was progressively increased from control to breast cancer group; it was 26.77 ± 10.8 in controls, 51.44 ± 48.04 in fibroadenoma, and 136.50 ± 88.87 in non-metastatic breast cancer and 137.78±80.86 in metastatic breast cancer.

Obviously, our study showed that serum YKL-40 level in breast carcinoma is significantly higher than the concentration in women with fibroadenoma ($p<0.001$). No statistical significant difference was found between the control group and fibroadenoma cases and non-metastatic breast cancer versus metastatic breast cancer cases. On the other hand, there is statistical significant difference between the control group versus non-metastatic group as well as metastatic group ($P<.001$ each). It is believed that increased expression of YKL-40 may improve the identification of women at increased breast cancer risk.

The present work was coincided with the clinical studies of [18,19] which revealed that serum levels of YKL-40 were elevated in patients with a series of carcinomas including breast, colorectal, ovary, prostate, brain and blood. They concluded that these increased levels were correlated with poorer survival of cancer patients suggesting that serum levels of YKL-40 serve as a prognostic cancer biomarker.

Our results are similar to Jensen et al. [20] who surveyed 78 age-matched healthy females and 100 breast cancer patients with local regional metastasis and distant metastasis including bone, lung and liver tumor and found that serum levels of cancer patients were significantly higher than those observed in healthy subjects. Patients with distant metastasis like liver metastasis demonstrated the highest serum levels of YKL-40 (an average of 230 ng/ml).

Also, our results go with hand with a study done by Yamac et al. [21] who demonstrated that the median serum YKL-40 concentration in patients with locally advanced breast cancer was 149.5 ng/ml and it was higher than levels observed in healthy female controls. They suggested that YKL-40 may be a useful prognostic indicator of outcome for patients with locally advanced breast cancer.

An in vitro study has shown that ectopic expression of YKL-40 in breast cancer cells led to tumor formation with an extensive angiogenic phenotype and that recombination YKL-40 protein promoted vascular endothelial cell angiogenesis both in vitro and in vivo [22]. Therefore, the occurrence of high YKL-40 levels in highly differentiated and advanced cancers and recurrent cancer states could be explained by the role of YKL-40 in both angiogenesis and fibrogenesis, since highly differentiated tumors are characterized by high vascularization and a high turnover of extracellular matrix.

On comparing our results of the levels of YKL-40 at different tumor stages among non-metastatic and metastatic groups, there was no statistical difference between T2 and T3 in non-metastatic as well as metastatic group. Yamac et al. [21] found in their study the Serum YKL-40 levels were also higher in patients with tumor size >2 cm and node-positive disease but the differences were not significant ($P>0.05$).

In the present study, YKL-40 was correlated to other variables among the whole groups with age ($r=.472$), with Nodal affection ($r=0.527$). There was statistical significant between YKL-40 and these 2 parameters. This results are similar in part to that of **Yamac** et al. [21] They did multivariate analysis including tumor size, lymph node status, estrogen and progesterone receptor status, tumor grade, and serum YKL-40 levels indicated that serum YKL-40 levels were an independent prognostic variable for overall survival (hazard ratio, 1.004; 95% confidence intervals: 1.00, 1.07; $P=0.027$). Tumor size, lymph node status and estrogen receptor status were also independent prognostic variables for overall survival ($P<0.05$).

We concluded that there is significantly elevated serum YKL-40 level in breast carcinoma compared to women with benign breast tumors and healthy controls and prospective investigations are aimed at evaluation of YKL-40 as a reliable biomarker and an appropriate target for development of anticancer therapy.

Recommendation

Future focused translational researches combining basic and clinical research are needed in a joint effort to answer the questions:

Is plasma YKL-40 a useful clinical biomarker in patients with cancer?

Is YKL-40 a target for development of new cancer therapeutics? with close collaborations between multidisciplinary teams including surgeons, oncologists, pathologists, biochemists, tumor biologists, molecular biologists, biotech companies and the pharmaceutical industry. Without such collaboration it is unlikely that these two questions will ever be answered.

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