Expression of Androgen, Estrogen and Progesterone Receptors in Mucinous Carcinoma of the Breast

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Hormone receptors play important roles in breast cancer. We investigated the expression of hormone receptors in breast cancer to evaluate the importance of hormone receptors in the clinicopathology of breast cancer. Androgen receptor (AR), estrogen receptor (ER) and progesterone receptor (PR) expression characteristics were evaluated using immunohistochemistry stain, comparing patient age, tumor size and axillary lymph node status for 23 pure mucinous and 105 non-mucinous infiltrating ductal carcinomas in the human female breast. Mucinous carcinoma with axillary lymph node metastasis occurred less frequently than non-mucinous carcinoma (11.8% *vs.* 55.2%; $p=0.01$). Compared with the non-mucinous type, mucinous carcinoma specimens showed less AR expression (21.7% *vs.* 51.4%; $p=0.01$) but more ER expression (78.3% *vs.* 52.4%; $p=0.02$). In addition, AR expression was also associated with ER and/or PR coexpression (37/74, 50%) in infiltrating ductal carcinoma. But only three of 20 (15%) mucinous carcinoma specimens with AR expression had associated ER and/or PR coexpression. Our findings revealed that mucinous carcinoma samples from the breast show distinct clinicopathologic and hormone receptor expression features compared to non-mucinous carcinoma.

Key Words: androgen receptors, breast carcinoma, infiltrating ductal carcinoma, mucinous carcinoma
(*Kaohsiung J Med Sci* 2008;24:227–32)

The role of estrogen receptors (ER) and progesterone receptors (PR) in promoting breast cancer has been documented [1]. These hormone receptors are present in a large proportion of breast cancer, from 50% to 80% of cases [2,3]. The prognostic value of ER and PR status in breast cancer in predicting a good response to hormone treatment has been established [4]. In contrast, the pathophysiologic mechanism of both androgen levels in circulating blood and androgen receptor (AR) expression in breast carcinoma are less well defined.

Received: Nov 22, 2007 Accepted: Jan 4, 2008
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The role played by androgens in the pathogenesis of breast cancer is not well understood, in particular, the mechanism by which testosterone exerts its proliferative or antiproliferative effects on breast carcinoma cells remains unclear [5]. Recent biochemical and immunohistochemical studies indicate that ARs are expressed in a considerable proportion of breast carcinomas, ranging from 35% to 90% of cases [6,7]. In addition, a consistent coexpression of ARs, ERs and PRs has been demonstrated in the same breast cancer [8].

Breast cancer is a heterogeneous disease in morphology, invasive behavior, metastatic capacity, hormone expression, oncogene, tumor-suppressor gene expression, and clinical outcome. Mucinous carcinoma is a specific histologic type of breast cancer that is characterized by abundant extracellular mucin. The reported frequency of mucinous carcinoma of the

breast is about 1–6% [9]. It is generally thought that the tumor is more prevalent in older women and has a better prognosis than the more common ductal type of breast cancer [10].

To evaluate and compare the clinicopathologic and steroid receptor-expression characteristics of mucinous and non-mucinous invasive breast cancers, we performed immunohistochemical staining using monoclonal antibodies of AR, ER and PR. The results revealed that mucinous carcinoma has distinct histopathologic features and hormone receptor-expression characteristics compared with non-mucinous carcinoma.

Materials and Methods

A total of 128 breast cancers including 23 cases of pure mucinous carcinoma and 105 cases of infiltrating ductal carcinoma were retrieved from the files of the Pathology Department at Tzu Chi Hospital in Hualien, Taiwan. Clinicopathologic information on patient age and tumor size were obtained from patient records.

Procedure

Individual tissue sections of 4–5 μm with 23 cases of mucinous carcinoma and 105 cases of infiltrating ductal carcinoma were deparaffinized and routine streptavidin-biotin-peroxidase antigen retrieval immunostaining [11] with 3-amino-9-ethylcarbazole was performed on paraffin-embedded archival tissues by using primary rabbit anti-AR (1:50), mouse anti-ER (1:100) and mouse anti-PR (1:50).

