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Hormone levels and clinicopathological features in patients with thyroid cancer complicated with breast cancer

Aliya Tayier, Wufaer Yimaer, Bogela Aersilan, WANG Huguo

Department of Vascular Thyroid Surgery, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang 830011, China

Corresponding author: WANG Huguo, E-mail: xjxjwhg@163.com

Abstract: Objective To study the hormone levels and clinicopathological characteristics of patients with thyroid cancer and breast cancer, and to explore the possible relationship between the two cancers. **Methods** Clinical data of 82 cases of thyroid cancer with breast cancer (combined cancer group) patients and 86 cases of simple thyroid cancer (thyroid cancer group) patients in The First Affiliated Hospital of Xinjiang Medical University from January 2010 to December 2022 were collected. According to whether the BMI was greater than 24, patients in combined cancer group were divided into overweight combined cancer group (n=37) and normal combined cancer group (n=45), and patients in thyroid cancer group were divided into overweight thyroid cancer group (n=44) and normal thyroid cancer group (n=42). The general characteristics, pathological characteristics, thyroid hormone and endocrine hormone levels of the two groups, and pathological features of different BMI subgroups were compared. **Results** There was no significant difference in age, BMI and menstrual status between the two groups (P>0.05). However, the tumor diameter of overweight patients in combined cancer group was (0.65±0.33) cm, which was significantly smaller than that of overweight patients in thyroid cancer group [(1.06±0.97) cm], and the difference was statistically significant (t=2.452, P=0.018). The proportion of patients with previous reproductive history in the combined cancer group was significantly higher than that in the thyroid cancer group (93.90% *vs* 80.23%, χ^2=6.892, P=0.009). The level of thyroxine (T4), estriol and progesterone were higher in the combined cancer group than those in the thyroid cancer group, and the differences were statistically significant (P<0.05). The level of testosterone in the combined cancer group was significantly lower than that in the thyroid cancer group [0.77 (0.48,1.02) nmol/L *vs* 0.88(0.68,1.21) nmol/L, z=3.008, P=0.003]. **Conclusion** Patients combined with thyroid cancer combined with breast cancer have higher serum T4, progesterone and estritol and lower testosterone levels on clinical biochemical markers compared with patients with thyroid cancer alone. Although no correlation was found between BMI and clinicopathologic features, the pathological features of overweight patients with cancer were smaller tumor diameter. Therefore, health education and disease screening for obese patients should be strengthened clinically, and thyroid and breast ultrasound examinations should be performed regularly if necessary.

Keywords: Thyroid cancer; Breast cancer; Hormone levels; Pathological features; Testosterone; Progesterone; Estriol; Thyroxine; Overweight

Thyroid cancer is the most common endocrine disorder in women and the fastest-growing malignant tumor. However, breast cancer still ranks highest among malignant tumors in women, and its screening and treatment play a crucial role in clinical practice. As both the thyroid and breast are regulated by the neuroendocrine axis, they may share common pathogenic factors in their development and progression [1]. In this study, 86 patients with thyroid cancer and breast cancer were selected as the research subjects, and the hormone levels and clinicopathological characteristics were analyzed in depth.

1 Data and Methods

1.1 General Information

Clinical data of 82 cases of patients with thyroid cancer combined with breast cancer and 86 cases of patients with thyroid cancer admitted to the First Affiliated Hospital of Xinjiang Medical University from January 2010 to December 2022 were collected.

Inclusion criteria: (1) Patients were female. (2) Diagnosis of breast cancer referred to the "Guidelines for breast cancer diagnosis and treatment by China Anti-Cancer Association (2024 Edition)" [2], and diagnosis of thyroid cancer referred to the "Guidelines for the diagnosis and management of thyroid nodules and differentiated thyroid cancer (Second edition)" [3]. All

cases were confirmed by pathology. (3) Clinical data were complete.

Exclusion criteria: (1) Recurrence or metastasis of malignant tumor; (2) Patients with concomitant lesions in other organs. (3) Clinical data were incomplete.

1.2 Observation Indicators

The following data were collected, including age at diagnosis of malignant tumors, menopausal status, reproductive history, duration of estrogen exposure, estrogen levels and tumor characteristics. Estrogen levels: free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), thyroglobulin antibody (TGAb), thyroid peroxidase antibody (TPOAb), triiodothyronine (T3), thyroxine (T4) estradiol, prolactin, progesterone, follicle-stimulating hormone, testosterone, luteinizing hormone, and estrone. Tumor characteristics: pathological type, lymph node metastasis, maximum tumor diameter, multifocality, $BRAF^{V600E}$ mutation status.

