RESEARCH COMMUNICATION

Relationships among Serum CA15-3 Tumor Marker, TNM Staging, and Estrogen and Progesterone Receptor Expression in Benign and Malignant Breast Lesions

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Abstract

Serum tumor marker CA15-3 is widely used in follow-up for assessment of breast cancer prognosis. The aim of this study was to evaluate levels among healthy females and patients, to assess differences with tumor stage and grade, and to determine the relationship with estrogen and progesterone receptor expression. One hundred and thirty six Jordanian females were enrolled in this study: Forty-five were healthy females; seventy-two were diagnosed with breast cancer and nineteen diagnosed with benign breast lesions. Elevated serum CA15-3 level was significantly observed among breast cancer patients (37.95±6.65) compared to both healthy (14.97±0.8) and benign females (12.30±1.55), but no significant association was detected between serum CA15-3 level and age of cancer onset, menarche age, menopause age, parity and BMI. Decreased CA15-3 level was significantly associated with hormone therapy and oral contraceptive consumption among breast cancer patients. Significantly elevated CA15-3 serum levels were found among grade II, III and stage II and III breast cancer females compared to normal healthy females. Elevated CA15-3 serum levels were also found among ER+/PR+(54.242±7.89) and ER+/PR- (37.08±8.22) compared to healthy control females.

Keywords: Serum CA15-3 - healthy females - breast cancer - benign lesions - Jordan

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Introduction

CA15-3 is a high-molecular-mass mucin-like glycoprotein expres¬sed at the luminal surface of most secretary epithelia and associated with mammary tumors (Taylor et al., 2002). Increased levels were observed in patients with breast cancer (Kobayashi et al., 1989). Clinical uses of this marker include monitoring of patients with breast cancer (Duffy, 1999; Duffy et al., 2006), prognosis (McLaughlin et al., 2000), recurrence (Busetto et al., 1995; Molina et al., 1996; Molina et al., 1999) and metastasis (Elston et al., 1999; Thompson et al., 1991). CA15-3 level correlate exclusively with tumor size; higher CA15-3 serum level was found in advanced cancer stages, higher grades and metastasis (Berruti et al., 1994; Gang et al., 1985; Kikuchi et al., 1987; Theriault et al., 1989:2007; Tampellini et al., 1997; Gion et al., 2002). CA15-3 level increased in 10% stage I breast cancer disease, 20% stage II disease, 40% stage III disease, and 75% with stage IV disease (Duffy 2006). Elevated levels of this biomarker were detected among certain benign diseases, primary breast carcinoma (Coveney et al., 1995) and in patients with advanced adenocarcinomas (Anonymous, 1996; Cheung et al., 2000; Nicolini & Carpi; 2000).

Aging and menopause disturb the hormonal status among females and increase the chance of breast cancer development (Crump et al., 2000; Rymer & Morris, 2000; Pike et al., 2004; Hulka & Moorman; 2008), at the same time, serum CA15-3 level showed a significant increase within elderly menopause patients with breast cancer (Dehaghani et al., 2007). The aim of this study is to determine serum level of the tumor marker CA15-3 among Jordanian healthy, benign breast lesions and breast cancer females, as well as to highlight relationship between CA15-3 level with cancer onset age, menarche, menopause, body mass index (BMI), oral contraceptives (OCP), hormonal therapy (HT), tumor grade, stage and hormonal receptor status among breast cancer females.

Materials and Methods

A series of 136 Jordanian female were enrolled in this study (2007 to 2010). Forty-five asymptomatic control healthy females were referring to outpatient clinics affiliating King Hussein Medical City with no evidence of malignancy or familial history of breast cancer. Seventy-two were histopathologically diagnosed with breast cancer and nineteen with benign breast lesions attending the same Medical City.

Data was collected from breast cancer females, benign

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and control includes age, menarche age, menopause age, BMI, OCP, HT and parity. A one year period was the minimal period to consider HT and OCP as positives.

Blood samples were collected in plain tubes, serum was separated by centrifugation and CA15-3 levels measured using AxSYM CA15-3 Microparticle Enzyme Immunoassay (MEIA) in AxSYM system automated analyzer (Ireland). Serum CA15-3 levels were assayed as recommended by the manufacturer (Abbott, Ireland). Cut-off value was determined by the 95 percentile of healthy individuals and the upper normal limit of CA15-3 was calculated (30.0 U/ml). Values higher than (30.0U/ml) were considered as elevated values. Breast cancer staging was classified according to NCI-NIH (National Cancer Institute- National Institute of Health) (Singletary et al., 2002). Progesterone and Estrogen receptors were assayed by DakoCytomation CA (USA).

Statistical analysis

Data were analyzed using SPSS software (version 11.5.0; SPSS Inc., Chicago, IL, USA). The mean serum level of the marker was compared using t-test (Independent Sample T-test) and one-way ANOVA. P value < 0.05 was considered as significant.

