

# Over expression of Her- 2 neu in ovarian surface epithelial carcinoma in a sample of Iraqi patient at Al-kindy Teaching Hospital.

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## Abstract

**Background:** Although expression of the HER-2/neu oncogene may be of some prognostic importance in advanced ovarian cancer, its role in early-stage disease has not been established. The current study examined the prevalence and significance of HER-2/neu expression in different grades of different types of surface epithelial ovarian carcinoma.

**Methods:** Thirty eight female patients with surface epithelial ovarian cancer were included in this study. The blocks of corresponding formalin fixed, paraffin-embedded ovarian biopsies were retrieved from the archives and hematoxylin-eosin slides of each ovarian biopsy were reviewed and marked their grades of differentiation, then a new sections from each sample stained by her2/neu as immunohistochemical technique and classified according to degree of intensity regarding to dependable scoring system, also ten cases taken as control group from normal ovarian tissue.

**Results :-**Thirty eight sample of surface ovarian carcinoma were collected, twenty six were serous ovarian carcinoma, eleven cases were mucinous carcinoma type and one case was endometrioid carcinoma. The samples were classified according to their histological types and according to their grading. The mean age of SC type was 54.52 with SD 7.17

while the mean age of mucinous carcinoma was 49.36 with SD 4.9. There is no significant relation between each type and grading system ( P Value = 0.9 ), also there is no significant relation between age group distribution and types of ovarian carcinoma ( P value = 0.14 ). Instate that statically no significant relation between intensity of expression Her2/neu and high grading of each types of collected sample ( P value = 0.22) and this may be due to small sample size but still there are obvious criteria showing that her2/neu expression relatively increase in higher grade of each types of studied ovarian surface epithelial carcinoma.

**Conclusion :-**In conclusion, the overexpression of the HER-2/neu gene product appears to be an unusual occurrence in early epithelial ovarian cancer and may occur less frequently than in advanced disease. Early ovarian cancer will eventually progress to advanced disease if undiagnosed and untreated, then, HER-2/neu overexpression does not appear to be a general early event in the development of ovarian cancer. Instead, it seems that increased expression develops in many instances after the malignant phenotype has already arisen.

**Key words:** (epidermal growth factor Her2/neu, serous carcinoma SC, Mucinous carcinoma MC).

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## Introduction

The epithelial ovarian carcinomas, which make up more than 85% of human ovarian cancer, arise in the ovarian surface epithelium (OSE). The etiology and early events in the progression of these carcinomas are among the least understood of all major human malignancies because there are no appropriate animal models, and because methods to culture OSE have become available only recently. The ovarian tumors are at the sixth common tumor in the rank of most ten common type of malignant tumor in Iraq (1). Symptoms are frequently very subtle early on and may include: bloating, [pelvic pain](#), difficulty in eating and [frequent urination](#), and are easily confused with other illnesses (2). Most (around 90%) ovarian cancers are classified as "epithelial" and are believed to arise from the surface ([epithelium](#)) of the ovary. However, some evidence suggests that the [fallopian tube](#) could

also be the source of some ovarian cancers (3). The relationship between use of oral contraceptives and ovarian cancer was shown in women who used oral contraceptives for 10 years had about a 60% reduction in risk of ovarian cancer (4). There is good evidence that in some women genetic factors are important. Carriers of certain [BRCA mutations](#) are notably at risk. The [BRCA1](#) and [BRCA2](#) genes account for 5%–13% of ovarian cancers (5). Amplification or overexpression of the [ERBB2](#) gene occurs in approximately 30% of breast cancers. It is strongly associated with increased disease recurrence and a worse prognosis; overexpression is also known to occur in ovarian, stomach, and aggressive forms of uterine cancer, such as uterine serous [endometrial carcinoma](#) (6, 7). HER2 is encoded by [ERBB2](#), a known [proto-oncogene](#) located at the long arm of human

[chromosome 17](#) (17q12). HER2 is named because it has a similar structure to human epidermal growth factor receptor, or HER1. Neu is so named because it was derived from a rodent [glioblastoma](#) cell line, a type of neural tumor. ErbB-2 was named for its similarity to *ERBB* (avian erythroblastosis oncogene B), the [oncogene](#) later found to code for EGFR. Gene cloning showed that HER2, Neu, and ErbB-2 are all encoded by the same [gene](#) (8). The surface ovarian neoplasms are classified into distinct morphologic categories based on the appearance of the epithelium into tumors of serous, mucinous, endometrioid, clear cell, and transitional types. Histological type of ovarian cancer is one of the major prognostic factors determining clinical outcome. Recent studies indicate that each of these histological subtypes possess distinct morphological and molecular alterations (9). The aim of this study is to examine the prevalence and significance of HER-2/neu expression in different grades of ovarian carcinoma in a sample of Iraqi patient at Al-Kindy Teaching Hospital.

