C-ERB-4 GENE EXPRESION IN CANCER BREAST PATIENTS AND ITS CORRELATION WITH CLINICO PATHOLOGIC PARAMETERS

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ABSTRACT

Breast carcinoma ranks as first malignancy affecting females, contributing 33% of all female cancers. C-erbB-4 a class of oncogenes prevalent in breast cancer and plays a role in cancer development. This research was performed to assess C-erbB-4oncogene amplification by RT- PCR technology. These markers were studied in 50 breast female cancer patients by RT-PCR Technique. Define their relation to various clinical and other prognostic markers and correlate their expression to each other. The results of this study were that C-erbB-4 gene amplification, by RT-PCR was positive in 54% .C-erbB-4 was significantly associated with favorable prognostic markers as absence of lymph nodes involvement and presence of Estrogen and progesterone receptors.

KEYWORDS: Cancer breast, C-erbB-4 -RT-PCR – IHC

INTRODUCTION

Breast cancer is ranking number one after urinary bladder tumors and malignant lymphomas at National Cancer Institute (NCI), Cairo University in Egypt. Breast carcinoma constitutes 33% of all females' cancers in Egypt (El-Bolkainy et al., 2010). Prognostic factors identify patients at higher or lower risk of breast cancer recurrence or death. Useful prognostic factors can be applied broadly to large, heterogeneous

patient groups (Kathy and Miller, 2000). Immunohistochemistry (IHC) techniques are widely used in diagnostic histopathology to help re-differentiate the light microscopically undifferentiated tumors (Ross and Fletcher, 2000). Estrogen and Progesterone are well established steroid endocrine regulators. Estrogen promotes breast epithelial cell proliferation, development as progesterone (Greene et al., 2004). Signal transduction of C-erbB-4 receptor may play an important role in cell growth and differentiation and its expression may be linked to cell differentiation and favorable prognosis in breast cancers (Knowlden et al., 2002). The aim of this investigation was to study of histopathological parameters using light microscopy in breast cancer cases including mitotic Index, immunohistochemical analysis of estrogen, progesterone receptors in breast cancer cases, Assessment of C-erb4 gene amplification and Correlate their expression to each other in newly diagnosed female cancer patients.

MATERIALS AND METHODS

Patients

The present study was performed on 50 diagnosed female breast cancer patients presented to surgical Department, National Cancer Institute (NCI), Cairo University, during the period from 2008 to 2011. Their ages ranged from 27 to 60years old. The fresh tumor tissues were divided into two fragments; one fragment was fixed in 10% neutral buffered formalin (18 to 24 hours), and processed for histological, and immunohistological analysis from paraffin embedded tissues. The second fragment of the tissue was frozen in a dry ice and stored at –80ºC. The latter was used for RNA extraction from cancer breast tissue and adjacent normal tissue as control. One step RT-PCR for C-erbB-4 gene.

Histological diagnosis

For histological diagnosis, tissues were fixed in 4% phosphate-buffered formalin and routinely processed to wax. Paraffin sections (5

μm) were stained with heamatoxilene and eosin and examined with the microscope. (Bancroft and Gamble, 2002).

Immunostaining

Estrogen receptors (ER) and progesterone receptors (PR) were detected using an improved Biotin-Streptavidin Amplified (B-SA) detection system (Taylor and Kledzik, 2002).

RNA Isolation from the tumor extract and RT-PCR analysis

Total RNA was isolated using RNeas total RNA isolation kit supplied by Qiagen (Suo et al., 2002).Gene copy determination using Qiagen one step RT-PCR kit was used in a thermal cycler (Perkin Elmer Cetus).A 100 μl RT-PCR was prepared containing 10 μl of 10x buffer, 200 mM of dNTPs , 1 mM of each primer (erbB4/β-actin), 6 μl 25 mM MgCℓ2, 5 μl Taq DNA polymerase (2.5μ). Then, the volume of 100 μl mix is added to each sample (1μg) DNA. Finally, the samples were loaded in the thermal cycler blocks. Primers (25-mers) were obtained from Gibco BRL, USA. Two primers were used to amplify part of the erbB4 and β-actin as shown (Table 1). PCR was performed in the thermal cycler, Roobycycler gradient 96 Stratagene. Initially, samples were heated for 5 min at 94 oC for denaturation, and then cycled 20 times at 94oC for 1 min, 56 oC for 2 min, and 72 oC for 3 min, followed by a final extension cycle at 72 oC for 5 min.

