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COMPARATIVE EVALUATION OF CA15-3 EFFICIENCY AS A DIFFERENTIAL BIOMARKER TO THE EARLY DIAGNOSIS OF BOTH BREAST AND OVARIAN CANCER IN EGYPTIAN FEMALES

Samia A Ahmed[1], Hanan F. Aly[1*] and Omar S. Omar[2]

[1]Therapeutic Chemistry Department, National Research Center , Cairo , Egypt

[2]Department of Surgery, Breast Cancer Clinic, Cairo University Hospital, Cairo, Egypt

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***Correspondence for Author:**
Prof. Dr. Hanan Farouk Aly
Therapeutic Chemistry Dep.
National Research Center
Egypt.
hanan_abduallah@yahoo.com

ABSTRACT

To examine the possible involvement of human CA15-3 in in early diagnosis of breast and ovarian cancer among Egyptian females, serum activity of this biomarker was demonstrated by the method of Enzyme Linked Immunosorbant Assay. Five groups of subjects (20 for each), were examined in this study for breast cancer. Healthy control ,breast cancer patients with grad I , II and two treated groups with grade I and II . In addition, five groups of ovarian cancer women (25 each), were divided similarly as in breast cancer groups. The present results declare that, drastic significant increase in CA15-3 level ($p \leq 0.05$), in breast than ovarian cancer patients, with age and grade dependent (grade II in both tumor types showed significant increase in CA15-3 level than grade I), as compared to healthy control group ($p \leq 0.05$) . In addition, treatment of breast and ovarian cancer exhibited significant increase in CA15-3 levels with age and grade dependent. Moreover, the manipulated data showed, positive Pearson's correlations between CA15-3 biomarker, age, grade , breast , ovarian cancer and the corresponding treatments .These findings imply that, CA15.3 is expressed in many malignant disease including breast and ovarian cancer. Although, CA15-3 has high specificity low sensitivityand it more expressed in breast than ovarian cancer and it can be used as a prognostic marker in breast cancer as well as after treatment more than in preoperative surgery of ovarian cancer and treated patients.

Key words: Breast cancer, Ovarian cancer, Tumor, CA15-3, biomarkers.

INTRODUCTION

Cancer is the most devastating disease in the world, causing about 7.6 million deaths (around 13% of all deaths) in 2008. Deaths from cancer world wide are projected to continue to rise to over 11 million in 2030 [Xue et al., 2008 and WHO, 2011]. Breast cancer (BC) is the leading cause of death among women. It is responsible for approximately 15% of all cancer-related deaths, and the incidence of breast cancer (BC), may increase substantially in the future [3–5]. BC affects women of all ages and the mortality rate among the patients is also high. The high rate of mortality in BC patients can be attributed in part to the late diagnosis of the disease, and consequently the delayed initiation of the medical treatment by, radio therapy and/or chemo therapy. The late diagnosis/treatment of BC is usually associated with poor prognosis [Khatib and Aljurf 2008]. Early detection and proper monitoring of patient status during therapy is urgently needed to decrease the rate of mortality among BC patients (Ibrahim et al., 2012). Identification of biomarkers that can be used for the early diagnosis of the disease and/or the prognosis of the patient in therapeutic programs would be clinically very valuable and ultimately reduce the rate of mortality among BC patients.

Breast as well as ovarian cancer result from a succession of genomic alterations involving oncogenes (c-myc, HER 2 neu and k-ras) and tumor suppressor genes (p53) that have a critical role in normal cell growth regulation (Mabrouka and Labib, 2003).

In addition , ovarian cancer is one of the most lethal malignancies. Patients with early stage ovarian cancer are often asymptomatic or report nonspecific symptoms so ovarian canceris mostly diagnosed at an advanced stage (Engelstaedter et al., 2012).Primary treatment includes operative cyto –reduction and subsequent combined platinum-based chemotherapy. Though reported primary response rates are around80%, ovarian cancer is the most lethal gynecological malignancy since 60-70% of the patients relapse or die within5 years after primary diagnosis (Cannistra ,2004). The prognosis of the disease could be improved by early detection, but thisis difficult to achieve. Epithelial ovarian cancer (EOC) represents the most lethalmalignancy of the female genital tract. Now a day's ovarian cancer patients' prognosis mostly relies on completeness of surgical tumor resection , clinical staging and histological tumor grading(Scholz et al ., 2012). Thus there is a compelling need to identify and validate tumor specific antigens which are suitable to individualize therapeutic strategies. Interestingly, during EOC evolvement and progression host anti-tumor immune defense seems to be actively blocked by tumor derived mediators. By creating this highly suppressive

environment, EOC manages to extensively grow and spread in the peritoneal cavity (Scholz et al ,. 2012)

Cancer-associated protein markers are present in the blood, and are important for early diagnosis of cancer. Cancer marker proteins may be produced by cancer cells, by the body's reaction to cancer, or by other various conditions(Park et al., 2013). There are many types of breast cancer markers that can be used to obtain an early diagnosis of breast and ovarian cancer(Park et al., 2013).

Cancer antigen 15-3 (CA15-3), is one of the most accepted markers for the early detection of breast cancer (Nishimura et al., 2003). Its concentration in healthy human blood is maintained usually less than30U/mL. However, as breast cancer progresses, CA15-3 is over expressed on cell surfaces and secreted into the blood. Previous studies have shown that CA15-3 levels in the blood of patients with breast cancer were significantly higher than in healthy person (Park et al., 2013).