Following treatment with chromogen-AEC, the sites for immunoprecipitate formation were identified by light microscopy. Positive and negative control sections were included with each assay. Samples were regarded as positive for AR, ER and PR when at least 10% of the tumor cells were assessed as nucleus immunoreactive [8].

Statistical analysis

Associations for mucinous and non-mucinous carcinomas for AR expression and other tumor characteristics were calculated using χ^2 or Fisher's exact tests. A two-tailed p value of less than 0.05 was declared as statistically significant.

Results

All breast cancer patients were female, with 23 cases of mucinous carcinoma and 105 cases of infiltrating

Table 1. Clinicopathology and immunohistochemistry of 128 breast cancers

	Mucinous carcinoma ($n=23$)	Infiltrating ductal carcinoma ($n=105$)	p
Age (yr)			0.92
≥50	11 (47.8%)	49 (46.7%)	
<50	12 (52.2%)	56 (53.3%)	
Mean	54.7	54.0	
Tumor size (cm)			0.23
≤5	23 (100%)	96 (91.4%)	
>5	0	6 (8.6%)	
Axillary node status			0.01
Positive	2 (11.8%)	53 (55.2%)	
Negative	15 (88.2%)	43 (44.8%)	
Estrogen receptor			0.02
Positive	18 (78.3%)	55 (52.4%)	
Negative	5 (21.7%)	50 (47.6%)	
Progesterone receptor			0.24
Positive	17 (73.9%)	64 (60.9%)	
Negative	6 (26.1%)	41 (39.1%)	
Androgen receptor			0.01
Positive	5 (21.7%)	54 (51.4%)	
Negative	18 (78.3%)	51 (48.6%)	

ductal carcinoma. There were no significant differences in age and tumor size between the two carcinoma types. Mucinous carcinoma with axillary lymph node metastasis occurred less frequently than non-mucinous carcinoma (11.8% *vs.* 55.2%; $p=0.01$). All relevant clinicopathologic data on tumor size and axillary node status are listed in Table 1. Hormone receptor-expression characteristics of the 23 mucinous carcinomas and 105 non-mucinous infiltrating ductal carcinomas are also listed in Table 1.

Hormone receptor study revealed greater expression of ER (Figure 1) (78.3% *vs.* 52.4%; $p=0.02$) and less expression of AR (Figure 2) (21.7% *vs.* 51.4%; $p=0.01$) in the mucinous type, with no significant difference in the expression of PR (Figure 3) (73.9% *vs.* 60.9%; $p=0.24$).

AR expression was also associated with ER and/or PR coexpression (37/74, 50%) in infiltrating ductal carcinoma. But only three of 20 (15%) mucinous carcinomas with AR expression had associated ER and/or PR coexpression (Table 2).

Discussion

Numerous studies have demonstrated the role of ER and PR as strong predictors of a good response to

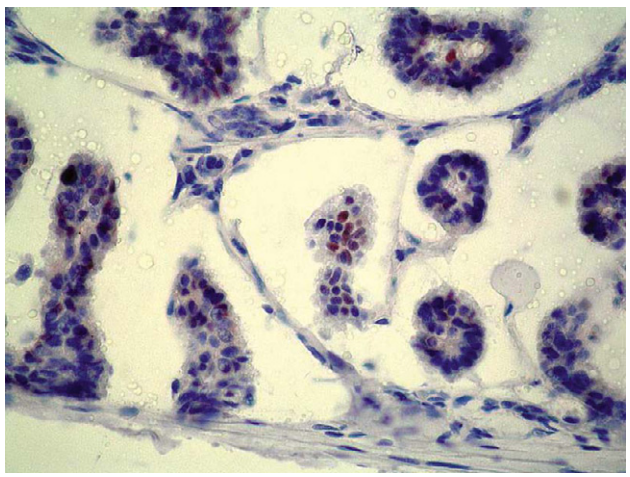

Figure 2. *Immunohistochemical staining of AR reveals nuclear staining in mucinous carcinoma (AEC, 400×).*

