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ORIGINAL ARTICLE

The expression of estrogen receptors in thyroid cancer and its significance

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Abstract

Objective The study aimed to detect the expression of estrogen receptors (ERs) in thyroid cancer and investigate the correlation between their expression and clinical features and different pathological types.

Methods The expression of ERs in 56 samples of thyroid cancer tissues was detected by an immunochemical approach. The expression of ERs in thyroid cancer tissues and different pathological types were analyzed using the χ^2 test.

Results The number of cases with positive expression of ER in thyroid cancer tissues was 36. The number of papillary thyroid cancers (PTCs) was 48, with positive expression of ERs in 32 cases. The number of follicular thyroid cancers was 4, with positive expression of ERs in 2 cases. The number of medullary thyroid cancers was 4, with negative expression of ERs in all cases. The difference between the expression and different pathological types showed statistical significance. The expression of ERs showed no correlation with sex, age, or TNM stage, with no statistical significance. However, the expression of ERs was correlated with metastasis of lymph nodes, which had statistical significance. The expression of ERs was negatively correlated with pathological types and metastasis of lymph nodes. The correlated coefficient index was –0.313 and –0.334, respectively.

Conclusion The expression of ERs showed no correlation with sex, age, or TNM stage, but was negatively correlated with pathological types and metastasis of lymph nodes.

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Key words: thyroid cancer; estrogen receptor (ER); pathological type

Although the incidence of thyroid cancer accounts for 5% of thyroid nodules [1] and 1% of all tumors, thyroid cancer is the most common cancer of the endocrine glands [2]. According to the data from the American Cancer Society, the incidence of thyroid cancer has increased significantly since the 1990s. Some reports demonstrated that the incidence of thyroid cancer shows no gender difference before the age of 10. However, the female incidence was three or four times higher than the male incidence after 10 years of age and women of child-bearing age were the major proportion of female patients, although the incidence decreased in postmenopausal women [3–4]. Sungwalee *et al* proposed that women with early menarche, oral contraceptive use, or no pregnancy tend to suffer from thyroid cancer to some extent [5]. Thus, it can be seen that endogenous estrogen does play an important role in the occurrence and development of thyroid cancer.

Materials and methods

Tissues and clinical data were obtained from 56 thyroid cancer patients who underwent radical thyroidectomy in the Second Affiliated Hospital of Dalian Medical University (China) from October 2014 to September 2015 and the pathological diagnosis was confirmed as thyroid cancer. All 56 patients had not accepted chemotherapy or radiotherapy before the operation. The number of male patients was 19 and that of female patients was 37. Their ages ranged from 23- to 71-years-old and the average age was (63.20 ± 10.18) years. There were 32 patients under 45-years-old and 24 patients beyond 45-years-old. Regarding the TNM stage, there were 31 patients with T1 and T2 stages, and 25 with T3 and T4 stages. There were 24 patients with lymph node metastasis and 32 patients without lymph node metastasis. Regarding the pathological

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type, there were 48 patients with papillary thyroid cancer (PTC), 4 patients with medullary thyroid cancer, and 4 patients with follicular thyroid cancer.

The expression of estrogen receptors (ERs) in the 56 tissue samples of thyroid cancer was detected by an immunochemical approach. The expression of ERs in thyroid cancer tissues and different pathologic types were analyzed by the χ^2 test. The value of $P < 0.05$ was considered to indicate a statistically significant difference.

Results

The expression of estrogen receptors in thyroid cancer tissues

The positive expression result of ERs in thyroid cancer tissues was showed in Table 1. The positive expression of ERs displayed brownish yellow granules which mainly locates on the cell nucleus, partially on the cytoplasm (Fig. 1–4).

The relationship of estrogen receptors expression in thyroid cancer tissues and clinical features

The relationship of ERs expression in thyroid cancer tissues and clinical features was showed in Table 2. The expression of ERs has no correlation with sex, age and TNM stage, which has no statistical difference ($P > 0.05$). There are 24 patients with lymph metastasis and 32 patients without lymph metastasis, which had statistical significance ($P = 0.013$).

The expression of estrogen receptors in the different histopathological types

The expression result of ERs in the different histopathological types was shown in Table 3, and the expression had statistical significance ($P = 0.029$).