CA15-3 is a glycoprotein and a member of the mucin family. Mucins, the main class of membrane bound O-linked glycoproteins, contain a repeating amino acid sequence that is rich in serine and threonine (Cazetet al., 2010). In healthy humans, O-linked glycans have a linear polylactosaminic chain that can be fucosylated(Hanisch et al., 1989). In contrast, breast cancer cells express incomplete O-linked glycans, resulting in the aberrant expression of short O-linked glycan chains with dense Thomsen–Friedenreich (T/TF) antigens or sialylated TF-antigens . The truncated TF-antigen on the breast cancer-associated protein includes the sugar N-acetyl galactosamine (GalNAc) or sialylated GalNAc. In particular, GalNAc is linked to galactose on the surfaces of cancer-associated mucins (Park et al., 2013).

Pharmacological intervention, revealed that CA15-3 , may not only be detected in blood, but also in other biological fluids, including breast cysts. In breast tumors, its preoperative serum concentrations are related to tumor size, axillary nodular involvement, distance metastases and histological degree and behave (Ruibal et al ., 2007), following multi-variant analysis, as an independent prognosis factor of disease-free interval, both in the group considered globally and in positive axillary tumours. Its relationship with hormone dependence is not unanimous. Serum CA15.3 is also of an a poorer response to chemotherapy, and together with lymphovascular invasion and the expression of the erbB2 encogen, it behaves as a prognosis factor in locally advanced breast cancer (Ruibal et al ., 2007)

MUC1, human polymorphic epithelial mucin, is an indicator of highly glycosylated transmembrane protein with protective functions that is aberrantly over-expressed in many tumors, including a high percentage of breast origin tumors. This is why it is regarded as a tumor associated antigen. It behaves as an oncoprotein, and its greater cellular expression is correlated to tumor. The aggressiveness and to lower survival. It also seems to play an important role *in situ* ductal hyperplasia carcinoma transition. At biological level, many of its actions have been seen to be carried out by means of biochemical mechanisms related to its cytoplasmic dimension. Thus, it intervenes in cell proliferation, apoptosis, invasion and transcription, and is directly correlated to the genes of the tumor necrosis factor (TNF), kinase serine/threonine RAF1 and the matrix metalloproteinase -2 (MMP-2). At protein level it is related to the c-myc gene and phosphorylated AKt. Its C-terminal fragment interacts with the alpha estrogen receptor, and this is stimulated by estradiol which induces the growth and survival of the tumour cells.15 Similarly, it inhibits E cadherin-mediated cell(Ruibal et al ., 2007)

Aggregation and the cytotoxic action of the K cells. Some variants modulate the localization of certain growth factor receptors, which entails a different response to external stimuli continuing in our line of work, and in view of the above, we have analyzed, in women with carcinoma of the breast and ovary , the behavior of serum CA15.3 according to the tumor grade and chemotherapy(Ruibal et al ., 2001),

It was notice that, patients with high serum CA15-3 concentrations have a significantly worse prognosis than those with low concentrations, both in terms of disease-free survival and overall survival, probably due to a larger burden of occult disease. CA15-3 measured during follow-up has been consistently shown to predict liver and bone metastases(Darwish et al ., 2012).

Engel staedter et al. (2012) reported that,CA15-3 is routinely utilized as a diagnostic and prognostic markers in breast cancer but the diagnostic relevance for patients with ovarian tumors of uncertain dignity remains unclear.

Discovering an effective means for the early evaluation of ovarian or breast cancer has been intensively sought goal. The ability to evaluate the condition preoperatively would significantly improve patients' survival time and quality of life, while potentially reducing health care costs. Because of the overall oncological importance of CA15.3, this study was

planned to investigate the preoperative sera expression of CA15.3 markers in the breast cancer patients with grade 1 and 11 with correlation to age as well as the detection of CA15-3 level in response to treatment is evaluated . In assertion, the present study is also designed to examine the significance of CA15.3 as perspective diagnostic indicator of ovarian cancer and its responsiveness to chemotherapeutic treatment.

Clinical Examination and Subjects

This study included one group of healthy control subjects and two groups of patients with grade I and II of breast and ovarian cancer. In addition, grade I and II treated groups. Samples were given from National Cancer Institute, Cairo, Egypt and Kasr Aini – Breast Cancer Clinic, Cairo, Egypt. Each group in breast cancer and treated one consisted of 20 subjects, while each group in ovarian cancer patients consists of 25 subjects.

Blood sample

Blood was drawn by vein puncture into Venoject tubes in the morning after an overnight fast. Blood was centrifuged at 3000 rpm and serum was used for all the laboratory determinations including CA15-3.For healthy controls, blood samples were drawn during a medical checkup and were normal for blood biochemical and immunological examinations.

Patients

- Complete history taking and physical examination with special emphasis on family history, contraceptive history, obstetric history, menstrual history and lactational history.
- Bilateral soft tissue mammography and breast ultrasound for patients elder then 35 years. If the breast is extremely dense then bilateral MRI is being performed. For those younger than 35 the initial assessment is by bilateral breast ultrasound followed by bilateral MRI.
- Full laboratory investigations (CBC, SGOT, SGPT, Albumin, Bilirubin, Createnin, Urea, Ca , ALP)
- Chest X-ray
- Abdomino pelvic ultrasound
- Bone scan. (However in early cases and in normal level of ALP it could be omitted)
- Tru cut biopsy with special emphasis on the biological profile (Estrogen receptor, progesterone receptor, Her 2 neu& KI67)

Eighty patients with breast cancer were undergo Mammography and MRI as they are considered a complementary examinations, both should be performed as well as histological

analysis established by reviewing hematoxylin-stained slides, as recommended by FIGO(1989). The following histological criteria were used to identify borderline tumors: (a) stratification of the epithelial lining of the papillae, with microscopic papillary projections or tufts arising from the epithelial lining of the papillae b) nuclear atypia, (c) mitotic activity, (d) intracystic clusters of free-floating cells, and (e) absence of stromal invasion .Microinvasion and micropapillary features were also recorded(Poncelet et al., 2010).