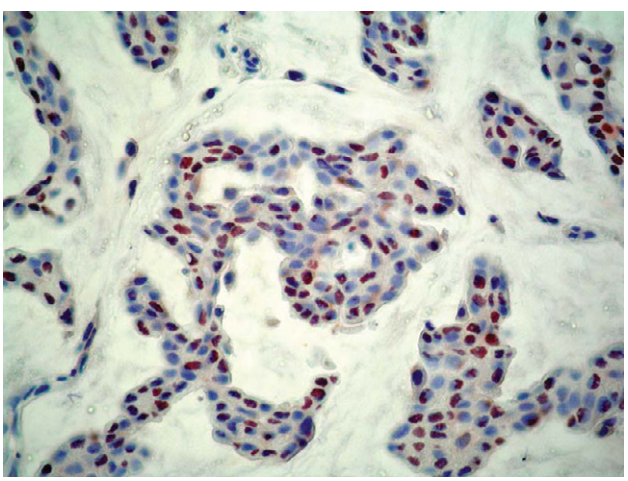

Figure 1. *Immunohistochemical staining of ER reveals nuclear staining in mucinous carcinoma (AEC, 400×).*

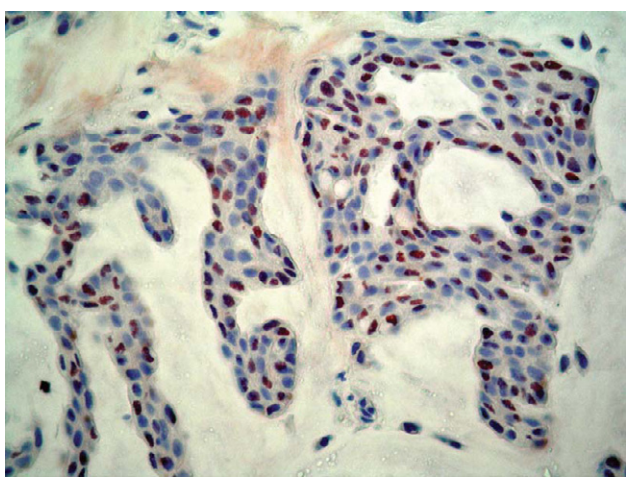

Figure 3. *Immunohistochemical staining of PR reveals nuclear staining in mucinous carcinoma (AEC, 400×).*

Table 2. Androgen receptor (AR) expression and simultaneous estrogen receptor (ER) and progesterone receptor (PR) immunoreactivity in breast carcinoma

	Mucinous carcinoma ($n=23$)		Infiltrating ductal carcinoma ($n=105$)	
	AR (+)	AR (–)	AR (+)	AR (–)
ER (+) PR (+)	3 (20%)	12 (80%)	26 (58%)	19 (42%)
ER (+) PR (–)	0 (0%)	3 (100%)	4 (40%)	6 (60%)
ER (–) PR (+)	0 (0%)	2 (100%)	7 (37%)	12 (63%)
ER (–) PR (–)	2 (67%)	1 (33.3%)	17 (55%)	14 (45%)

hormone therapy and chemotherapy in the management of patients with breast carcinoma [12]. However, the clinical significance and functional role of androgen levels and of AR expression in breast cancer has not been well defined. There is evidence that androgens can directly stimulate the growth of human breast cancer cell lines [13].

AR is a member of the larger nuclear receptor family that mediates the biological functions of androgens [14]. Some biochemical and immunohistochemical data have indicated the presence of AR in breast cancer tissue. In particular, recent studies show that AR is expressed in a considerable proportion of breast cancer, from 35% to 90% of cases. The results of our study are consistent with those of previous studies [6,7].