RESULTS AND DISCUSSION

Histology

Light microscope was used to study the cases of malignant breast lesions, from invasive ductal carcinoma of the breast by hematoxelin and eosin stain (Fig. 1). Malignant cells and high level of mitotic division were observed.

Table (1). RT-PCR primer pairs used in the co- amplification of c-erbB-4 and B-actin RNAs according to (Suo et al., 2002).

Primer Name	Nucleotide sequence 5`-3`	Expected size bp
erbB4-P1	CTC TGG TGG TCT TCC TTC TAC C	**232**
ErbB4-p2	TGA TAG TAG GCA GCA TTG CC	
B-actin-P1	CTT TGA TTG CAC ATT GTT GT	**160**
B-actin -P2	GAA AGC AAT GCT ATC ACC TC	

Table 2. Correlation between Cerb-4 amplification by RT-PCR and estrogen, progestron receptors.

Immuno parameters		Cerb4- RT-PCR					P value
		+ve		-ve		Total	
		No	%	No	%		
ER	+ve	21	65	11	35	32	(p<0.0035) **
	-ve	12	66	6	34	18	
PR	+ve	19	73	7	27	26	(p<0.0001)***
	-ve	14	58	10	42	24	

Correlation between Cerb-4 amplification by RT-PCR and estrogen, progesterone receptors.

Table (2) shows direct statically significant association was detected between Cerb-4 amplification by RT-PCR (Fig.2) and estrogen receptors (ER) expression by immunohistochemistry. 65 % (21/32) of Cerb-4 positive cases were ER positive, While 35 % (11/32) of negative Cerb-4 cases were ER positive. Direct statically significant association was detected between Cerb-4 and progesterone receptors (PR) expression by

immunohistochemistry, 73% (19/26) of Cerb-4 positive cases were PR positive, while 27% (7/26) of negative Cerb-4 cases were PR positive. The material of this work comprised tumor tissue obtained from 50 diagnosed female breast cancer patients presented to the surgical Department, NCI, and Cairo university.during period from 2008 to 2011.Their age ranged from 27 to 60 with a mean of 44.74 ± 1.432, median of 44 years. They underwent surgery either in the form of conservative wide local excision and axillary lymph node dissection or modified radical mastectomy. In this work C-erbB-4 amplification wase determined in 50 newly diagnosed female breast cancer patients with invasive duct carcinoma, trying to correlate such markers with prognostic markers. The mean age of female patients reported in this study was 44.74 years. This was in agreement with results reported by other studies on Egyptian females cancer patients, as those described by El Bolkainy et al., (2010) reported that a mean age of 46.9 years. Western studies reported a mean age of 57 years by Henerson, (2008). However these figures are about 10 years lower than those mentioned by researchers in western countries. Gasparini, (2009), and Chaprin et al., (2009) reported that a mean age of 56.60 and 56.7 years respectively among breast cancer patients. As shown in the results; all cancer cases were IDC the most common histopathological type of cancer breast as it represents 70% of all breast cancer in Western countries and 85.02% in Egypt NCI series (Mokhtar et al., 2007). In the present study, malignant breast tissues invasive duct carcinoma by Hematoxelin and Eosin stain showed groups and clusters of malignant ductal cells, of highly anaplasia and mitosis. This was in agreement with El-Bolkainy et al., (2010). In this study, the incidence of c-erbB-4 amplification was 54% (27/50). Our results were in accordance with Srinivasan, (2009) who studied the prevalence and sites of amplification of c-erbB-4 in 178 human breast cancers cases, which was 49%. Higher incidence was reported by Suo et al., (2009) who studied c-erbB-4 amplification in 100 IDC pateints, it was 82%. This could be explained by the fact that our patients present usually late with big sized tumor and thus higher tumor load. Also this aggressiveness

could be attributed to a biologically different disease. A direct significant association between c-erbB4, and PR and ER status, this was in accordance with Powlawski, (2009), and Suo et al., (2009). So c-erbB-4 amplification could be considered as one of the favorable prognostic markers in cancer breast being directly associated with ER and PR status.

