The Expression of c-erbB-2、p53、PCNA、nm23 in Breast Cancer and Their Clinical Significance

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Abstract **Objective** To detect the correlation between the expression and prognostic evaluation of tumor biomarkers (c-erbB-2、P53、PCNA、nm23) in breast cancer. **Methods** Expression of four biomarkers in 1180 breast cancer patients were determined by immunohistoche mistry. **Results** The expression of c-erbB-2 was negatively correlated with age, clinical stage, axillary lymph node status, histological classification and positively related with ER, PR; p53 was negatively correlated with clinical metastasis, histology classification, pathologic type and positively related with axillary lymph node metastasis; PCNA was negatively correlated with clinical stage, axillary lymph node metastasis and positively related with ER、PR; nm23 was negatively correlated with axillary lymph node metastasis and positively related with pathologic type, ER, PR. **Conclusions** The biological markers should be considered together with clinical stage, histological degree, lymph node metastasis and pathological type for enhauing the accuracy of progrostic evaluation in breast cancer.

Key Words breast cancer; immunohistochemistry; oncogenes; gene expression.

Breast cancer is the most common cancer, whose disease rate is obviously increasing and more occur in youngs. Traditional prognosis factors of breast cancer are relevant to age, the state of emmenia, clinical stages, histological classification, the state of axillary lymph nodes, pathogenic types, estrogen receptor and progesterone. However, identical pathogenic morphology and clinical stages have entirely different prognosis.

With rapid development of molecular biology, the gene theory of tumorigenesis has been increasingly recognized. Abundant research indicated that tumorigenesis is resulted from the interactions of multiple genes and stages. Cancer genes responsible for cell tumorigenesis could arise from mutations. The detection of cancer genes and their products could provide scientifical objective references for pathogenesis mechanism of cancer, tumorigeneic grade, transferred capability and prognostic assessment[1]. Immunohistochemical S-P method was used in our hospital to detect the protein expressions of cancer gene c-erbB-2, proliferated cell antigen PCNA, cancer repressed gene P53, and metastasis suppressor gene nm23 in the tissues of human breast cancer; also, their clinical values were discussed together.

MATERIALS AND METHODS

Clinical materials

1180 specimens of breast cancer excised from the patients in our hospital were collected, the patients were all females and aged from 18-78 years old, the medium age is 48 years old. The clinical stages were classified in terms of 1997UICC: 868 cases in stage I-Ⅱ and 312 cases in stage Ⅲ. The histological classifications were listed as described: 206 cases in stage I, 561 in stage II, and 413 in stage III. Negative and positive axillary node metastasis were 779 cases and 401 cases respectively. Specific and nonspecific pathogenic soakage types were 134 cases and 1046 cases, respectively. The receptors of female and pregnant hormones included 692 cases ER(+), 488 cases ER(−), 767 cases PR(+) and 413 cases PR(−).

Methods

S-P immunohistochemical method was used for protein determination of c-erbB-2, PCNA, P53 and nm23. The hypersensitive kit was provided by Fuzhou Maxin-Bio Corp. Ltd. Data analyses were conducted by X^2-test with the statistical software of SPSS 11.0.

RESULTS

The expression of c-erbB-2 was negatively correlated to patients' age of more than 35 years old, and histological classification, positively correlated to axillary node state, EP and PR receptors ($P<0.05$), and was not correlated to pathogenic types ($P>0.05$). The expression of protein P53 was negatively correlated to clinical stages, histological classification and pathogenic types, positively correlated to axillary node states ($P<0.05$), but not correlated to age, ER and PR ($P>0.05$). The expression of PCNA was negatively correlated to clinical stages and axillary node states, positively correlated to ER and PR ($P<0.05$), and was not correlated to age, histological classification and pathogenic types ($P>0.05$). The results were presented in tables 1 and 2.

DISCUSSION

As one of the family members of epidermal growth factors and gene markers conventionally used in breast cancer, cancer gene c-erbB-2 localized on the q21 region of chromosome 17 in human is a 185 KD transmembrane glycoprotein, having tyrosine kinase activity and participating in multiple signal transductions. In recent years, the relationship between its expression and occurrence, biological behaviors and prognosis was more studied [2]. Revious references showed that, c-erbB-2, as one cancer gene related to cell proliferation, whose protein expression was correlated to high degree cancer, rapid growth and poor prognosis[3].

Gene P53 was 53KD nuclear phosphoprotein, localizing on 17P1 and constituting with 11 exons. It could be classified into wild types and mutant types. Wild-type p53 is cancer repressed gene, and the mutant P53 protein could promote cell tumorigenesis and activate other cancer genes[4]. What presented in immunohistochemical detection was mutant-type p53 protein. Its expression is significantly correlated to ER and PR states, lymph node metastasis, cell specialization, proliferation degree, and so on[5].

PCNA is an assistant factor of DNA polymerase and 36 KD acid nuclear protein, widely expressed at the S stage of proliferated cells, which is great interest in the identification of normal and cancer cell cycle and detection of cell proliferation scores and diagnosis[6].

The expression level of PCNA in cancer tissues significantly correlated to cancer histological classification and clinical stages. If the expression level is higher, cancer histological classification is poorer, survival duration of patients is shorter and the clinical stage is later.