In addition, hundred patients from our study whose sera were tested for CA15–3 underwent surgery. Blood samples were obtained prior to surgery and were assigned to either the group of patients with malignant grade I or II of the ovary after histopathological examination. Histological evaluation and staging of tumor tissue was performed by an experienced gynecological pathologist (M.D.) in National Cancer Institute, Cairo, Egypt according to the criteria of the International Federation of Gynecologists and Obstetricians (FIGO) and the World Health Organization (WHO).Patients with ovarian border line tumors were excluded from the study. Again, histological evaluation and staging was performed by an experienced gynecological pathologist. The extent of the primary tumor (pT) is defined according to the UICC: pT1= the tumor is limited to the ovaries, pT2= the tumor has spread to the pelvis. pT3= the tumor has spread beyond the pelvis and/or to regional lymph nodes

Treatment protocol for patients with early breast cancer

The golden rule in defining the treatment for patients with breast cancer at our facility is based on multidisciplinary approach. Beside the weekly breast cancer surgery clinic and the twice weekly breast cancer medical oncology clinic, a weekly multidisciplinary breast cancer meeting is being conducted with participation of all the breast care providers (surgeons, radiologists, medical oncologists, radiotherapists, pathologists and psychologists).After obtaining all the clinical, radiological as well as the histopathological results, the case is presented in the weekly multidisciplinary meeting for defining the treatment protocol.

In non-metastatic breast cancer patients the treatment options include

- **Surgery first**

  Breast conserving surgery
- This includes wide tumor excision, axillary lymph node assessment (Either sentinel node biopsy or complete axillary dissection. In this type of surgery where less than 20% of the breast is being resected there is no need for any corrective maneuvers. At our institution

this is defined case by case). Postoperative irradiation to the breast together with a boost at the operative bed is an integral component of this type of treatment (Fig. 1)

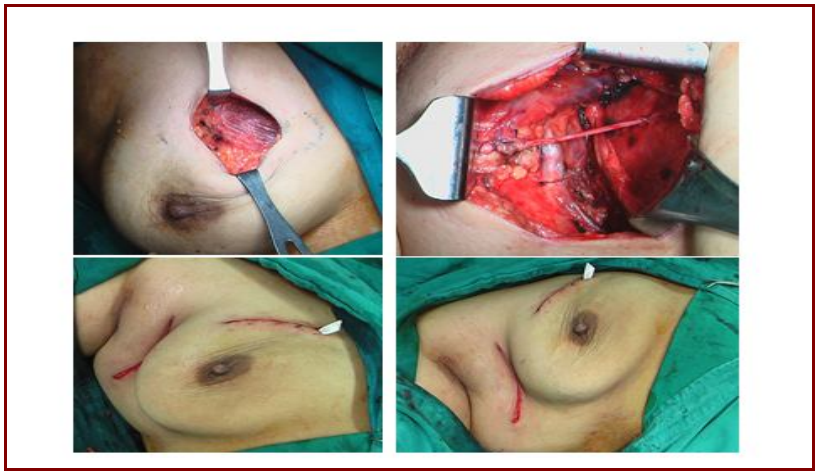


Fig 1: Breast conserving surgery

Oncoplastic breast surgery

- This is defined as tumor specific immediate breast reconstruction. This approach allows wide tumor excision with an adequate free resection margin (>20% of the breast will be removed) and yet obtain a cosmetically good result.The use of this approach prevents many ugly esthetic results after classic breast conservative surgery (Fig2).

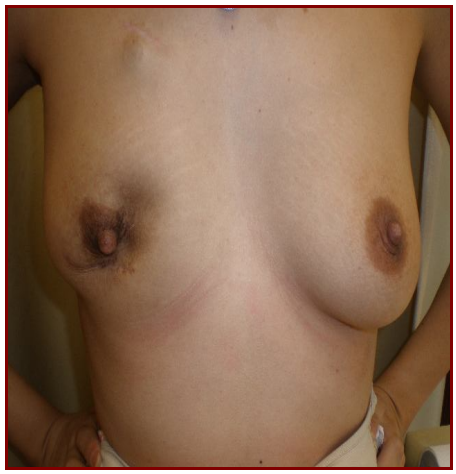


Fig.2: Ugly appearance after conservative breast surgery

- It is based on choosing an approach that utilizes the cosmetic defect in this breast which allows for wide excision followed by correction of this cosmesis. Contralateral symmetry procedure is performed to obtain optimum bilateral esthetic result (Fig. 3). Identification of the tumor bed by clips is an essential component in this technique since the incision lines should not be necessarily at the site of the tumor (Fig. 4).