1.3 Statistical Analysis

Statistical analysis was performed using SPSS 23.0 software. The Shapiro-Wilk test was used to test the normality of the measurement data. Normal distribution of data was expressed as $\bar{x}\pm s$, and one-way analysis of variance was used if the variance was homogeneous, otherwise Kruskal-Wallis H test was used for comparison. Abnormal distribution of data was expressed as M (P_{25}, P_{75}), and the Mann-Whitney U test was used for comparison between two groups. Count data were expressed as case (%), and inter-group comparisons were made using chi-square and its correction. The significance level was set at α=0.05 and the analysis was two-tailed.

2 Results

2.1 Comparison of General Clinical Data between Combined Cancer Group and Thyroid Cancer Group

The age of patients in the combined cancer group was slightly higher than that in the thyroid cancer group, but the difference between the two groups was not statistically significant (P=0.217). There was no statistically significant difference in body mass index (BMI) and duration of estrogen exposure between the two groups (P>0.05). In terms of reproductive history, the number of patients with a history of childbirth was significantly higher than that of nulliparous women, especially in the combined cancer group, which was significantly higher than in the thyroid cancer group (P=0.009). **[Table 1]**

2.2 Comparison of Tumor Characteristics between Overweight and Normal Patients

According to whether the BMI was > 24 kg/m^2, the 82 patients with thyroid cancer combined with breast cancer were divided into a normal group of 45 cases and an overweight group of 37 cases. The differences between the two groups were compared in terms of tumor diameter, lymph node metastasis, multifocality, unilateral or bilateral involvement, and pathological type. The results showed that the multifocality in the overweight group (27.03%) was higher than that in the normal group (20.00%), but the difference was not statistically significant (P>0.05). **[Table 2]**

The 86 cases in the thyroid cancer group were also grouped and compared using the same method, and the results showed that the overweight thyroid cancer group had higher tumor diameter, lymph node metastasis rate, and multifocality than the normal thyroid cancer group, but the differences were not statistically significant (P>0.05). **[Table 2]** Inter-group comparison revealed that the tumor diameter of overweight patients in the combined cancer group was significantly smaller than that of overweight patients in the thyroid cancer group, and the difference was statistically significant (t=2.452, P=0.018).

2.3 Comparison of Clinical Pathological Features between Combined Cancer Group and Thyroid Cancer Group

There was no statistically significant difference between the two groups of patients in terms of surgical method, tumor diameter, pathological type, lymph node metastasis, multifocality, and V600E mutation (P>0.05). **[Table 3]**

2.4 Comparison of Hormone Levels between Combined Cancer Group and Thyroid Cancer Group

The expression levels of T4, estradiol, and progesterone in patients in the combined cancer group were significantly higher than those in patients in the thyroid cancer group, and the differences were statistically significant (P<0.05). However, the testosterone levels were significantly lower in the combined cancer group than in the thyroid cancer group, and the difference was statistically significant (P=0.003). There were no statistically significant differences in the serum levels of other indicators such as T3, TSH, TGAb, TPOAb, FT3, FT4, prolactin, and other hormones (P>0.05). **[Table 4]**

Tab.1 General clinical data

Item	Combined cancer group (*n*=82)	Thyroid cancer group (*n*=86)	$\chi^2/t/z$ value	*P* value
Age (years, $\bar{x}\pm s$)	46.42±8.62	44.58±10.47	1.240	0.217
Menopause [case (%)]	25(30.5)	25(29.1)	0.040	0.841
BMI (kg/m^2, $\bar{x}\pm s$)	24.63±3.58	25.13±4.19	0.830	0.408
Duration of estrogen exposure(year)[a]	32(26,36)	31(22,35)	0.860	0.390
Having childbirth history [case (%)]	77(92.7)	69(80.2)	6.892	0.009

Note: [a] represents data in *M* (P_{25}, P_{75}).

Tab. 2 Comparison of oncological characteristics of patients in different groups [case (%)]

Item	Combined Cancer Group		Thyroid Cancer Group		F/χ^2 Value	*P* Value
	Normal	Overweight	Normal	Overweight		
Case	45	37	42	44		
Tumor Diameter (cm, $\bar{x}\pm s$)	0.69±0.29	0.65±0.33	0.87±0.67	1.06±0.97	3.673	0.013
Lymph Node Metastasis	18(40.00)	10(27.03)	13(30.95)	16(36.36)	1.808	0.613
Multifocality	9(20.00)	10(27.03)	13(30.95)	17(38.64)	3.887	0.274
Location						
Unilateral	37(82.22)	27(73.03)	28(66.67)	31(70.45)	2.952	0.399
Bilateral	8(17.78)	10(27.03)	14(33.33)	13(29.55)		
Pathological Type						
Microcarcinoma	8(17.78)	10(27.03)	5(11.90)	5(11.36)		
Papillary Carcinoma	37(82.22)	27(72.97)	37(88.10)	38(86.36)	7.192	0.303
Medullary Carcinoma	0	0	0	1(2.27)		