### Methods:

Thirty eight female patients with surface epithelial ovarian cancer were included in this study. The present study was performed in the Department of Pathology and Forensic medicine, Alkindy College of Medicine, Baghdad University. The cases were collected from the Alkindy teaching hospital and some of the private laboratories in local areas. The blocks of corresponding formalin fixed, paraffin-embedded ovarian biopsies were retrieved from

the archives and hematoxylin-eosin slides of each ovarian biopsy were reviewed and marked their grades of differentiation. All biopsies were graded according to WHO classification into three grades, malignant Grade I (well differentiated), malignant Grade II (moderately differentiated) and malignant Grade III (poorly differentiated). Patient's ages ranging from 40 to 70 years, with a mean age of Serous, mucinous and endometrioid carcinoma were ( 49.6 , 54.5 and 49.0 ) years old respectively . Avidin-Biotin Complex (ABC) method was employed for immunohistochemical of her2/neu. A control group of 10 samples with normal ovarian tissues were involved in this study. While positive & negative controls were processed with each run. Scoring of her2/neu by objective X40 and as follow(7): Score 0 (negative), no membrane staining observed, Score +1 (negative), faint partial membrane staining in >10% of cancer cells with rare or absent circumferential staining, Score +2 (positive), weak circumferential membrane staining in >10% of cancer cells but the membrane staining ring is thin, Score +3 (positive), intense circumferential membrane staining in >10% of cancer cells and the membrane staining ring is thick ( 10 )

### Results:

Mean age of serous carcinoma ( SC ) cases was ( 54.5 ) years , with SD of ( 7.17 ) in a median of ( 54 ) years , while mean age of mucinous carcinoma ( MC ) cases was ( 49.36 ) years with SD of ( 4.97 ) in a median of ( 48 .00 ) years , as we see in table ( 1 ) .

**Table ( 1 ):-Age distribution of 38 cases of malignancy surface epithelial tumors of ovary .**

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Q1	Median	Q3	Maximum
Se.	26	4	54.52	1.43	7.17	41.00	48.50	54.00	61.50	68.00
Variable	N	N*	Mean	SE Mean	StDev	Minimum	Q1	Median	Q3	Maximum
Mu.	11	2	49.36	1.50	4.97	43.00	46.00	48.00	52.00	59.00
Variable	N	N*	Mean	Mean	StDev	Minimum	Q1	Median	Q3	Maximum
en	1	2	49.000	*	*	49.000	*	49.000	*	49.000

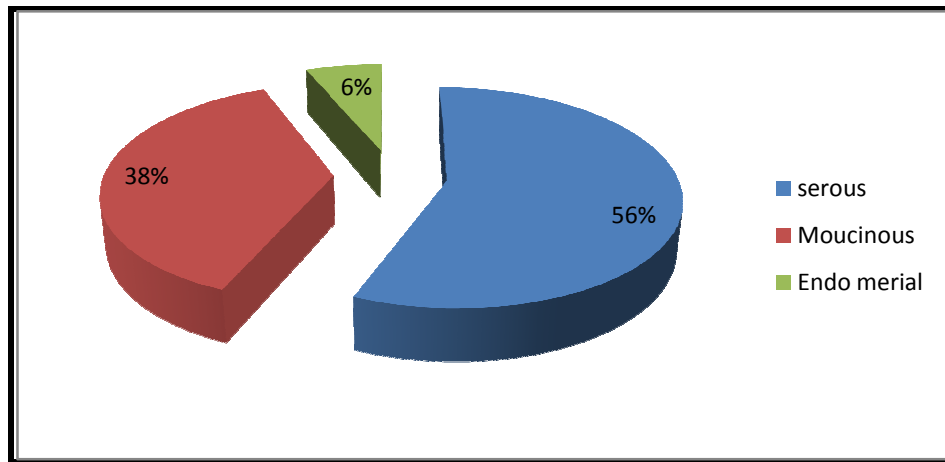
There is no significant relation between the age distribution and different surface epithelial carcinoma as shown in table ( 2 ) with P – value ( P – 0.149 ) as shown in table ( 2 ) & figure (1).