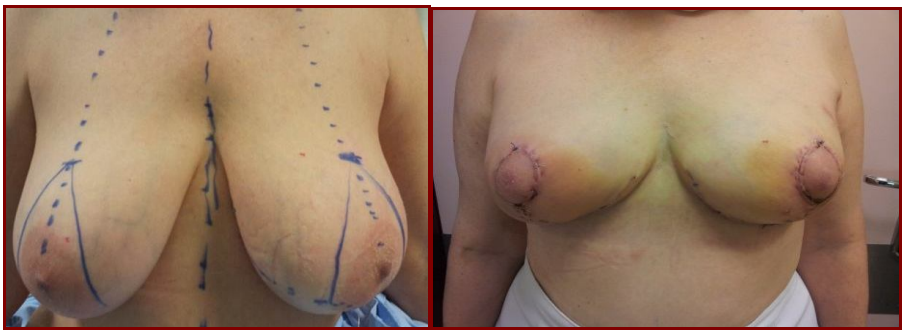


Fig 3:Oncoplastic reduction pattern approach with contralateral symmetry

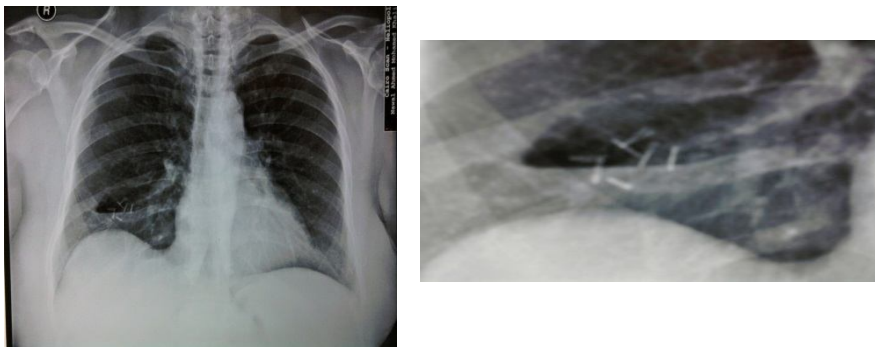


Fig 4: Clipping of the operative bed for future tumor bed localisation

- In this approach there is maximum benefit in terms of the following:
- Oncologic safety (wide tumor excision)
- Good esthetic result.
- Reduction of the size of the breast and hence better for the patient by reducuing the dose of irradiation.

  Modified radical mastectomy (Fig. 5)
- This is reserved for the cases where breast conservative and breast oncoplastic surgery are technically not feasible as well as inflammatory breast cancer.

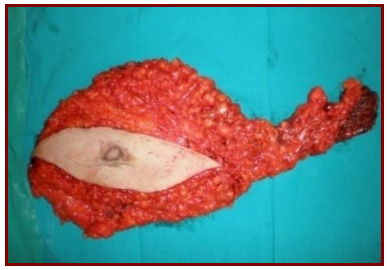


Fig. 5: Modified radical mastectomy

- **Neoadjuvant chemotherapy (Chemotherapy before surgery)**
- Locally advanced breast cancer with the aim of initial systemic control and will be followed by modified radical mastectomy.

- Locally advanced breast cancer where conservative breast surgery is not feasible. Here the aim is to convert a mastectomy case to conservative breast surgery case.
- Inflammatory breast cancer.
- A small sized breast where a better oncologic and cosmetic result will be obtained by the reduction of the tumor size.

Choice of adjuvant regimen

Low risk group

- **Tumors with all the following**
- pT1
- grade I
- ER and /or PR positive
- Her2neu negative
- Age > 35 years
- Ki 67 < 14%
- Hormone therapy only

Intermediate risk node negative group

Tumors with any of the following

- pT>2cm
- Grade 2-3
- Presence of extensive peritumoral vascular invasion
- ER & PR negative
- Her 2 neu overexpression
- Ki67 > 14%
- Age < 35 years
- 6 cycles of FAC/FEC is considered the standard for this subgroup.

Intermediate risk node positive group

- Node positive (1-3) , ER and / or PR positive and Her2neu negative.
- 3 cycles of anthracyclinebased regimen followed by 3 cycles of taxane based regimen.

High risk group

4 or more involved nodes or

- 1-3 involved nodes and ER & PR negative or
- Her 2neu overexpressed
- 4 cycles of anthracyclin based regimen followed by 4 cycles of taxane based regimen.

Sample description

Tumor samples of 50 primary ovarian carcinoma were evaluated by IHC for MUC1. Median a great primary diagnosis was 58.8 years (range 40–67).

Table 1: Patient characteristics of ovarian carcinoma

Stage Patientsstage (FIGO)	**n**	**%**
I	4	12.5
II	10	6.5
III	4	6.5
IV	3	1.9
Grade		
G1	10	6.7
G2	10	6.1
G3	5	1
cystic lesions	2	
inflammatory diseases	0	
benign tumors	0	
malignant tumors	2	
Histology(%)serous		20.8
Mucinous		8.4
endometrioid		10.6
clear cell		7.1
total	50	

METHODS

Surgical treatment was considered conservative when at least one ovary and the uterus were spared then chemotherapeutic treatment was applied . Conservative treatment consisted of

unilateral cystectomy (UC) or unilateral salpingo-oophorectomy (USO), as well as bilateral cystectomy(BC) and USO þ contralateral UC (USO þ UC).The present study is applied for 40 treated breast cancer as well as 50 pateints of treated ovarian cancer . Serum tumor marker levls of CA15.3 was measured with Enzyme-linked-immunosorbent-assay (ELISA),Labor Diagnostika Nord(LDN) GmbH and Co ,KG. As previously described (Engel staedter et al., 2012). Values were considered elevated whenCA15.3 > 30 IU/ml. Serum tumor marker levels in a given patient was considered abnormal if at least one of the markers was elevated.