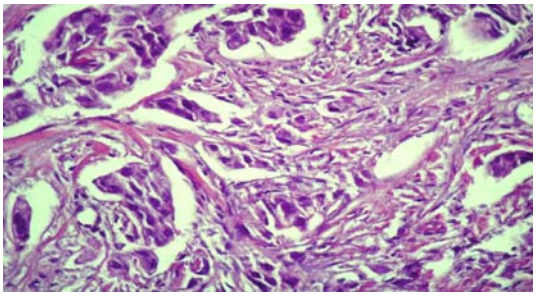

Fig. (1). Histology study. (a) A case of IDC by hematoxelin and eosin stain (X 400) showing mitosis.

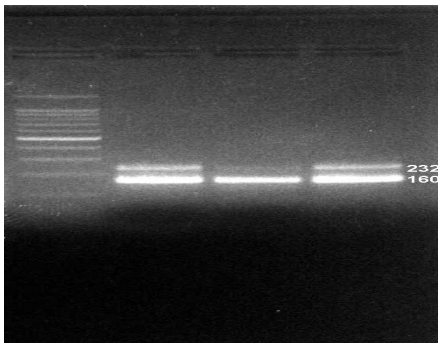

Fig 2. Detection of C-erbB-4 gene amplification, electrophoresis separation of C-erbB-4 (232 bp) and single copy gene B-actin (160 bp) RT- PCR amplified fragments on 2% agarose gel. Lane 2, 4. Positive for C-erbB-4 amplification, lane 3 IDC tumors negative for C-erbB-4 amplification, lane 1: 100 bp molecular weight marker.

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التعبير الجينى للجيين س-ارب-٤ فى مرضى سرطان الثدى وعلاقتهم بالعوامل الاكلينيكية الباثولوجية

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يعتبر سرطان الثدى فى ا لمرتبة الأولى با لنسبة لجميع أنواع السرطانات الاخرى فى جمهوررية مصر العربية و ذ لك من واقع سجلات المعهد القومى للأورام- جامعة القاهرة.تم دراسة الجين المسرطن س ارب-٤ بطريقة ار تى ب س ار ومقارنته با لعوامل الهستوباثولوجيه ، ومستقبلات هرمون الاستروجين والبروجسترون فى ٥٠ سيدة مصابة بسرطان الثدى ، تتراوح اعمارهن بين ٢٧-٦٠ عاما بمتوسط قدره حوالى ٤٤ عاما. تبين من هذة الدراسة وجود الجين المسرطن س ارب-٤بطريقة ار تى ب س ار بنسبة ٥٤% فى مرضى سرطان الثدى . وقد تبين ايضا وجود علاقة مباشرة بين وجود الجين س ارب-٤ ووجود المرض مع غياب الغدد اليمفاوية مع وجود مستقبلات هرمون الاستروجين والبروجسترو

EGFR GENE EXPRESION IN CANCER BREAST PATIENTS AND ITS CORRELATION WITH CLINICO PATHOLOGIC PARAMETERS

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ABSTRACT

Breast carcinoma ranks as first malignancy affecting females, contributing 33% of all female cancers. EGFR a class of oncogenes prevalent in breast cancer and play a role in cancer development. This research was performed to assess EGFR expression using immunohistochemical (IHC) staining. These marker was studied in 50 breast female cancer patients by IHC Technique. Define their relation to various clinical and other prognostic markers and correlate their expression to each other. The results of this study was that EGFR gene amplification, by immunohistochemistry was positive in 66% of invasive duct breast cancer and showed the EGFR was significantly associated with bad prognostic markers as lymph nodes involvement and absence of Estrogen and progesterone receptors.