**Table 2 ; -Show the Relation between age distribution and the types of ovarian surface epithelial carcinoma.**

Age	serous	Moucinous	Endomaterial	
40 -50	9	6	1	16
51-60	10	5	0	15
61-70	7	0	0	7
total	26	11	1	38

Chi-Sq = 3.812; DF = 3; P-Value = 0.149

**Figure ( 1 )**  
Percentage of ovarian surface epithelial carcinoma



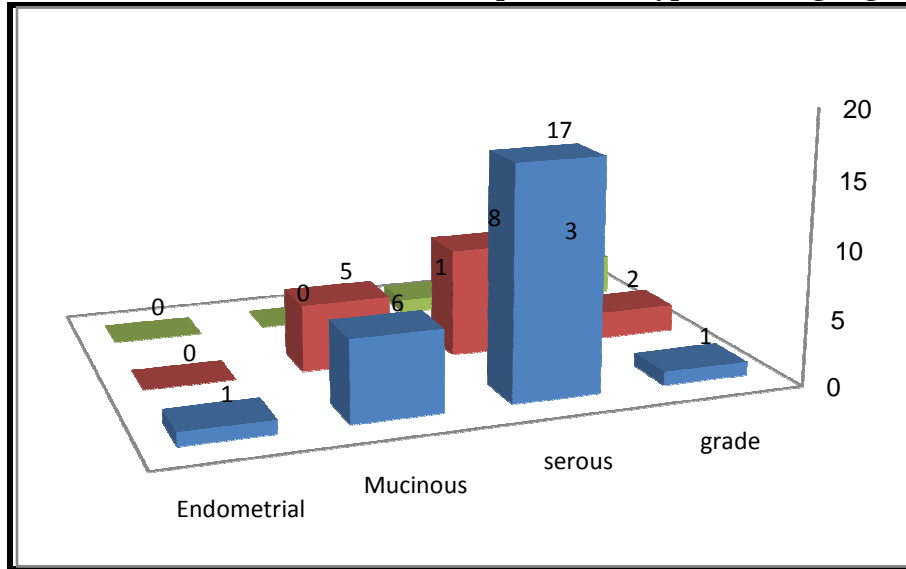
There is no significant relation between grading and each types of surface epithelial carcinoma and P-value was ( P =0.9 01 ) as shown in table ( 3 ) and figure ( 2 ) .

**Table ( 3 ) show the relation between grading and each types of surface epithelial ovarian carcinoma.**

grade	serous	Mucinous	Endometrial	
1	17(65%)	6 (54%)	1(100%)	24 (63%)
2	8 (30%)	5 (46%)	0	14 (35%)
3	1 (3%)	0	0	1 (2%)
total	26 (68%)	11(28%)	1(3%)	38

**P=0.901**

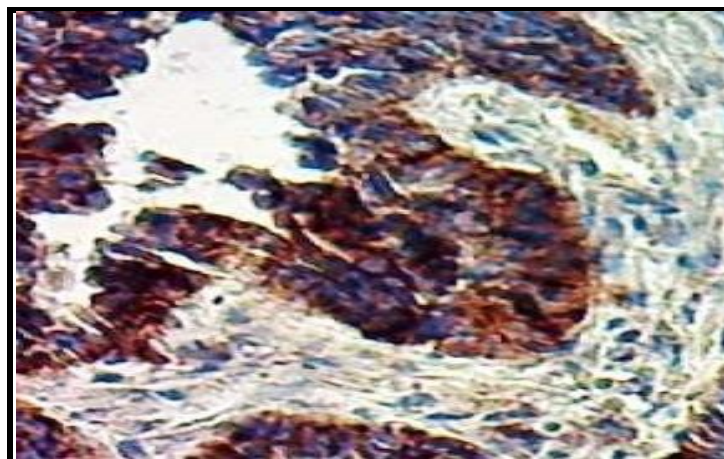
Figure (2) :. Show the Distribution of number of sample for each type according to grade of tumor.



Serous carcinoma Her/2 neu expression was strong positive in ( 6 ) cases ,score ( 2 & 3 ) , while was negative in ( 20 ) , ( score 0 &1 ) . Mucinous carcinoma cases Her/2 neu expression showed ( 2 ) cases were strongly positive as shown in (figure 3 ) , while it was negative in ( 9 ) cases . Endometriod ovarian carcinoma was Negative one case and there is no significant

changes between the different type of surface ovarian tumor and Her2/neu expression in our cases with ( P- value = 0.22 ) as shown in table ( 4 ) but there is increase in scoring of degree of expression of her2/neu with increase in grading of both serous and mucinous carcinoma as shown in Figure ( 4 )

Figure ( 3 ) :- Mucinous carcinoma , her2/neu expression ( strong positive ).