Tab. 3 Comparison of clinicopathological characteristics between two groups [case (%)]

Clinicopathological characteristics	Combined cancer group (*n*=82)	Thyroid cancer group (*n*=86)	χ^2 value	*P* value
Surgical method				
Total thyroidectomy	62(74.7)	64(74.4)	0.032	0.858
Partial thyroidectomy	20(24.1)	22(25.6)		
Tumor diameter				
<0.5cm	17(20.5)	18(20.9)	0.001	0.975
⩾0.5cm	65(78.3)	68(79.1)		
Pathological type				
Microcarcinoma	18(21.7)	27(31.4)		
Papillary carcinoma	64(77.1)	58(67.4)	3.002	0.223
Medullary carcinoma	0	1(1.2)		
Lymph node metastasis	28(33.7)	29(33.7)	0.003	0.954
Multifocality	19(22.9)	30(34.9)	2.787	0.095
V600E mutation	29(34.9)	35(40.7)	0.506	0.477

Tab.4 Comparison of hormone levels between two groups

Item	Combined cancer group (*n*=82)	Thyroid cancer group (*n*=86)	χ^2/t value	*P* value
T3(nmol/L)[a]	1.68±0.35	1.63±0.25	0.110	0.912
T4(nmol/L)[b]	99.18(82.54,111.33)	89.20(79.10,99.55)	2.796	0.049
TSH(mIU/L)[b]	2.01(1.50,3.53)	2.41(1.68,3.28)	0.633	0.530
TGAb(IU/mL)[b]	16.35(12.10,119.90)	20.18(13.35,180.40)	1.166	0.470

TPOAb(IU/mL)[b]	13.45(8.43,24.69)	13.75(9.51,22.28)	0.627	0.530
FT3(pmol/L)[a]	4.39±0.90	4.50±0.90	0.792	0.430
FT4(pmol/L)[a]	15.50±4.40	14.74±4.41	1.118	0.265
Estriol (pmol/L)[b]	0.03(0.02,0.04)	0.02(0.01,0.03)	2.851	0.004
Prolactin (μg/L)[b]	341.60(209.56,519.13)	345.42(230.84,490.44)	0.276	0.780
Progesterone (nmol/L)[b]	1.37(0.68,4.80)	0.95(0.32,3.55)	2.114	0.034
FSH (IU/L)[b]	7.94(4.75,38.47)	10.81(4.71,49.43)	0.616	0.540
Testosterone (nmol/L)[b]	0.77(0.48,1.02)	0.88(0.68,1.21)	3.008	0.003
LH (IU/L)[b]	7.67(3.90,19.21)	9.07(4.32,22.43)	0.808	0.420
Estradiol (pmol/L)[b]	122.50(45.74,363.43)	139.00(37,356)	0.076	0.940

Note: a represents data in $\overline{x} \pm s$; B represents data in M (P_{25}, P_{75}).

3 Discussion

Malignant thyroid tumors are a common type of malignant disease of the endocrine system, closely related to various factors such as individual genetic factors, environmental conditions, and hormone levels. Studies have found that patients with thyroid malignant tumors often have a history of breast disease in their past medical records or during regular follow-ups after surgery [4]. Therefore, we speculate that gene mutations related to thyroid cancer and changes in hormone levels may be the main reasons for the development of breast cancer. Epidemiological investigations have shown a certain correlation between thyroid cancer and breast cancer. The results revealed in patients with breast tumors, the levels of T4, estradiol, and progesterone were significantly elevated, while testosterone levels were significantly decreased. This result suggests that hormones may play an important role in the process of thyroid cancer patients developing breast cancer.

In vitro experiments have shown that thyroid hormones can exert estrogen-like effects, stimulating the growth of tumor cells [5]. Under *in vitro* conditions, T4 has also been confirmed as a proliferative factor, enhancing the proliferation of estrogen-dependent breast cancer cells [6]. This study found that patients with combined cancer had significantly higher levels of T4 than those with thyroid cancer, suggesting that long-term elevated levels of T4 may stimulate the overexpression of estrogen receptors on breast cells' surface, leading to the growth and metastasis of tumor cells. However, opinions on the relationship between thyroid hormones and breast cancer are not consistent. This study did not find differences in thyroid-related hormones such as T3, TSH, and TPOAb between the two groups, possibly due to the small sample size. Therefore, this conclusion needs further long-term, large-sample studies for verification.