Ethics approval

The informed consents were taken from the patients of our studied groups according to guideline of the Medical Ethical , National research Center. The study participants gave their written consent, samples and clinical information wereUsed anonymously. Committee of National Research Centre, Dokki, Giza. All the studied groups were subjected to full history report including personal history, complete present history, family history, social history and past history.

Statistical Analysis

The results are expressed as mean ± SD. Data of the five groups were analyzed using Co-state computer program where unshared letter is significant at $p \leq 0.05$. The Correlations between CA15-3 marker, age and grade in the breast cancer as well as ovarian cancer patients were analyzed using Pearson's correlation analysis.

RESULTS

The present result shows that, CA15-3 significantly increased $p \leq 0.05$), in serum of patients with both breast and ovarian cancer as compared to the normal healthy subjects with percentage increase of 485.86 and 911.96 %, respectively for grade I and II of breast cancer as compared to the normal subjects. While, the percentages increase in CA15-3 level reached to 260.34 and 314.46%, respectively for grade I and II of ovarian cancer. Although, treatment of both breast and ovarian cancer showed significant increase in CA15-3 level with percentages increase amounting to 231.48 and 365.38 %, respectively for treated breast cancer patients with grade I and II. Whereas, the percentages recorded 92.54 and 122.22%, respectively for treated ovarian cancer with grade I and II (Tables 2, 3 and Fig. 1). Thus, remarkable expression for CA15-3 was noticed depending on the type of cancer and its grade. This observation is documented by

the finding of significant increase in CA15-3 in breast and ovarian cancer patients that correlated positively with age and grade (Table 4).

Table 2: Levels of CA15-3 in normal, breast cancer and therapeutic patients with respect to grade and age.

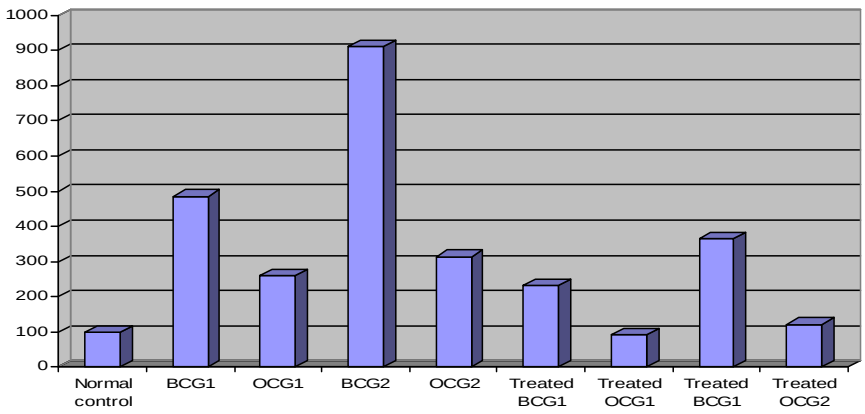
Markers / Groups	Group 1 (Normal control) (n=20), Mean ± SD	Group2 (Breast cancer grade I) (n=20), Mean ± SD	Group 3 (Breast cancer grade II) (n=20) Mean ± SD	Group 4 Breast cancer treated grade I n=20 Mean ± SD	Group 5 Breast cancer treated grade II n=20 Mean ± SD
CA15-3(U/L)	20.65± 1.00[a]	120.98± 10.00[b]	208.97± 16.00[c]	68.45±8.00[d]	96.10±6.90[e]
Age	26.90± 1.80[a]	48.90±4.00[b]	58.50±6.00[c]	43.60±5.00[b]	67.30± 10.30[d]

Statistical analysis is carried out using SPSS computer program coupled with post hoc and Co-state computer program, where unshared letter is significant at P value ≤0.05**.**

Table 3: Levels of CA15-3 in normal, ovarian cancer and therapeutic patients with respect to grade and age.

Markers / Groups	Group 1 (Normal control) (n=20), Mean ± SD	Group2 (Ovarian cancer grade I) (n=25), Mean ± SD	Group 3 (Ovarian cancer grade II) (n=25) Mean ± SD	Group 4 Ovarian cancer treated grade I n=25 Mean ± SD	Group 5 Ovariancancer treated grade II n=25 Mean ± SD
CA15-3(U/L)	23.45±2.12[a]	84.50±6.10[b]	97.19± 11.23[c]	45.15±4.45[d]	52.11±6.90[e]
Age	40.30±5.10[a]	49.10±5.56[b]	59.23±3.00[c]	44.56±4.78[b]	58.88±8.45[c]

Statistical analysis is carried out using SPSS computer program coupled with post hoc and Co-state computer program, where unshared letter is significant at P value ≤0.05**.**



BCG: Breast cancer grade and OCG :Ovarian cancer grade

Fig 6. Level of GA15-3in malignant breast ovarian cancer and chemotherapeutic treatment.

