RELATIONSHIP AMONG PS_2 PROTEIN EXPRESSION, ESTROGEN AND PROGESTERONE RECEPTOR STATUS, AND PROGNOSIS OF BREAST CANCER

LIU Jingxian 刘静贤,[1] LI Jiyou 李吉友,[1] HE Luowen 何洛文 [2] ZHAO Yajuan 赵雅娟 [1]

[1] *Department of Pathology, Beijing Cancer Hospital, Beijing Medical University, Beijing 100036, China*
[2] *Department of Biochemistry, Beijing Institute for Cancer Research, Beijing Medical University, Beijing 100034, China*

ABSTRACT

Objective: To study the relationship between the expression of PS_2 protein and Estrogen (ER) and Progesterone Receptor (PR) status and their prognotic value in breast cancer. Methods: Using the immunohistochemical method, PS_2 protein expressions were detected in 105 cases with breast cancer. Results: The positive rate of PS_2 protein was 50.48% (53/105) in 105 cases. The positive rate of PS_2 in the patients who survived five years or more was 56.96% (45/79), which was higher than that of those who lived less than five years (30.77%, 8/26). In the ER, PR (+) patients, the positive rate of PS_2 was higher (76.74%, 33/34), than that of those with ER, PR (–) (22.5%, 9/40). Conclusions: Our results suggest that the expression of PS_2 protein was positively correlated with the 5-year-survival and that of ER and PR in breast cancer. It is considered that PS_2 may be as a prognostic predictor, and detection of PS_2 protein expression was useful for a guiding treatment of breast cancer.

Key words: PS_2 protein, ER, PR, Breast cancer, Prognosis

The PS_2 protein was secreted from estrogen-dependent cells. In recent studies, it has been demonstrated that the expression of PS_2 was closely correlated with the estrogen receptor (ER) and progesterone receptor (PR) in cancer tissues. Detection of PS_2 gene expression was more valuable than that of ER as a prognostic index of breast cancer.[1] The aims of this study were to determine the relationship among the expression of PS_2, ER and PR status, menopausal status, lymphatic metastases, as well as survival time after operations in 105 cases with invasive ductal breast carcinoma.

Accepted for publication: September 16, 1999
Correspondence to: Liu Jingxian, Department of Pathology, Beijing Cancer Hospital, No.52, Fucheng Road, Haidian District, Beijing 100036, China; Phone: (0086-10)-88121122 ext. 2054; Fax: (0086-10)-88122437

MATERIALS AND METHODS

Samples

One hundred and five cases of invasive ductal breast cancer, who had undergone modified mastectomy, being hospitalizing in Beijing Cancer Hospital, Beijing Medical University from 1991 to 1992 were studied. All of them were females. The age of the patients ranged from 27 to 73 years old (average 50). There were 40 cases who had isolateral axillary lymph node metastasis found at the time of operations. Of them, 26 patients have died during the 5 years after operations.

Agents and Methods

The PS_2 was detected with routine paraffin sections. The first antibody was mouse anti-human monoclonal antibody (Zymed, Cat No. 003118) at a dilution of 1 to 30. The detection procedure was done as described in LSAB Kit protocol (DAKO, K681). TBS instead of the first antibody was used in the negative control.

ER and PR were detected by dextran-coated charcoal (DCC) method. More than 10 fmol/mg of ER or PR was defined as positive expression.[2]

Results Determination

The PS_2 positive cell was defined when there was an aggration of brown particles in the cytoplasm of the breast cancer cells and there was a tendency to assemble around the nucleus. The positive expression of PS_2 was determined when the positive cells were more than ten percent[3,4].

Statistical Analysis

X^2 test was used in this study.

RESULTS

The Rate of PS_2 Expression in Invasive Ductal

Breast Carcinoma

The rate of positive expression of PS_2 was 50.48 % (53/105) in all 105 patients.