Table 2 The expression of protein nm23 and the correlation with clinical pathogenic factors.

index		pons/case	nm23		
			pon cases	postive rate	*P* value
Age	<50	372	186	50%	$P_{1,2,3}<0.05$
	35~50	731	383	52.39%	
	>35	77	44	57.14%	
Clinical stage	Ⅰ~Ⅱ	868	452	52.07%	$P<0.05$
	Ⅲ	312	161	51.6%	
Histological classification	Ⅰ	206	106	51.46%	$P_{1,2,3}<0.05$
	Ⅱ	561	288	51.34%	
	Ⅲ	413	219	53.02%	
Axillary node state	(−)	779	372	47.75%	$P<0.05$
	(+)	401	241	60.09%	
acceptor	ER(+)	692	408	58.96%	$P<0.05$
	ER(−)	488	205	42%	
	PR(+)	767	460	59.97%	$P<0.05$
	PR(−)	413	153	37.05%	
Pathogenic factors	Infiltrating special type	134	101	75.37%	$P<0.05$
	Infiltrating inspecial typoe	1046	512	48.95%	

nm23 was firstly found by Steeg[7] in 1988, relevant with cancer transfer capability, whose mRNA expression level in cell lines with lowly transfer potent is 10 times than those in cell lines with highly transfer potent. nm23 was localized on the far end of human chromosome 17, constructed with gene family highly relating to structural functions. The protein expression level of nm23 is significantly correlated to the state of lymph nodes metastasis and specialization degree of cancer cells in the patients, also repressed lymph nodes metastasis and far-end transfer, whose expression level positively correlated to prognosis of breast cancer [8]. It could be used as key indices for the judgment of breast cancer transfer and prognosis. Also, it could contribute to select dangerous ones with high transfer from the patients of breast cancer to be treated[9].

Tianjin Cancer Hospital used the immunohistochemical method to detect and analyze c-erbB-2、P53、nm23protein and PCNA in 204 cases by more than 7 years in breast cancer olefin specimens, indicating that expression level of c-erbB-2 was negatively correlated to survival duration of patients, incorrelated to clinical stages and the state of lymph nodes metastasis. The expression level of P53 was positively correlated to the state of lymph nodes metastasis, negatively correlated to survival rate of patients. The expression level of nm23 was positively correlated to survival duration of patients and negatively correlated to lymph nodes metastasis. The expression level of PCNA was negatively correlated to survival duration of patients and positively correlated to cancer clinical stages[10].

Currently, although there are many prognosis indices, clinical stages, lymph nodes metastasis and pathogenic characters (type and classification) are still the most important assured ones in breast cancer. Hormone receptor level is the mere index of incretory therapy reactivity to predict breast cancer patients. In our studies, the expression of c-erbB-2 would arise in the young age, late clinic stage, lymph nodes metastasis and high histological classification. The expression of P53 would enhance in later clinical stage of patients, high histological classification and poor pathogenic type. The expression of PCNA would accelerate in later clinic stage and lymph nodes metastasis. Meanwhile, the expression of nm23 would attenuate with poor pathogenic type, negative ER and PR. All results above are corroborated with most reports at home and abroad, which suggesting that c-erbB-2, P53 and PCNA were negatively correlated to prognosis of breast cancer and could be used as their significant indices for identification.

However, some results in this paper have some differences from other reports. For examples, the expressions of c-erbB-2 and PCNA were higher in ER and PR positive patients. The expression of P53 was lower and highly correlated with lymph nodes metastasis in the patients, which corresponded to the report of Tianjin Cancer Hospital[10]. Especially, the expression of nm23 would be enhanced with lymph nodes metastasis, which was not identical in most reports[11].

Combined with our results, the function of nm23 would need further discussion in cancer development. The reasons causing no match between our results and other reports are mainly due to deficiency of united operation steps and uniform reagents, therefore led to different conclusions, simultaneously reflected that sole biological factors could be impossibly compared with affirmative prognosis. This may be conduced to the complicate mechanism of tumorigenesis and accumulation of multiple genes and stages. In addition, among each biological index, their potential functions are not definitely identical on prognosis identification. To date, the prognosis value of P53 was controversial, although major researchers deem that gene mutation or expression of P53 were related to lower DFS and OS, since its function for prediction is not so sure for chemotherapy and incretory therapy and insufficient for guiding auxillary cure [12]. c-erbB-2 is the first factor to predict therapeutical effect of chemotherapy.

Most retrospective studies indicated that the patients expressing c-erbB-2 were insensitive to CMF chemotherapy and sensitive to anthracene-loop-type pharmaceuticals [13]. Moreover, it could predict the therapeutical effect of incretory therapy. At late stage of breast cancer, some specialists consider [14] that the patients with over expression of c-erbB-2 are likely to be resistant to tamoxifen.

The strong positive expression of c-erbB-2 could be applied as the criteria of biological target therapy, choosing to use herceptin. Hence, in the "clinical practice manual" issued by American Society of Clinicalal Oncology (ASCO), ER, PR and HER-2 receptors are commonly recommended to be as conventional detection.

In this paper, the expression of c-erbB-2 was negatively correlated to lymph nodes metastasis,

histological classifications and clinical stages, whereas the expression of P53 was negatively correlated to clinical stages, pathogenic types and histological classifications, but positively correlated to lymph nodes metastasis. This result suggested that c-erbB-2 was a more important index than P53 for prognosis identification of breast cancer.

As suggested, when identifying prognosis of breast cancer in the clinic, the expression of c-erbB-2 and P53 were not consistent, c-erbB-2 should be chose as prior criteria. Besides, some clinical indices, including the state of lymph nodes, clinical stages, pathological elements and multiple biological indices of tumor should be systematically applied to improve the accuracy of prognosis of breast cancer, from which the surgery techniques would be decided to make the therapy of breast cancer more individualized.

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