Table (4). Pearson's correlations between CA15-3 biomarker , age , grade , breast , ovarian cancer and Corresponding treatments

Parameters	CA15-3	Age	Grade	Breast cancer	Ovarian cancer	Treated breast cancer	Treated ovarian cancer
CA15-3	1	0.614(**)	0.746(**)	0.882(**)	0.996(**)	0.925(**)	0.909(**)
Age		1	0.769(**)	0.896(**)	0.945(**)	0.981(**)	0.989(**)
Grade			1	0.980(**)	0.785(**)	0.922(**)	0.999(**)
Breast cancer				1	.0.687(**)	0.806(**)	0.986(**)
Ovarian cancer					1	0.895(**)	0.960(**)
Treated breast cancer						1	0.984(**)
Treated ovarian cancer							1

**** Correlation is significant at P ≤0.01 level (2-tailed**

DISCUSSION

The present results reveal the significant increase in CA15-3 in response to breast and ovarian cancer as compared to the normal level. In addition, the detected CA15-3 level showed higher level in breast than ovarian cancer and this increment is age and grade dependent . Interestingly, CA15-3 level still showed significant higher value in treated breast than ovarian cancer treated women with age and grade dependent as compared to the normal level.

The rapidly growing array of therapeutic agents addressed against molecular targets is sharply renewing the role of biomarkers for a comprehensive investigation of tumor phenotype and/or genotype (Giona et al ., 2002) .However, the increasing awareness of women towards the importance of the early diagnosis of breast cancer is leading to a progressive reduction of the size of the detected tumor. This makes the choice of the panel of tumor markers to be measured more and more problematic, due to the decreasing amount of available tissue. New technologies, such as micro-array, are expected to overcome this problem in the near future. In the meantime, serum markers seem ideal candidates to tackle with the practical problem of reduced tissue availability. In addition, serum markers may provide information on the tumor phenotype at the relapse, when the collection of tissue specimen is usually not convenient. In spite of these putative roles, the associations of preoperative marker levels with prognosis have been rarely evaluated. Horobin and

colleagues (1991) and Iaffaioli and colleagues (1991), showed a weak prognostic role of CA15.3 levels in a small patient series without performing a multivariate analysis. Jaffaioli and colleagues (1991) evaluated 60 patients with primary breast cancer and dichotomised CA15.3 values using a cut-off point of 30 U/ml. They found a significant prognostic role of CA15.3 in node-positive patients, while the role of the antigen was not assessable in node-negative cases since no positive values of the antigen were found in this group. More recently, Molina and colleagues (1998) evaluated the relationship between CA15.3 and prognosis in a subset of 186 patients with primary breast cancer. They dichotomised CA15.3 values using a cut-off point of 35 U/ml; however, they did not specify how this cut-off was obtained. Using multivariate analysis, they did not find any significant association between CA15.3 positivity and prognosis. Shering and colleagues (1998) performed a study specifically aimed at evaluating the prognostic role of CA15.3 in primary breast cancer. They studied 368 patients with primary breast cancer, 184 with axillary metastasis and 184 without. They categorized the antigen values as positive or negative, according to a cut-off of 30.38 U/ml, obtained by the recursive partitioning technique. They found a significant association between CA15.3 positivity and prognosis in node-positive cases, but not in node-negative ones. The lack of prognostic significance of serum CA15.3 may be due, at least in part, to the categorization of the antigen according to cut-off points. Thus,

1. CA15.3 is shown to be a prognostic marker in node-negative breast cancer;
2. The relationship of the marker with prognosis is continuous;
3. The risk of relapse increases progressively starting from a value of approximately 10 U/ml of CA15.3.
4. Dycotomic cut-off points aimed at an easier clinical application of the marker in decision making could be obtained in an advanced phase of the statistical evaluation (i.e., after generation of the statistical model) being aware of the underlying continuous prognostic relationship. On the basis of the present results, before considering CA15.3 for clinical decision-making, further studies.

The increase in CA15-3 in the present cases of tumor can be explained on the basis of , it usually associated with a solid neoplasm and it has been occasionally reported to be elevated in some hematologic malignancies. CA15.3, also known as MUC, is the soluble form of mucin-1, a trans- membrane glycoprotein (Takahashi et al., 1991). High serum levels have been observed in patients with adenocarcinoma mainly breast cancer, and correlate with tumor burden (Vizcarra et al., 1996).

Expression of mucin-1 in B-cell lymphomas, T-cell lymphomas and Hodgkin disease has also been reported. The expression of mucin-1 has been shown in the surface of plasma cell tumors and in MM cells and has been related to MM tumor burden. Moreover, it has been suggested that the expression of mucin-1 plays a role in tumor progression in plasma cell dyscrasia (de Larrea et al., 2008).

Surprisingly, information on solid tumor markers in plasma cell dyscrasia is scarce. There is one report in which all 9 patients with MM showed CA125 serum levels below the ULN. On the other hand, sMUC-1 levels were found increased in 13 out of 76 patients with MM and 3 out of 6 patients with plasma cell leukemia (PCL)(Iwasaki et al ., 1997) In this series, the increased sMUC-1 levels were associated with low hemoglobin levels, high lactase dehydrogenase, and short survival. Two single cases, one in which the patient with MM had ascites and another in which the patient had PCL with increased CA125 levels, have been reported (Luminari et al., 2003).

In our patient, the high levels of CA15.3 in both breast and ovary, which is to our knowledge the highest reported so far, suggested the existence of a concomitant solid tumor. This led to the use of a CT scan, an extensive breast and pelvic examination, and an ultrasound-guided biopsy of one of the focal liver lesions. While these examinations were carried out, the patient developed progressive disease with quickly evolving PCL. In fact, the increase in the number of peripheral blood plasma cell count (PBPC) along with the simultaneous increase in the tumor markers and the dramatic decrease of both after treatment with cyclophosphamide and dexamethasone, strongly suggested that a plasma cell proliferation by itself can result in high levels of these tumor markers, thus, the extremely high levels of CA15.3 in both breast and ovarian tumor was observed. In fact, this tumor marker was strongly expressed in breast cancer and treated woman than ovarian tumor so, it should be performed in the screening evaluation of patients with breast cancer (de Larrea et al., 2008).