These data suggest that ARs are involved in the pathogenesis of at least a subset of breast carcinomas. Some studies have focused on the pattern of AR expression in different histologic subtypes of breast cancer, but the majority of data refer only to ductal carcinomas [1]. A strong and consistent AR positivity has been described in *in situ* and invasive apocrine carcinomas as well as apocrine metaplasia, and the intense expression of AR was often accompanied by a lack of ER and PR immunoreactivity. AR positivity was therefore proposed as a specific marker of apocrine differentiation [15]. In one series of invasive breast carcinomas, intense AR was frequently expressed in lobular carcinoma [16]. Moreover, our study showed a strong widespread AR positivity in the majority of infiltrating ductal carcinoma (54/105, 51.4%) and rare expression in mucinous carcinoma (5/23, 21.7%; $p = 0.01$). Only one previous study reported mucinous carcinoma exhibiting a relatively high frequency of positivity for AR (3/6, 50%) in women over 85 years old [17]. The reason why there was a low incidence of expression (21.7%) of AR in mucinous carcinoma in our study and the mechanism of AR in this type of breast cancer are still unknown. Further study of more cases should be performed in the future to resolve these issues.

There was also a significant difference in ER expression between the two types of breast carcinoma (52.4% in infiltrating *vs.* 78.3% in mucinous; $p = 0.02$). Our results are again consistent with those of previous studies, which demonstrated a high frequency of expression of ER protein in mucinous breast cancer [18,19].

AR expression was associated with ER and/or PR coexpression—50% (37/74) in infiltrating ductal carcinoma. But in mucinous carcinoma, it was only 15% (3/20).

In addition to breast cancer, AR also plays an important role in the development and progression of prostate cancer. Both AR and androgen-converting enzymes were found to be upregulated in high-grade or advanced prostate cancer [20]. Recently, dibenzoylmethane has been applied for advanced prostate cancer through suppression of the function of AR [21]. In future, this drug may be a new choice for the treatment of advanced breast cancer with high AR expression.

In conclusion, mucinous carcinomas of the breast demonstrate less axillary lymph node metastasis, more frequent expression of ER, and have a low frequency of AR and low incidence of AR with ER and/or PR coexpression compared to infiltrating ductal carcinoma. Our results revealed that mucinous carcinoma samples from the breast showed distinct clinicopathology and hormone receptor-expression features when compared to non-mucinous carcinoma samples.

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黏液性乳癌內雄性激素受體，動情激素受體及黃體激素受體之表達

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荷爾蒙受體在乳癌佔重要角色。我們觀察乳癌內荷爾蒙受體之表達以了解這些受體在臨床病理研究的重要性。我們研究 **23** 例黏液性乳癌及 **105** 例非黏液性侵浸性女性乳癌用免疫組織化學染色觀察雄性激素受體，動情激素受體及黃體激素受體並比較兩組病人年齡、腫瘤大小及腋下淋巴腺轉移與否。黏液性乳癌比非黏液性乳癌有較低腋下淋巴腺轉移 (**11.8%** 比 **55.2%**；$p = 0.01$)，黏液性乳癌有較低雄性激素受體表達 (**21.7%** 比 **51.4%**；$p = 0.02$)，此外，侵浸性乳腺管癌內雄性激素受體表達合併動情激素受體和黃體激素受體共同表達率 (**37/74**，**50%**)。而黏液性乳癌只有 **3** 例 (**3/20**，**15%**) 有雄性激素受體合併動情激素受體或黃體激素受體共同表達率。本研究顯示黏液性乳癌與非黏液性乳癌在臨床病理及荷爾蒙受體表達明顯不同。

關鍵詞：雄性激素受體，乳癌，侵浸性乳管癌，黏液性乳癌

(高雄醫誌 **2008;24:227－32**)

收文日期：**96** 年 **11** 月 **22** 日

接受刊載：**97** 年 **1** 月 **4** 日

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