Results

Serum CA15-3 levels among healthy, benign and breast cancer groups were shown in Table (1). Elevated serum (CA15-3 37.95±6.65) was observed among breast cancer patients and was statistically different from both healthy and benign lesions groups, respectively.

Breast cancer onset age, menarche, menopause age and parity had no significant association with serum level of CA15-3 among all study groups (Table 2). Based on body mass index, females were categorized into two groups, below 30 kg/m2 and above or equal 30 kg/m2. No significant associations were found between CA 15-3 level and BMI categories (Table 2).

Serum CA15-3 level was significantly higher in non OCP (42.9±8.97) consumers and non HT users (43.7±10.2) compared to the consumers and users in breast cancer females as shown in table 2.

Table (3) shows serum CA15-3 levels of and its relationship with different breast cancer stages, grades, and progesterone and estrogen hormones receptor status. Breast cancer stages were determined for 70/72 female patients. Serum CA15-3 level was statistically significant higher among stage II, stage III, grade II and III patients. A significant association also found between serum CA15-3 level and ER+/PR+ (42.0±7.89 U/ml) and ER+/PR- (37.08±8.22 U/ml).

Table 1. Mean Pattern of Serum CA15-3 Level in Study Groups

	N	%	Mean±SEM	P value
Healthy control females				
	45	33.1	14.97±0.80	
Benign breast disorder patients				
	19	13.9	12.30±1.55[a]	0.004
Breast cancer patients				
	72	52.9	37.95±6.65[b]	0.001
All groups				
	136	100		

* 'CA15-3: Cancer antigen 15-3 (U/ml), N number of subjects. SEM: stander error of mean, [a]P<0.05 between benign and breast cancer patients, [b]P<0.05 between healthy control and breast cancer patients

Table 2. The Impact of Some Personal Parameters on Serum CA15-3 Levels within Study Groups.

	Healthy control females		Benign patients		Breast cancer patients	
	N%	Mean±SEM	N%	Mean±SEM	N%	Mean±SEM
Age (Years)						
< 40	17 (38)	13±1.7	9 (47)	12.±1.9	12 (17)	32±9.2
40-55	17 (38)	15±1.4	7 (37)	19±1.9	28 (39)	36±9.2
56-70	11 (24)	16±1.1	3 (16)	21±3.9	28 (39)	46±19
> 70	0	-	0	-	4 (5.6)	72±59
		p>0.05		P>0.05		p>0.05
Age at Menarche (Years)						
12-14	31 (69)	15±1.1	14 (74)	14±1.9	52 (72)	40±8.2
> 14	14 (31)	14±1.4	5 (26)	9±2.0	20 (28)	36±11
		p>0.05		p>0.05		p>0.05
Age at Menopause (Years)						
	N=21		N=5		N=48	
40-50	12 (57)	43±1.5	2 (40)	44±5.2	35 (73)	42±5.9
> 50	9 (43)	54±1.8	3 (60)	47±7.0	13 (27)	52±17
		p>0.05		p>0.05		p>0.05
Parity (children)						
Have	37 (82)	15±0.8	14 (74)	11±1.6	63 (87)	36±7.4
non	8 (17)	15±2.4	5 (26)	13±2.0	9 (13)	55±28
		p>0.05		p>0.05		p>0.05
BMI (Kg/m2)						
³30	13 (29)	15±1.8	6 (32)	15±3.1	33 (46)	42±9.5
<30	32 (71)	15±0.9	13(68)	11±1.7	39 (54)	34±9.3
		p>0.05		p>0.05		p>0.05
OCP						
User	13 (29)	15±1.4	7 (37)	12±3.1	20 (28)	23±.3.6[a]
non	32 (71)	15±0.9	12 (63)	13±1.8	52 (72)	43±8.9
		p>0.05		p>0.05		P=0.001
HT						
User	0	-	2 (11)	10±2.2	27 (38)	26±5.3[a]
non	0	-	17 (89)	13±1.8	45 (63)	44±10
				p>0.05		P=0.018

* 'SEM: stander error of mean, BMI: Body mass index, OCP: Oral contraceptive, HT: Hormonal Therapy. N number of subjects, [a]P<0.05 within each group

Discussion

Breast cancer is the most common cancer overall as well as the most common malignancy afflicting women in Jordan. According to the latest statistics from the Jordan National Cancer Registry (2012), breast cancer ranked first among cancer in females, accounting for 36.7% of all female cancers, and is the leading cause of cancer deaths among Jordanian women (Jordan breast cancer program, 2012).

CA15-3 is a mucin belonging to a large family of glycoprotein encoded by the MUC1 gene (Hayes et al., 1991) that are heterogeneously expressed on the apical surface of normal epithelial cell types, including those of the breast (Hayes et al., 1991). CA15-3 is elevated in breast

Table 3. Serum CA15-3 Levels in Breast Cancer Patients and Some Clinicopathological Factors Compared to Healthy Female Controls.