Both the thyroid and breast belong to the endocrine system, regulated by the hypothalamic-pituitary axis hormones, with estrogen being the most critical regulator of both. Many studies have confirmed that estrogen has a promoting effect on the development and progression of differentiated thyroid cancer [7]. Additionally, there is evidence showing that pregnancy might increase the risk of patients with thyroid cancer developing breast cancer. This was validated in this study: compared to nulliparous patients, we found a significantly higher proportion of patients with a history of childbirth in combined group. This may be related to the increased estrogen levels during pregnancy. However, estrogen levels in women are positively correlated with the proliferation and metastasis of malignant breast tumor cells, and lower levels of estrogen have an inhibitory effect on tumor cell growth [8]. This study compared the duration of estrogen exposure in the combined cancer group [31.5 (26,36) years] with the thyroid cancer group [31 (22,35) years], but the difference was not statistically significant.

Lalitkumar *et al.* [9] first revealed the impact of progesterone on thyroid cells and further confirmed that progesterone can enhance the expression of genes involved in thyroid protein expression differences through its receptors, thereby affecting the growth and differentiation of thyroid tissue. Some related studies have shown that hormone therapy during menopause can relieve menopausal symptoms, but postmenopausal women taking long-term estrogen combined with progesterone may increase their risk of breast cancer [10]. The data from this study revealed that sustained high levels of progesterone can stimulate the growth of breast cells, thereby increasing the possibility of breast cancer in patients with thyroid cancer.

In the human body, testosterone is an important androgen, and its secretion is also controlled by the pituitary and hypothalamus. Before sexual maturity, estrogen from the ovaries' endometrial cells can promote calcium retention and growth of the long bone matrix. After sexual maturity, it can promote the closure of the bone epiphysis. When testosterone interacts with androgen receptors to form hormone receptor complexes, they interact with specific targeted gene response elements, entering the growth control pathway of cancer cells [11]. Regardless of the tumor type, the presence of androgen receptors is a good prognostic indicator, with its expression inversely proportional to the invasiveness and pathological grading of tumors [12]. The results of this study showed a significant decrease in testosterone levels in patients with combined breast cancer, with a significant difference compared to patients with pure thyroid cancer. It is speculated that higher testosterone hormone levels in patients with pure thyroid tumors may inhibit tumor cell proliferation and improve prognosis. However, the

specific correlation needs further research for verification.

Data from the National Cancer Database (NCDB) indicated that patients with both thyroid and breast cancer had a higher rate of lymph node metastasis compared to patients with solitary thyroid cancer, but the tumor diameter was relatively smaller [13]. In this study, tumors with a diameter of ⩾0.5 cm were predominant in both pure cancer group and combined cancer group, accounting for 79.1% and 78.3%, respectively. Additionally, the pure cancer group had 58 cases of unilobular papillary carcinoma (67.4%), while the combined cancer group had 64 cases (77.1%), which was higher than bilobular papillary carcinoma. However, this study did not find differences between the two groups in terms of tumor size and lymph node metastasis, possibly due to the small number of cases, requiring further clinical data for validation.

Some studies have suggested a positive correlation between BMI index and the risk of malignant thyroid tumors [14]. Similarly, in breast cancer-related studies, the risk of breast cancer increases linearly with increasing BMI. Analyzing the pathological characteristics of BMI in this study did not show significant differences between the two groups. However, further analysis revealed that overweight patients in the pure cancer group had larger thyroid cancer tumors compared to overweight patients in the combined cancer group, with a statistically significant difference. Therefore, we conclude that compared with patients with thyroid cancer alone, patients with thyroid cancer and breast cancer often have smaller tumor diameter and may be more invasive when their BMI is >24 kg/m^2. However, due to the quality of data and methods, this study has not yet conducted research on tumor invasion.

To sum up, compared with patients with simple thyroid cancer, patients combined with breast cancer have higher levels of serum T4, progesterone and estriol, and lower levels of testosterone. The detection of the above indicators is of great significance for the diagnosis and evaluation of the progression of thyroid cancer. There is no significant difference in BMI and clinical pathological characteristics between the two groups of patients. However, further analysis revealed that overweight patients combined with cancer had a smaller tumor diameter. Therefore, it is necessary to strengthen health education and disease screening for obese patients in clinical practice, and regularly perform thyroid and breast ultrasound examinations if necessary.