KEYWORDS: Cancer breast, EGFR - IHC

INTRODUCTION

Breast cancer is ranking number one after urinary bladder tumors and malignant lymphomas at National Cancer Institute (NCI), Cairo University in Egypt. Breast carcinoma constitutes 33% of all females' cancers in Egypt (El-Bolkainy et al., 2010). Prognostic factors identify patients at higher or lower risk of breast cancer recurrence or death. Useful prognostic factors can be applied broadly to large, heterogeneous patient groups (Kathy and Miller, 2000). Immunohistochemistry (IHC)

techniques are widely used in diagnostic histopathology to help re-differentiate the light microscopically undifferentiated tumors (Ross and Fletcher, 2000). Estrogen and Progesterone are well established steroid endocrine regulators. Estrogen promotes breast epithelial cell proliferation, development as progesterone (Greene et al., 2004). Expressions of the epidermal growth factor receptor (EGFR) have been shown to be adverse prognostic factors in mammary carcinoma. EGFR, C-erbB-2, C-erbB-3 and C-erbB-4 (alternatively, authors use the HER terminology (HER1-4), are class of oncogenes prevalent in several solid tumors. They play an important role in breast cancer development and in regulating cell growth, survival and differentiation in a complex manner. Receptor heterodimerization between cell surface HER receptor monomers form homodimers with the same receptor or heterodimers with other members of the HER family in response to ligand binding (William and Gregory 2009). The aim of this investigation was to study of histopathological parameters using light microscopy in breast cancer cases, immunohistochemical (IHC) analysis of estrogen, progesrone receptors in breast cancer cases, assessment of EGFR gene expression by IHC and Correlate their expression to each other in newly diagnosed female cancer patients.

MATERIALS AND METHODS

Patients

The present study was performed on 50 diagnosed female breast cancer patients presented to surgical Department, National Cancer Institute (NCI), Cairo University, during the period from 2008 to 2011. Their ages ranged from 27 to 60years old. The fresh tumor tissues were fixed in 10% neutral buffered formalin (18 to 24 hours), and processed for histological and immunohistological analysis from paraffin embedded tissues.

Histological diagnosis

For histological diagnosis, tissues were fixed in 4% phosphate-buffered formalin and routinely processed to wax. Paraffin sections (5 μm) were stained with heamatoxilene and eosin and examined with the microscope. (Bancroft and Gamble, 2002).

Immunostaining

Estrogene receptors (ER) and progesterone receptors (PgR) were detected using an improved Biotin-Streptavidin Amplified (B-SA) detection system (Taylor and Kledzik, 2002). The over expression of EGFR protein was examined immunohistochemically using autostainer machines. EGFR was categorized into negative showing Homogenous or heterogenous tumour membrane and cytoplasm immunoreactivity was utilized to indicate tumour EGFR expression (Park et al., 2005).

RESULTS AND DISCUSSION

Histology

Light microscope was used to study the cases of malignant breast lesions, from invasive ductal carcinoma of the breast by hematoxelin and eosin stain (Fig. 1). Malignant cells and high level of mitotic division were observed. **Table 9. Correlation between EGFR by immunohistochemestry and estrogen, progestron receptors.**

Immuno parameters		EGFR by IHC				Total	P value
		+ve		-ve			
		No	%	No	%		
ER	+ve	14	44	18	56	32	(p<0.001)**
	-ve	13	72	5	28	18	
PR	+ve	9	35	17	65	26	(p=0.022) *
	-ve	18	75	6	25	24	

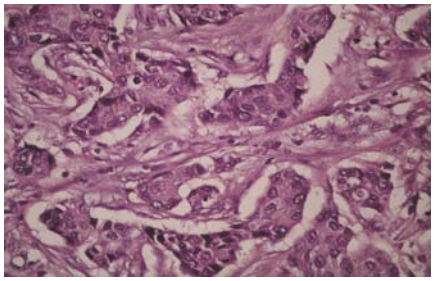

Fig. (1). Histology study. (a) A case of IDC by hematoxelin and eosin stain (X 400) showing mitosis.