The prognostic value of preoperative CA15.3 is uncertain. Current ASCO recommendations do not support prognostic use of preoperative CA15.3. Although, most studies found at least some prognostic value for CA15.3, many series are limited in the number of patients included (usually less than 1000 patients), have not performed multivariate statistical analysis, may have short follow-up and use different cut-off values for CA15.3 (Lazzarinoet al ., 1998). It was showed that preoperative CA15.3 has prognostic value, but limited to women with luminal A and B breast cancer. However, the additional information on preoperative CA15.3

did not result in improved discrimination in a prognostic model already containing other prognostic variables. This is in contrast with Sandri'sfindings(2012).They found that preoperative CA15.3 was prognostic in luminal B and HER2 like breast cancers and that preoperative CA15.3 had additional value in prognostic modeling. Thus, Sandri's suggested that preoperative CA15.3 yields minimal to no additional prognostic information in prognostic models already including other prognostic variables. Previously, few studies have examined whether comparing pre and postoperative values of tumor markers may result in improved prognostication (Duffy, 1999).Ebeling's study(2002), did not yield prognostic value for change in CA15.3 (it did for CEA), but only 740 patients were included for that analysis(Duffy ,1999).Furthermore, postoperative CA15.3 was assessed within 6 months following surgery, not allowing completion of adjuvant chemotherapy, that may significantly affect change in CA15.3. Including >3500 patients, It was found that postoperative CA15.3 and change in CA15.3 are able to improve prognostic modeling for distant metastatic relapse and breast cancer specific survival. Overall, no change in CA15.3 was associated with the lowest risk and both positive/negative changes in CA15.3 were associated with increased risk. Interestingly change in CA15.3 remained prognostic across all breast cancer subtypes. In contrast with the overall effect, a decreasing change in CA15.3 is associated with improved prognosis in basal like and HER2 like breast cancer (Brouckaert et al., 2013).

In addition, it was found that, CA153 is a marker of distant metastasis in breast carcinoma with high specificity and moderate sensitivity. In some patients with distant metastasis disease, CA153 levels may be raised before metastases can be detected by other means. Patients whose bone scan andCA15-3 results are concordant may be told with confidence whether or not they have bony metastases. CA153 levels are also raised in the great majority of patients with non-bony distant metastasis breast cancer. The potential uses of CA153 in clinical practice fall into two main categories: improved or more accurate diagnosis and increased convenience or cost-effectiveness. Thus, CA15-3 might be used in diagnosis by improving the diagnostic accuracy of bone scans, monitoring patients in follow-up and detecting metastases early. Attempts to substitute CAlS-3 for other investigations are likely to be less successful, owing to its only moderate sensitivity (that is, the number of false (negatives will be too great to be tolerated) (Tomlinson et al., 1995).It could be concluded that, CA15.3 is expressed in many malignant disease including breast and ovarian cancer. Although, CA15-3 has high specificity and low sensitivity. So, it can be used as a prognostic marker in breast cancer as well as after chemotherapeutic treatment more than in

preoperative surgery of ovarian cancer and chemotherapeutic treatment that may be due to CA15-3 is more expressed in breast than ovarian cancer.

REFERENCES

1. Xue H, Lu B, Lai M.2008. Transl J Med ; 6 : 1–12.
2. WHO.2011. Factsheetno, 297, Geneva, Switzerland, February 2011, Available from: /http://www.who.int/mediacentre/factsheets/fs 297/en/S, 2011.
3. Khatib O, Aljurf M. 2008.Hematol Oncol Stem Cell Ther; 1:44–52.
4. Ibrahim A, Tanveer A, Nasr Y, Diane A. 2012. Novel automated flow-sedim munosensor for real time measurement of the breast cancer biomarker CA15-3 inserum. Talanta ;97: 499–504
5. Mabrouka RA and Labibb RA.2003. Detection of urokinase plasminogen activator receptor and c-erbB-2 insera of patients with breast and ovarian carcinoma. Clinical Biochemistry; 36: 537–543.
6. Engelstaedter V, Heublein S, Schumacher AL, Lenhard M, Engelstaedter H, Andergassen U, Guenthner-Biller M, Kuhn C, Rack B, Kupka M, Mayr D. and Jeschke U.2012. Mucin-1 and its relation to grade, stage and survival in ovarian carcinoma patients. BMC Cancer; 12:600.1-9.
7. Cannistra SA.2004. Cancer of the ovary. N Engl J Med; 351:2519–2529.
8. Scholz C, Heublein S, Lenhard M, Friese K, Mayr D and Jeschke U. 2012. Glycodelin A is a prognostic marker to predict poor outcome in advanced stage ovarian cancer patients. BMC Research Notes; 5(551): 1-7.
9. Park YM, Kim SJ, Kim K, Han YD, Yang SS and Yoon HC. 2013. Lectin-based optical sensing for quantitative analysis of cancer antigen CA15-3 as a breast cancer marker. Sensors and Actuators B; 186 : 571– 579.
10. Nishimura R, Nagao K, Miyayama H, Matsuda M, Baba KI, Matsuoka H, Yamashita Y. 2003. Elevated serum CA15-3 levels correlate with positive estrogenreceptor and initial favorable outcome in patients who died from recurrent breast cancer. Breast Cancer ;10 : 220–227.
11. Cazet A., Julien S., Bobowski M., Burchell J., Delannoy P. (2010). Tumour-associated carbohydrate antigens in breast cancer, Breast Cancer Res. 12, 204.
12. Hanisch FG, Uhlenbruck G, Peter-Katalinic J, Egge H, Dabrowski J, Dabrowski U. 1989. Structures of neutral O-linked polylactosaminoglycans on humanskim milk mucins. A

novel type of linearly extended poly-N-acetyl lactosamine back bones with Gal beta(1-4)GlcNAc beta(1-6) repeating units. J Biol Chem; 264: 872–883.