Conflicts of Interest: None

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·论　著·

甲状腺癌合并乳腺癌患者的激素水平及临床病理特征

阿丽雅·塔依尔，　吾甫尔·依马尔，　博格拉·阿尔斯兰，　王护国
新疆医科大学第一附属医院血管甲状腺外科，新疆 乌鲁木齐 830011

摘要：目的　调查甲状腺癌合并乳腺癌与单纯甲状腺癌患者的激素水平和临床病理特征，以探索这两种恶性肿瘤之间的潜在联系。**方法**　收集 2010 年 1 月至 2022 年 12 月新疆医科大学第一附属医院收治的 82 例甲状腺癌合并乳腺癌患者（合并癌组）及 86 例单纯甲状腺癌患者（单纯癌组）的临床资料，根据身体质量指数（BMI）是否大于 24 kg/m^2，将合并癌患者分为超重合并癌组（37 例）和正常合并癌组（45 例），单纯癌患者分为超重单纯癌组（44 例）和正常单纯癌组（42 例）。比较两组患者一般特征、病理特征、甲状腺激素和内分泌激素水平以及不同 BMI 患者间的病理特征。**结果**　两组患者年龄、BMI 及雌激素暴露时间比较差异无统计学意义（P>0.05）。但超重合并癌组患者肿瘤直径为（0.65±0.33）cm，明显小于超重单纯癌组患者的（1.06±0.97）cm，差异有统计学意义（t=2.452，P=0.018）。合并癌组既往有生育史的比例明显高于单纯癌组（93.90% *vs* 80.23%，χ^2=6.892，P=0.009）。与单纯癌组相比，合并癌组甲状腺素（T4）、雌三醇、孕酮水平更高，差异均有统计学意义（P<0.05）。合并癌组睾酮水平明显低于单纯癌组，差异有统计学意义［0.77（0.48，1.02）nmol/L *vs* 0.88（0.68，1.21）nmol/L，z=3.008，P=0.003］。**结论**　合并乳腺癌的甲状腺癌患者与单纯甲状腺癌患者相比，在临床生化指标上有更高的血清 T4、孕酮和雌三醇以及更低的睾酮水平。虽然未发现 BMI 与临床病理特征之间的关联，但超重的合并癌患者其病理特征表现为肿瘤直径更小，因此临床上要加强肥胖患者健康宣教及疾病筛查。

关键词：甲状腺癌；乳腺癌；激素水平；病理特征；睾酮；孕酮；雌三醇；甲状腺素；超重
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Hormone levels and clinicopathological features in patients with thyroid cancer complicated with breast cancer

Aliya Tayier, Wufaer Yimaer, Bogela Aersilan, WANG Huguo
Department of Vascular Thyroid Surgery, The First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang 830011, China
Corresponding author: WANG Huguo, E-mail: xjxjwhg@163.com

Abstract: Objective　To study the hormone levels and clinicopathological characteristics of patients with thyroid cancer and breast cancer, and to explore the possible relationship between the two cancers. **Methods**　Clinical data of 82 cases of thyroid cancer with breast cancer (combined cancer group) patients and 86 cases of simple thyroid cancer (thyroid cancer group) patients in The First Affiliated Hospital of Xinjiang Medical University from January 2010 to December 2022 were collected. According to whether the BMI was greater than 24, patients in combined cancer group were divided into overweight combined cancer group (n=37) and normal combined cancer group (n=45), and patients in thyroid cancer group were divided into overweight thyroid cancer group (n=44) and normal thyroid cancer group (n=42). The general characteristics, pathological characteristics, thyroid hormone and endocrine hormone levels of the two groups, and pathological features of different BMI subgroups were compared. **Results**　There was no significant difference in age, BMI and menstrual status between the two groups (P>0.05). However, the tumor diameter of patients in overweight combined cancer group was (0.65±0.33) cm, which was significantly smaller than that of patients in overweight thyroid cancer group [(1.06±0.97) cm], and the difference was statistically significant (t=2.452, P=0.018). The proportion of patients with previous reproductive history in the combined cancer group was significantly higher

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通信作者：王护国，E-mail：xjxjwhg@163.com
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than that in the thyroid cancer group (93.90% *vs* 80.23%, $\chi^2=6.892$, $P=0.009$). The levels of thyroxine, estriol and progesterone were higher in the combined cancer group than those in the thyroid cancer group, and the differences were statistically significant ($P<0.05$). The level of testosterone in the combined cancer group was significantly lower than that in the thyroid cancer group [0.77 (0.48, 1.02) nmol/L *vs* 0.88 (0.68, 1.21) nmol/L, $z=3.008$, $P=0.003$]. **Conclusion** Patients with thyroid cancer combined with breast cancer have higher serum thyroxine, progesterone and estritol and lower testosterone levels on clinical biochemical markers compared with patients with thyroid cancer alone. Although no correlation was found between BMI and clinicopathologic features, the pathological features of overweight patients with breast cancer and thyroid cancer showed smaller tumor diameter. Therefore, health education and disease screening for obese patients should be strengthened clinically.