Table 1 The expression of estrogen receptors in thyroid cancer tissues

Group	Cases	Positive cases	Positive rate (%)
Thyroid cancer tissues	56	36	64.3

Table 2 The relationship of estrogen receptors expression in thyroid cancer tissues and clinical features

Clinical features	Cases	Estrogen receptors			χ^2	P
		Positive cases	Negative cases	Positive rate (%)		
Sex					0.016	0.900
Male	19	12	7	63.2		
Female	37	24	13	64.9		
Age (years)					0.104	0.747
≤ 45	32	20	12	66.7		
> 45	24	16	8	62.5		
Stage					1.350	0.245
T1 + T2	31	22	9	71.0		
T3 + T4	25	14	11	56.0		
Lymph metastasis					6.229	0.013
Yes	24	11	13	45.8		
No	32	25	7	78.1		

Table 3 The expression of estrogen receptors in the different histopathological types

Groups	Cases	Positive cases	Positive rate (%)	χ^2	P
Papollary carcinoma	48	32	66.7	7.087	0.029
Follicular carcinoma	4	2	50.0		
Medullary carcinoma	4	0	0.0		

Discussion

Thyroid cancer is the most common malignancy of the endocrine system [2] with increasing incidence, especially of papillary carcinoma. Eheman *et al* demonstrated that the male incidence of thyroid cancer was 5.5/100 000 and the female incidence was 16.3/100 000 from 2004 to 2008 in America [6]. The occurrence of thyroid cancer may be related to the exposure to radiation or hyperplastic diseases of thyroid tissues in family history [7–9]. Moreover, an increasing number of studies show that endogenous estrogen may play an important role in the occurrence and progression of thyroid cancer.

ERs play an important role in non-genomic or classical genomic estrogen signaling. Estrogen enters target cells via passive diffusion, and then the binding of ligand E2 to ERs results in the conformational changes of ERs. These conformational changes cause the dissociation of the ER from its ligand proteins, and then regulate gene expression through the combination of homo- or hetero-dimerization of E2-ER and the nucleotide sequence located in the promoters of target genes, known as estrogen response elements (EREs). However, in humans, one-third of genes regulated by estrogen do not contain ERE-sequences [10–11]. Under these circumstances, estrogen can regulate the expression of target genes by modulating the functions of other transcriptional factors in the nucleus, which results in chromatin alteration via the interactions between proteins. This process is collectively known as the ERE-independent genomic actions of estrogen [12]. Estrogen exerts biological effects in the bone, breast, vasculature, and nervous system through its interaction with related estrogen binding proteins on the cell membrane, instead of the gene transcription and protein synthesis mediated by E2-ER. These actions are referred to as non-genomic estrogen signaling.

Estrogen signaling is mediated primarily through two isoforms of the ER: ERα and ERβ. ERα can promote the growth of thyroid cancer cells (including papillary

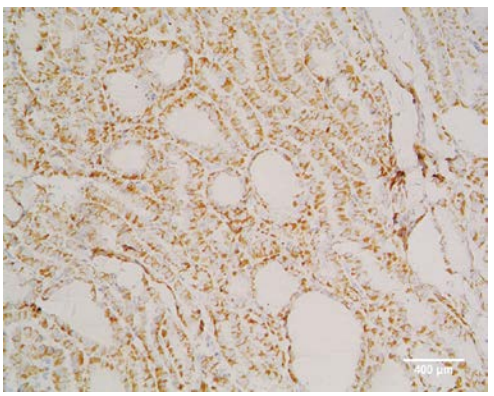

Fig. 1 The positive expression of estrogen receptors in papillary thyroid cancer cells (HE, ×200)

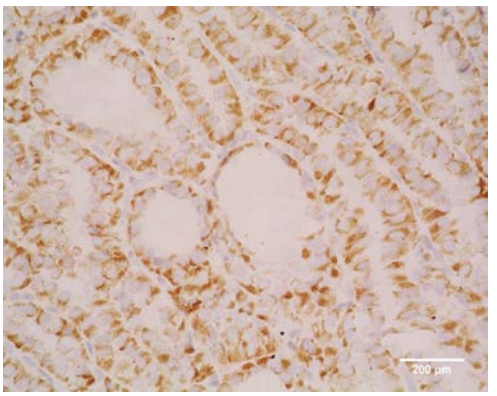

Fig. 2 The positive expression of estrogen receptors in papillary thyroid cancer cells (HE, ×400)