	No.	%	CA15-3 Mean±SEM	P Value
Breast cancer patients with known histological grades:				
Grade I	3	4.16	12.27±1.82	
Grade II	47	65.27	26.97±7.29	0.0*
Grade III	22	30.55	64.90±13.8	0.001*
Total	72			
Breast cancer patients with known stages:				
Stage 0	1	1.43	17.8±0.0	
Stage I	1	1.43	14.00±0.0	
Stage II	22	31.4	68.10±26.48	0.001*
Stage III	46	65.7	33.61±6.54	0.005*
Stage IV	0	0	0	
Total	70			
Breast cancer patients				
ER+/PR+	72	39	54.242±7.89	0.011*
ER+/PR-	14	19.4	37.08±8.22	0.004*
ER-/PR+	12	16.7	18.97±7.93	0.500
ER-/PR-	7	9.72	16.87±4.87	0.090
Total	72			
Healthy control females				
	45		14.97±0.802	

cancer patients with distant metastases and recurrences (Shering et al., 1998).

In this study, serum CA15-3 values was evaluated in different breast cancer stages, up to our knowledge, this the first study that determine the cut off value among Jordanian breast cancer females. There is no clear clinical cut-off for abnormal CA15-3 among Jordanians which could be varied from (22 to 60 U/ml) (Hayes et al., 1986). Therefore, cut off values for serum CA15-3 was calculated (30.0U/ml) from healthy Jordanian women who had no breast, benign or family history of any cancer. Our data showed that CA15-3 serum level is exceed the upper normal limit (30.0U/ml) in a noticeable manner among breast cancer subjects (72/136= 52.9%). However, normal CA15-3 levels (≤30.0U/ml) were found within females with benign breast lesions (12.3±1.55U/ml) and healthy females with no evidence of any malignancy (14.97±0.80U/ml) as shown in (Table 1).

Consistent with other studies (Brekelmans 2003; Lumachi et al., 2004), our study shows no significant association between breast cancer onset age, menarche age, menopause age, parity, BMI, and CA15-3 level among all study groups (Table 2). However, serum CA15-3 level showed a non-significant increase within elderly menopause patients with breast cancer, in contrast to what was reported by Dehaghani et al., (2007) who found statistically significant values. Aging and menopause usually disturb immunity and hormonal status (Pike et al., 2004; Rymer & Morris, 2000). So screening this marker is recommended for females above forty years since Jordanian develop breast cancer at a much younger age (median age is 51) than women in Western countries (median age is 65) (Jordan breast cancer program, 2012). Above all the menopausal age for our groups ranging between 41.65 ± 5.9 and 54.30 ± 1.84 Table (2).

A significant association was found between serum level of CA15-3 and history of OCP, HT use in breast cancer females (Table 2). The effect of hormones on the serum level of CA15-3 tumor marker is still under debate. Few studies shown no effect of HT on serum CA15-3 levels (Seregni et al., 1999; Kochańska et al., 2000), others reported a statistically sig¬nificant decrease in CA15-3 level among healthy cancer free HT users (Dehaghani et al., 2007; Cengiz et al., 2003). Our results agree with the later group, showing a remarkable significant decrease in the CA15-3 serum level among HT users in breast cancer females group.

Serum CA15-3 marker is a reliable tumor marker in breast carcinoma patient with distant metastases, however the marker level is rarely elevated in patients with local or primary carcinoma as found in several studies (Gang et al., 1985; Kikuchi et al., 1987; Berruti et al.,1994). In this study, significant association was found between serum CA15-3 level in patients with stages II, stage III breast disease as shown in Table 3, and in patients with grade II and III, respectively. So serum CA15-3 may be a reliable biomarker in screening breast cancer since thirty seven percent of breast cancer cases in Jordan are presented at advanced stages (III-IV) during which survival rates are low and the disease is less curable and 52% of cases are diagnosed in early stages (0-II) (Jordan breast cancer program, 2012)

Serum CA15-3 was increased among 39/72 ER+/PR+ and among 14/72 ER+/PR-. So estrogen receptors status is strongly correlated with elevated CA15-3 level and this result is consistent with what's reported by (Bensouda et al., 2009). Thus, preoperative serum tumor markers measurements are of value, especially in patients with advanced stage breast cancer, and maybe useful in the therapeutic decision-making of patients with breast cancer.

In conclusion, CA15-3 serum level is independent on age, menarche age, menopause age, and parity among healthy females, benign and breast cancer groups. Elevated serum CA 15-3 level was found in breast cancer and directly related to advanced stages and advanced tumor grades within breast cancer females. OCP consumption and HT use were statistically among breast cancer females; finally serum CA15-3 was correlated with estrogen receptor status which may be useful in therapeutic decision.

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