Keywords: Thyroid cancer; Breast cancer; Hormone levels; Pathological features; Testosterone; Progesterone; Estriol; Thyroxine; Overweight

甲状腺癌是最常见的内分泌疾病,并且目前也已发展成增长速度最快的恶性肿瘤;乳腺癌仍旧高居女性恶性肿瘤之首,其筛查和治疗在临床上起着至关重要的作用。由于甲状腺和乳腺均受神经内分泌轴的调控,因此两者的发生和发展可能存在着相同的致病因素[1]。为了对甲状腺癌伴随乳腺癌患者的病情特征进行更深入的分析,本研究选取 86 例甲状腺癌伴随乳腺癌患者的激素水平和临床病理特征作为研究对象。

1　资料与方法

1.1　一般资料　收集新疆医科大学第一附属医院 2010 年 1 月至 2022 年 12 月收治的 82 例甲状腺癌合并乳腺癌患者及 86 例单纯甲状腺癌患者的临床资料。纳入标准:(1) 均为女性;(2) 乳腺癌诊断参考《中国抗癌协会乳腺癌诊治指南与规范》[2],甲状腺癌诊断参考《分化型甲状腺癌诊治指南》[3],所有病例都经过病理检查确诊;(3) 临床数据资料完整。排除标准:(1) 复发的或转移的恶性肿瘤;(2) 合并其他器官病变的患者;(3) 临床资料不完整。

1.2　观察指标　收集患者确诊恶性肿瘤的年龄、绝经情况、生育史、雌激素暴露时间、激素水平及肿瘤特征相关数据。激素水平:血清游离三碘甲状腺原氨酸(free triiodothyronine, FT3)、游离甲状腺素(free thyroxine, FT4)、促甲状腺激素(thyroid-stimulating hormone, TSH)、甲状腺球蛋白抗体(thyroglobulin antibody, TGAb)、甲状腺过氧化物酶抗体(thyroid peroxidase antibody, TPOAb)、三碘甲状腺原氨酸(triiodothyronine, T3)、甲状腺素(thyroxine, T4)水平,雌三醇、泌乳素、孕酮、促卵泡生成素(follicle-stimulating hormone, FSH)、睾酮、促黄体生成素(luteinizing hormone, LH)、雌二醇水平。肿瘤特征:病理类型、淋巴结转移、肿瘤最大径、多灶性、$BRAF^{V600E}$突变情况。

1.3　统计学方法　采用 SPSS 23.0 软件进行统计学分析。计量资料采用 Shapiro-Wilk 法进行正态性检验。正态分布者以 $\bar{x}\pm s$ 表示,组间比较若方差齐采用单因素方差分析,否则采用 Kruskal-Wallis H 检验。偏态分布的计量资料以 $M(P_{25}, P_{75})$ 表示,两组比较用 Mann-Whitney U 检验。计数资料以例(%)表示,组间比较采用 χ^2 检验及其校正法。检验水准 $\alpha=0.05$,双侧检验。

2　结　果

2.1　合并癌组与单纯癌组一般资料比较　合并癌组患者年龄略高于单纯癌组,但两组间差异无统计学意义($P=0.217$)。两组身体质量指数(body mass index, BMI)、雌激素暴露时间差异无统计学意义($P>0.05$)。在生育状况上,有生育史的患者比例明显高于未生育,特别是合并癌组明显高于单纯癌组($P=0.009$)。见表 1。

表 1　一般资料
Tab. 1　General data

项目	合并癌组 ($n=82$)	单纯癌组 ($n=86$)	$\chi^2/t/z$ 值	P 值
年龄(岁, $\bar{x}\pm s$)	46.42±8.62	44.58±10.47	1.240	0.217
已绝经[例(%)]	25(30.49)	25(29.07)	0.040	0.841
BMI(kg/m^2, $\bar{x}\pm s$)	24.63±3.58	25.13±4.19	0.830	0.408
雌激素暴露时间(年)[a]	32(26,36)	31(22,35)	0.860	0.390
已生育[例(%)]	77(93.90)	69(80.23)	6.892	0.009