The Association of PS_2 Positive Expression and ER, PR Status

In 43 cases which both ER and PR were positive, thirty-three cases (76.74%) were PS_2 positive, and in 40 cases with both ER and PR negative. Only 9 cases (22.5%) were PS_2 positive. The PS_2 expression was significantly correlated with the steroid receptor status ($P<0.01$) (Table 1).

Table 1. The relationship between positive expression of PS_2 and ER, PR status

Steroid receptor	Cases	PS_2+ (%)	PS_2− (%)
ER-, PR-	40	9 (22.5)	31 (77.50)
ER-, PR+	7	1 (14.28)	6 (85.71)
ER+, PR-	15	10 (66.66)	5 (33.33)
ER+, PR+	43	33 (76.74)	10 (23.26)
Total	100	55 (50.48)	52 (49.52)

The Difference of PS_2 Expression in Patients with Different Menopasual Status, Axillary Lymph Node Metastasis at the Time of Operation and Survival Times

The rate of PS_2 positive expression in groups of premenopasual , negative metastasis of lymph node and survival time of more than 5 years after operation were significantly higher than that of the group of postmenopasual, positive metastases of lymph node and survival time of less than 5 years. ($P<0.05$) (Table 2)

Table. 2 The relationship among PS_2 expression, manopausal status, lymph node metastases and survival time

Clinical material	Cases	PS_2+ (%)
Manopausal status		
Pre	60	31 (51.67)
Post	45	22 (48.89)
Lymph node metastasis		
Positive	40	22 (55.00)
Negative	65	31 (47.69)
Survival time		
>5 years	79	45 (56.96)
<5 years	26	8 (30.77)

DISCUSSION

The PS_2 gene was located in chromosome 21q and was regulated by estrogen.[5] The coded protein was a kind of secretive protein which includes 84 amino acid residuals.[6] Many researchers used ER and PR status as the index of whether to apply endocrinotherapy or not, but about 30 to 50 per cent of breast cancer patients could not get the anticipanted results with endocrinotherapy. However, the effect of this therapy could be seen in some ER negative patients. It has been demonstrated by immunohistochemistry that the ER positive cells were not distributed evenly. According to reports of many researchers, the PS_2 protein is closely association with ER and PR status. General speaking, breast cancer patients with ER and PR positive were positive of PS_2 expression. The patients with negative of ER and PR had extremely less positive expression of PS_2. Therefore, PS_2 was more valuable than ER status in predicting the reaction on endocrinotherapy of breast cancer patients and the expression of PS_2 protein seemed to be correlated with the tumor's biological behavior.[5]

The rate of positive PS_2 expression in breast cancer was not identical. It was 43 to 58 per cent according to Thampson report.[5] We found that the incidence of positive expression of PS_2 was 50.48% in our 105 cases with invasive ductal breast cancer.

PS_2 was regulated by estrogen and its transcription was under control and induced through estrogen. The PS_2 protein was depended on the existence of ER. Therefore, there was close relationship between PS_2 protein and ER, PR status. The study of Coin on 446 cases of primary breast cancer found that there were 174 cases all positive with PS_2, ER and PR, 12 cases (less than 3%) were PS_2 positive but ER and PR were negative. 80 cases

(about 18%) were PS_2 negative but both ER and PR were positive[6]. We analyzed 105 cases with invasive ductal breast cancer. Among them the cases with all positive PS_2, ER and PR, and the cases with PS_2 positive but both ER and PR negative were 33 and 9, respectively ($P<0.01$). It means the positive expression of PS_2 was positively correlated with the steroid receptor status.

Most of the researchers thought that the correlation between PS_2 expression and ER status was more obvious in premenopausal women (less than 50 years old) than postmenopausal women (more than 50 years old). Detre reported that this correlation was 100 per cent in women less than 50 years old[3]. Our study showed that the positive expression of PS_2 in premenopausal women was higher than those of postmenopausal women. This result indicated that the positive expression of PS_2 might be affected by endocrine and may have instructive significance to the endocrinotherapy.