13. Ruibal A, Sánchez Salmón A, Garrido M, Bogdan Ciobotaru and Arias JI. 2007. Preoperative CA15.3 serum levels and cellular proliferation in patientswith infiltrating ductal carcinomas of the breast.Rev Esp Med Nucl ;26(6):367-71.
14. Ruibal A, Arias JI, del Río MC, Lapeña G, Schneider J, Tejerina A .2001. Histological grade in breast cancer: association with clinical and biological features in a series of 229 patients. Int J BiolMarkers;16: 56-61.
15. FIGO 1989. International Federation of Gynaecoloy and Obstetrics. Annual report and results of treatment in gynecologic cancer. Int J Gynaecol Obstet; 28:189–90.
16. Poncelet C, Fauvet R,Yazbeck C, Coutant C, Darai E. 2010. Impact of serum tumor marker determination on the management of women with borderline ovarian tumors: Multivariate analysis of a French multicentre study.EJSO; 36: 1066-1072.
17. Giona M, Boracchib P, Dittadia R, Biganzolic E, Peloso L, Mionea R, Gattid C, Paccagnellad A, Marubinib E. 2002. Prognostic role of serum CA15.3 in 362 node-negative breast cancers. An old player for a new game. European Journal of Cancer; 38: 1181–1188
18. Horobin JM, Browing MC, McFarlane NP. 1991. Potential use oftumour marker CA15–3 in the staging and prognosis of patients with breast cancer. J R Coll Surg Edinburgh; 36: 219–221
19. Iaffaioli RV, Caponigro F, Esposito G. 1991. Impact of preoperative CA 15–3 levels in operable breast cancer. Comparison with tissue polypeptide antigen (TPA) and carcinoembryonicantigen (CEA). Int J Biol Markers; 6: 21–24.
20. Molina R, Jo J, Filella X. 1998. C-erb B-2 oncoprotein, CEA, and CA 15.3 in patients with breast cancer: prognostic value. Breast Cancer Res Treat; 51: 109–119.
21. Shering SG, Sherry F, Mcdermott EW, O'Higgins NJ, Duffy MJPreoperative CA. (1998). 15-3 concentration predict outcome of patients with breast carcinoma. Cancer; 83: 2521–2527.
22. Takahashi T, Makigushi Y, Hinoda Y .1994. Expression of MUC1 on myeloma cells and induction of HLA-unrestricted CTL against MUC1 from a multiple myeloma patient. J Immunol ; 153:2102-9
23. Vizcarra E, Lluch A, Cibrián R .1996. Value of CA 15.3 in breast cancer and comparison with CEA and TPA: a study of specificity in disease free follow-up patients and

sensitivity in patients at diagnosis of the first metastasis. Breast Cancer Res Treat; 37:209-16.

24. de Larrea CF, Cibeira MT, Vallansot R, Colomo L, Bladé J. 2008. Increased Serum Tumor Markers (CA125 and CA15.3 in Primary Plasma Cell Leukemia: A case report and review of the literature.Clinical lymphoma and myeloma; 8: (5) 312-314.
25. Iwasaki T, Hamano T, Aizawa K. 1997. Increased serum CA125 levels in plasma cell dyscrasias.Acta Haematol; 98:104-8
26. Luminari S, Goldaniga M, Ceccherelli F. 2003. Prevalence and prognostic significance of sMUC-1 levels in plasma cell dyscrasias. Br J Haematol 2003; 121:772-4
27. Lazzarino M, Orlandi E, Catherine K . (1998). Serum CA 125 is of clinical value in the staging and follow-up of patients with non-Hodgkin's lymphoma correlation with tumor parameters and disease activity. Cancer ; 567: 82-83.
28. Sandri MT, Salvatici M, Botteri E, Passerini R, Zorzino L, Rotmensz N. 2012. Prognostic role of CA15.3 in 7942 patients with operable breast cancer Breast Cancer Res Treat; 132(1):317-226.
29. Duffy MJ. 1999. CA 15-3 and related mucins as circulating markers in breast cancer Ann Clin Biochem; 36:579-586.
30. Ebeling FG, Stieber P, Untch M, Nagel D, Konecny GE, Schmitt UM. 2002. Serum CEA and CA 15-3 as prognostic factors in primary breast cancer. Br J Cancer;86(8):1217..
31. Brouckaert O, Laenen A, Wildiers H, Floris G, Moerman P, Van Limbergen E, Vergote I, Billen J, Christiaens MR, Neven P. 2013.The prognostic role of preoperative and (early) postoperatively change in CA15.3 serum levels in a single hospital cohort of primary operable breast cancers.The Breast ;22 : 254- 262.
32. Tomlinson IPM, Whyman A, Barrett JA and Kremer JK. 1995. Tumour Marker CA153: Possible Uses in theRoutine Management of Breast Cancer. European journal of Concer; 31A (6): 899-902.