注:a 为数据以 $M(P_{25},P_{75})$ 表示。

2.2　超重和 BMI 正常患者肿瘤学特征比较　将 82 例甲状腺癌合并乳腺癌的患者,按照 BMI 是否大于 24 kg/m^2 为标准,分为超重组 37 例和正常组 45 例,比较两组在肿瘤直径、淋巴结转移、多灶性、单双侧及病理类型方面的差异,结果表明超重组多灶性(27.03%)高于正常体重组(20.00%),但差异无统计学意义($P>0.05$)。见表 2。86 例单纯癌组也按照前述方法进行了分组和对比,结果表明超重组肿瘤直径、淋巴结转移率及多灶性高于正常体重组,但差异

无统计学意义(P>0.05)。见表 2。另将合并癌组超重患者肿瘤直径与单纯癌组超重患者比较,其差异有统计学意义(t=2.452, P=0.018)。

2.3　合并癌组与单纯癌组临床病理特征比较　两组患者在手术方式、肿瘤直径、病理类型、淋巴结转移情况、多灶性以及 $BRAF^{V600E}$ 突变方面差异均无统计学意义(P>0.05)。见表 3。

2.4　合并癌组与单纯癌组激素水平比较　合并癌组患者其血液检验指标 T4、雌三醇、孕酮的水平明显高于单纯癌组患者,差异有统计学意义(P=0.049、P=0.004、P=0.034);然而,合并癌组睾酮水平明显低于单纯癌组,差异有统计学意义(P=0.003)。其余指标 T3、TSH、TGAb、TPOAb、FT3、FT4、催乳素及其他激素的血清学水平差异无统计学意义(P>0.05)。见表 4。

表 2　不同分组患者肿瘤学特征比较　[例(%)]

Tab. 2　Comparison of oncological characteristics of patients in different groups　[case (%)]

组别	例数	肿瘤直径(cm, $\bar{x}\pm s$)	淋巴结转移	多灶性	单双侧		病理类型		
					单侧	双侧	微小癌	乳头状癌	髓样癌
正常合并癌组	45	0.69±0.29	18(40.00)	9(20.00)	37(82.22)	8(17.78)	8(17.78)	37(82.22)	0
超重合并癌组	37	0.65±0.33	10(27.03)	10(27.03)	27(72.97)	10(27.03)	10(27.03)	27(72.97)	0
正常单纯癌组	42	0.87±0.67	13(30.95)	13(30.95)	28(66.67)	14(33.33)	5(11.90)	37(88.10)	0
超重单纯癌组	44	1.06±0.97	16(36.36)	17(38.64)	31(70.45)	13(29.55)	5(11.36)	38(86.36)	1(2.27)
F/χ^2 值		3.673	1.808	3.887	2.952		7.192		
P 值		0.013	0.613	0.274	0.399		0.303		

表 3　两组临床病理特征比较　[例(%)]

Tab. 3　Comparison of clinical and pathological characteristics between two groups　[case (%)]

临床病理特征	合并癌组(n=82)	单纯癌组(n=86)	χ^2 值	P 值
手术方式				
甲状腺全部切除术	62(75.61)	64(74.42)	0.032	0.858
甲状腺部分切除术	20(24.39)	22(25.58)		
肿瘤直径				
<0.5 cm	17(20.73)	18(20.93)	0.001	0.975
≥0.5 cm	65(79.27)	68(79.07)		
病理类型				
微小乳头状癌	18(21.95)	27(31.40)		
乳头状癌	64(78.05)	58(67.44)	3.002	0.223
髓样癌	0	1(1.16)		
有淋巴结转移	28(34.15)	29(33.72)	0.003	0.954
多灶性	19(23.17)	30(34.88)	2.787	0.095
$BRAF^{V600E}$ 突变	29(35.37)	35(40.70)	0.506	0.477

表 4　两组激素水平比较

Tab. 4　Comparison of hormone levels between two groups

项目	合并癌组(n=82)	单纯癌组(n=86)	$\chi^2/t/z$ 值	P 值
T3(nmol/L)[a]	1.68±0.35	1.63±0.25	0.110	0.912
T4(nmol/L)[b]	99.18(82.54,111.33)	89.20(79.10,99.55)	2.796	0.049
TSH(mIU/L)[b]	2.01(1.50,3.53)	2.41(1.68,3.28)	0.633	0.530
TGAb(IU/mL)[b]	16.35(12.10,119.90)	20.18(13.35,180.40)	1.166	0.470
TPOAb(IU/mL)[b]	13.45(8.43,24.69)	13.75(9.51,22.28)	0.627	0.530
FT3(pmol/L)[a]	4.39±0.90	4.50±0.90	0.792	0.430
FT4(pmol/L)[a]	15.50±4.40	14.74±4.41	1.118	0.265
雌三醇(pmol/L)[b]	0.03(0.02,0.04)	0.02(0.01,0.03)	2.851	0.004
泌乳素(μg/L)[b]	341.60(209.56,519.13)	345.42(230.84,490.44)	0.276	0.780
孕酮(nmol/L)[b]	1.37(0.68,4.80)	0.95(0.32,3.55)	2.114	0.034
FSH(IU/L)[b]	7.94(4.75,38.47)	10.81(4.71,49.43)	0.616	0.540
睾酮(nmol/L)[b]	0.77(0.48,1.02)	0.88(0.68,1.21)	3.008	0.003
LH(IU/L)[b]	7.67(3.90,19.21)	9.07(4.32,22.43)	0.808	0.420
雌二醇(pmol/L)[b]	122. 50(45.74,363.43)	139.00(37.00,356.00)	0.076	0.940