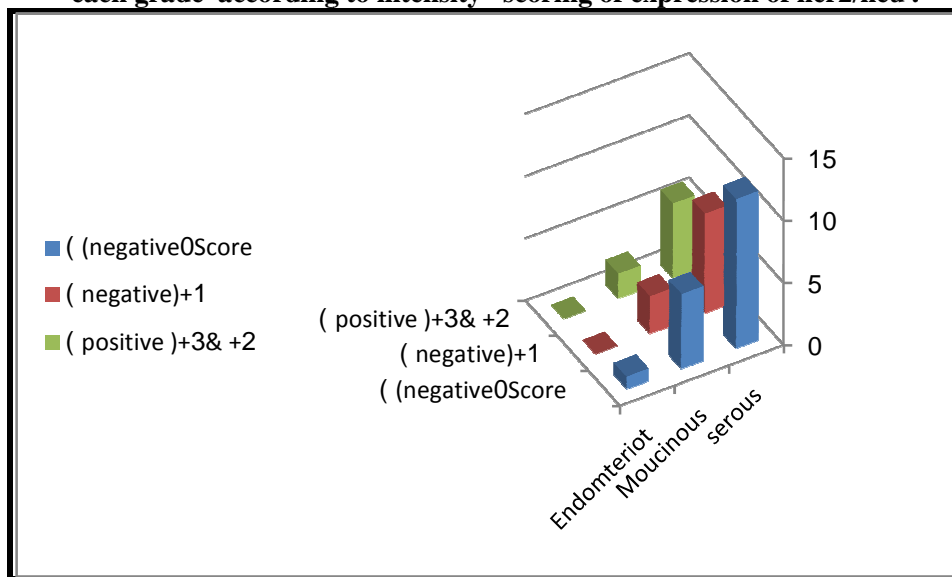


**Table ( 4 ) :- Show Relation between types of ovarian tumor and intensity scoring system of Her2/neu expression.**

Her2	serous	Moucinous	Endomteriot	
Score 0(negative )	12	6	1	19
1+(negative )	8	3	0	11
2+ &3+( positive )	6	2	0	8
total	26	11	1	38

P=0.22

**Figure ( 4 ) show Relation between each types of ovarian carcinoma in each grade according to intensity scoring of expression of her2/neu .**



**Discussion :**

The present study is designed to correlate the (her2 /neu) over-expression to the grade of differentiation in each studied types of ovarian surface carcinoma and to assess whether such relation could be used as a prognostic factor for the early diagnosis of the malignancy. Moreover, I attempted to assess whether there is any increase in the frequency of gene expression in comparison to studies done abroad due to other factors specially that our samples were taken from area suffered as a war zone.

Her2/neu oncogene which belongs to epidermal growth factor receptor family has been implicated in malignant transformation and may have a driving force in the carcinogenesis of

several human cancers including ovarian cancer.(11)

Several reports have examined the prognostic significance of her2/neu expression in epithelial ovarian cancer. The role of her2/neu immunohistochemistry in ovarian cancers is not that clear yet with contradicting results and conflicting data.(12) Thus, the prognostic influence of her2/neu is still a matter of debate since the percentage of her2/neu positive patients varies considerably among different individual studies dealing with different samples. Although expression of her2/neu oncogene may be of some prognostic importance in advanced ovarian cancer its role in early stage disease has not been established.(13). Many studies concluded that her2/neu overexpression has been associated with

advanced stages , poorly differentiated tumors, resistance to chemotherapy and shortening survival . However, other studies had the ability to prove a positive association of her2/neu overexpression with an increased risk of progression and death among women with early stage ovarian carcinoma. (14).

In my study I saw that overexpression of different types of surface epithelial carcinoma are increase in intensity in grade II & grade III while it was less expression in grade I and this compatible with some study in different degree as shown in following studies. Prema P et al (2003)(15) revealed 2% detection rate for her2/neu in sample of 43 cases which scored as zero in 30 patients, +1 in 12 patients and +3 in only one patient without significant difference. While her 2/neu overexpression were noted in only 21% of cases with advanced disease. (16) . Elena Verri et al (2005) revealed 27.3% positive immunostaining for her2/neu, among which 13.4% were weakly stained (score +1), and 13.9% were intensely positive , (score +2 to +3), without any significant relationship between her2/neu detection rate and intensity of immunostaining. ( 17 ) . Garcia-Velasco A et al (2008) revealed only 5% detection rate of her2/neu overexpression in 72 malignant samples of ovarian tissues without significant difference.( 18 ). Overexpression of the HER-2/neu gene product appears to be an unusual occurrence in early epithelial ovarian cancer and may occur less frequently than in advanced disease. In contrast to the approximately 30% rate of overexpression demonstrated in advanced ovarian cancer ( 19 , 20 ,21 ) Many other studies revealed various degrees of detection rate for her2/neu immunostaining such as Berchuch et al 1990 (32%), Salmon et al 1989 (26%), Bookman et al 2003 (11%), Dimova et al 2006 (11%), Nielsen JS et al 2004 (35%), and Malamou-Mitsi V 2007 (18%).( 22 )

### Conclusion :-

In conclusion, the overexpression of the HER-2/neu gene product appears to be an unusual occurrence in early epithelial ovarian cancer and may occur less frequently than in advanced disease. Early ovarian cancer will eventually progress to advanced disease if undiagnosed and

untreated, then, HER-2/neu overexpression does not appear to be a general early event in the development of ovarian cancer. Instead, it seems that increased expression develops in many instances after the malignant phenotype has already arisen.

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