Generally speaking, the prognosis of breast cancer patients with axillary lymph node metastases was not good. The study by Gion indicated that PS_2 expression was an important prognostic factor, especially for the patients with lymph node metastasis[6]. There was the tendency of early- relapse and insensitivity to endocrinotherapy in patients with PS_2 negative expression.[6]. In our study, 22 out of 40 patients with axillary lymph node metastasis were PS_2 positive (55%), whereas 47.6 per cent (31/65) patients had no auxillary lymph node metastasis. Eleven out of 26 patients who had axillary lymph node metastasis and whose PS_2 expression was negative died within 5 years after their operation.

Many researchers strongly recommended that PS_2 expression is a very useful prognostic factor for breast cancer. With the research on 205 cases of breast cancer, Fockens found that there was distinct difference of 5-year survival rate in the two groups of PS_2 positive and negative. The times of overall survival and disease free survival in the group of PS_2 negative were obviously shorter than that of PS_2 positive group. The rates of relapse and mortality of patients with PS_2 negative was 2.5 to 5.0 times higher than that of patients with positive PS_2[1]. In our study, the rate of PS_2 positive expression was 56.96% in the group of patients whose survival time were longer than 5 year (45/79), but it was 30.77% in the group of patients with survival time was less than 5 years (8/26). The difference was of significance.

Although the exact function of PS_2 is not clear, we demonstrated that positive expression of PS_2 is closely associated with ER and PR status, as well as a patient's 5-year survival rate. The factor of PS_2 can be as an important prognostic factor of patients with breast cancer and may have instructive significance to endocrinotherapy for the premenopausal patients.

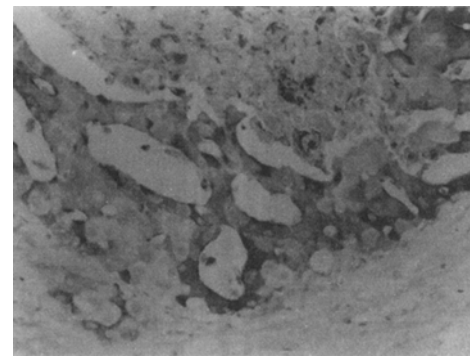

Fig. 1 invasive ductal carcinoma of breast 200 x PS_2 protein positive

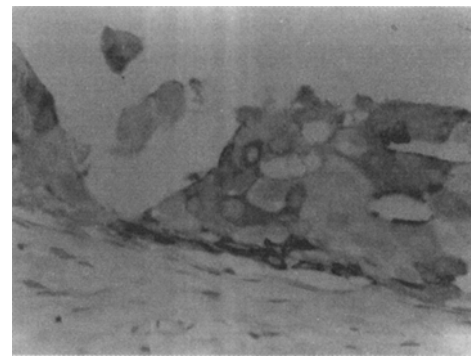

Fig. 2 invasive ductal carcinoma of breast 400 x PS_2 protein positive

REFERENCES

[1] Foekens JA, Rio MC, Seguinp, et al. Prediction of relapse and survival in breast cancer patients by PS_2 protein status. Cancer Res 1990; 50:3882.

[2] Zhang HY, He LW, Liu MS. Correlation between Overexpression of c-erbB-2 in breast cancer and receptors of estrogen and progesterone? Chin J Oncol 1983; 5:168.

[3] Detre S, King N, Salter J, et al. Immunohistochemical and biochemical analysis of the oestrogen regulated protein PS_2 and its relation with oestrogen receptor and progesterrone receptor in breast cancer. J Clin Pathol 1994; 42:240.

[4] Henry JA, Piggatt NH, Mallick UK, et al. PNR-2/PS_2 Immunohistochemical staining in breast cancer, correlation with prognostic factors and endoerine response. Br J Cancer 1991; 63:615.

[5] Thompson AM, Hawkins RA, Eltion RA, et al. PS_2 is an independent factor of good prognosis in primary breast cancer. Br J Cancer 1993; 68:93.

[6] Gion M, Mione R, Pappagallo GL, et al. PS_2 in breast cancer alternative or complementry tool to steroid receptor status evaluation of 446 cases. Br J Cancer 1993; 68:37