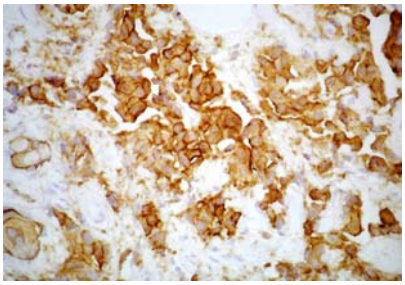

Fig. (2).IDC Showing strong expressing membranous reaction immunostaining of EGFR X400

Correlation between EGFR by immunohistochemestry and estrogen, progestron receptors

Table (1) shows. Direct statically significant association was detected between EGFR (Fig.2) and estrogen receptors (ER) expression (P value<0.001**), and progesterone receptor (P value<0.022*) by immunohistochemistry. The material of this work comprised tumor tissue obtained from 50 diagnosed female breast cancer patients presented to the surgical Department, NCI, and Cairo university.during period from 2008 to 2011.Their age ranged from 27 to 60 with a mean of 44.74 ± 1.432, median of 44 years. They underwent surgery either in the form of conservative wide local excision and axillary lymph node dissection or modified radical mastectomy. In this work EGFR expression wase determined in 50 newly diagnosed female breast cancer patients with invasive duct carcinoma, trying to correlate such markers with prognostic

markers. The mean age of female patients reported in this study was 44.74 years. This was in agreement with results reported by other studies on Egyptian females cancer patients, as those described by El Bolkainy et al., (2010) reported that a mean age of 46.9 years. Western studies reported a mean age of 57 years by Henerson, (2008). However these figures are about 10 years lower than those mentioned by researchers in western countries. Gasparini, (2009), and Chaprin et al., (2009) reported that a mean age of 56.60 and 56.7 years respectively among breast cancer patients. As shown in the results; all cancer cases were IDC the most common histopathological type of cancer breast as it represents 70% of all breast cancer in Western countries and 85.02% in Egypt NCI series (Mokhtar et al., 2007). In the present study, malignant breast tissues invasive duct carcinoma by Hematoxelin and Eosin stain showed groups and clusters of malignant ductal cells, of highly anaplasia and mitosis. This was in agreement with El-Bolkainy et al., (2010). In this work expression of EGFR by IHC method was 66% in breast cancer cases. Anwar et al., (2000), who worked on 36 Egyptian female patients with IDC breast cancer by IHC, reported a lower incidence being 66.6%. Moreover the incidence recorded by Western authors an incidence of 55% was reported by Tsutsui et al., (2009). In this study, no correlation could be found between EGFR expression and the age of breast cancer patients. The highest expression of EGFR among our patients was encountered in patients below 50 years (70%) and above 50 years (66%). While the percentage among patients of age less than 30 yeas was 25% only. But the differences were not statistically significant which could be attributed to the low number of the different age subgroups. Study of larger number of breast cancer patients could underline the impact of age as being one of the most important predictors of breast cancer progression and metastasis (Bhargava et al., 2005). Similarly to our results, and Bouter et al., (2007), found no correlation between EGFR expression and age. EGFR expression was inversly associated with the ER & PR status. This was in concordance with Steinman et al., (2007), Zhangi et al., (2011) who reported that the lack of expression of EGFR

correlated with high levels of steroids receptors and vice versa. So EGFR expression could be considered as one of the favourable prognostic markers in cancer breast being inversely associated with ER and PR status .

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التعبير الجينى لمستقبلات معامل نمو النسيج الطلائى فى مرضى سرطان الثدى وعلاقتهم بالعوامل الاكلينيكية الباثولوجية

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يعتبر سرطان الثدى فى ا لمرتبة الأولى بالنسبة لجميع أنواع السرطانات الاخرى فى جمهوررية مصر العربية و ذ لك من واقع سجلات المعهد القومى للأورام- جامعة القاهرة. تم دراسة مستقبلات معامل نمو النسيج الطلائى بطريقة الصبغات المناعية ومقارنته با لعوامل الهستوباثولوجيه ومستقبلات هرمون الاستروجين والبروجسترون فى ٥٠ سيدة مصابة بسرطان الثدى ، تتراوح اعمارهن بين ٢٧-٦٠ عاما بمتوسط قدره حوالى ٤٤ عاما.تبين من هذة الدراسة وجود مستقبلات معامل نمو النسيج الطلائى بطريقة الصبغات المناعية بنسبة ٦٦% فى مرضى سرطان الثدى . وقد تبين ايضا وجود علاقة مباشرة بين وجود مستقبلات معامل نمو النسيج الطلائى ووجود المرض با لغدد اليمفاوية مع غياب مستقبلات هرمون الاستروجين والبروجسترون المناعية