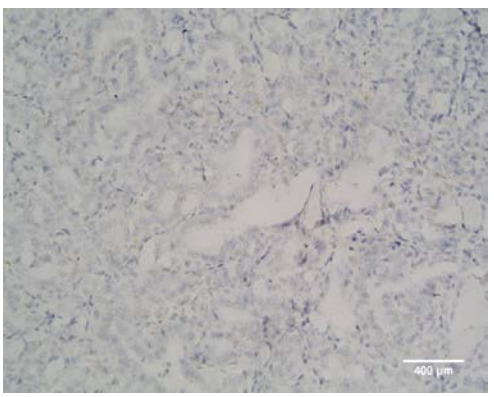

Fig. 3 The negative expression of estrogen receptors in thyroid thyroid cancer cells (HE, ×200)

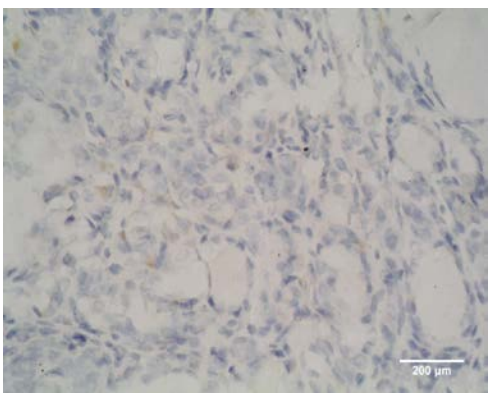

Fig. 4 The negative expression of estrogen receptors in thyroid cancer cells (HE, ×400)

cancer cells KAT5, follicular cancer cells FRO, and undifferentiated cancer cells ARO) by integrating with E2 [13]. Zeng *et al* demonstrated that the agonist and antagonist for ERα and ERβ can regulate the expression of ERs. Propylpyrazole triol (PPT), an ERα agonist, can enhance the proliferation of thyroid cancer cells and the expression of antiapoptotic protein Bcl-2, while diarylpropionitrile (DPN), an ERβ agonist, can inhibit the proliferation and enhance the expression of apoptotic gene Bax. In addition, the knockdown of ERα can significantly reduce the expression of Bcl-2, while the silencing of ERβ can enhance the expression of Bcl-2; this expression imbalance between ERα and ERβ may result in the occurrence of thyroid cancer [13]. ERα can promote the growth of cancer cells, while ERβ can inhibit the proliferation of cancer cells. Some reports proposed that the increased ratio of ERα to ERβ might influence the growth and progression of medullary thyroid cancer [14]. By investigating the genotype of 344 PTCs and 452 controls, Schonfeld *et al* identified that seven single nucleotide polymorphisms (SNPs) may relate to the development of PTC, four of which are located on the *CYP19A1*, *ESR1*, *HSD17B3*, and *SULF1* genes. However, they demonstrated that all the SNPs had no obvious correlation with the occurrence and progression of PTC [15]. On the other hand, RebaÏ *et al* reported that the polymorphism change in the A549G codon on the ER ESR1 might alter the recognition and combination of ER ligands, which may result in the occurrence of thyroid cancer [16]. Rajoria *et al* also identified that the expression of ERα and ERβ were both detected in the PTC cell lines KAT5, NPA87, and BCPAP, and E2 could promote the adhesion, invasion, and metastasis of BCPAP cells [17–18]. Dong *et al* found that E2 exposure can lead to the downregulation of E-cadherin and upregulation of vimentin and matrix metalloproteinase-9 (MMP-9). Additionally, ERα and ERβ play significant roles in BCPAP cell metastasis through the differential regulation of E-cadherin, vimentin, and MMP-9 [19]. In our study, we found that the positive expression of ERs was different in the three types of thyroid cancers, which indicated that the higher the expression of ER, the higher the

differentiation of thyroid cancer. In addition, we also found that the positive expression of ERs could indicate thyroid cancer without the metastasis of lymph nodes.

Conclusion

As a whole, our data demonstrates that the expression of ERs may correlate with the degree of differentiation and the metastasis of lymph nodes, and it might be a prognostic indicator that can be used in targeting ERs for the treatment of thyroid cancer.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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