注:a 为数据以 $\bar{x}\pm s$ 表示;b 为数据以 $M(P_{25},P_{75})$ 表示。

3　讨　论

甲状腺恶性肿瘤是一种常见的内分泌系统恶性疾病,其发生与个体的遗传因素、环境条件以及激素水平等多种因素密切相关。研究发现,甲状腺恶性肿瘤患者在过去的病史中或在术后的定期随访中,经常被发现同时患有乳腺疾病[4]。因此,笔者推测,与甲状腺癌相关的基因突变和激素水平的改变可能是导致乳腺癌发生的主要原因。流行病学调查结果显示,甲状腺癌和乳腺癌之间存在一定的关联性。本研究结果发现,相比于仅有甲状腺癌的患者,治疗前在伴有乳腺癌瘤的患者中,T4、雌三醇和孕酮的水平显著升高,而睾酮的水平则显著降低。这一结果提示,在甲状腺癌患者并发乳腺癌的过程中,激素可能扮演了一个重要的角色。

体外实验表明,甲状腺激素可以发挥雌激素样作用,刺激肿瘤细胞的增长[5]。在离体条件下,T4 还被证实为一种增殖因子,并能增强依赖于雌激素的乳腺癌细胞的增殖[6]。本研究发现,合并癌组患者 T4 水平明显高于单纯癌组,因此推测长期 T4 水平升高可能会刺激乳腺细胞表面的雌激素受体过度表达,从而导致肿瘤细胞的生长和转移。但对甲状腺激素与乳腺癌关系的看法并不一致,本研究尚未发现 T3、TSH 及 TPOAb 等甲状腺相关激素在两组中有差异性。

甲状腺与乳腺都属于内分泌系统,二者均受到下丘脑-垂体轴激素的调控,而雌激素对二者的调控最为关键。许多研究已经证实,雌激素对于分化

型甲状腺癌的产生及进展存在一定的推动效应[7]。此外,有证据显示,怀孕可能会提高患有甲状腺癌的患者再患乳腺癌的风险,本研究验证了这一点:相较于未生育的患者,患甲状腺癌同时患乳腺癌的患者生育比例明显升高,这可能和怀孕后雌激素水平的提高有关;然而,女性体内雌激素水平与乳腺恶性肿瘤细胞的增殖和转移成正相关,且体内较低水平的雌激素对肿瘤细胞的生长有一定的抑制作用[8]。本研究比较了雌激素暴露时间,在合并癌组[32(26,36)年]与单纯癌组[31(22,35)年],其差异无统计学意义。

Lalitkumar 等[9]研究首次揭示了孕酮对甲状腺细胞的影响,并进一步确认了孕酮能通过作用于其受体,提升参与甲状腺蛋白质表达差异的基因,从而对甲状腺组织的生长和分化产生效果。有相关研究显示,绝经期激素治疗可用于缓解更年期症状,但绝经后女性长期服用雌激素联合孕酮可使其乳腺癌风险增加[10]。本研究的相关数据揭示,持续高水平的孕酮能够刺激乳腺细胞的生长,进而提升单纯甲状腺癌患者同时患有乳腺癌的可能性。

在人体内,睾酮是一种重要的雄激素,它的分泌也同样受到了垂体和下丘脑的控制;雌性睾丸激素主要来源于卵巢内膜细胞,性成熟之前,其可以促进钙质的保留、促进长骨基质的生长,性成熟之后,可以促进骨骺的闭合。当睾酮和雄激素受体相互作用并产生激素受体复合物时,会与特定的靶向基因反应元素发生交互,进入癌症细胞的生长调控路径[11],无论是何种类型的肿瘤,雄激素受体的存在是一种良好的预测指标,其表达与肿瘤的侵袭性、病理分级成反比[12]。本研究结果显示,合并乳腺癌患者的睾酮水平明显降低,且与单纯甲状腺癌患者差异有统计学意义,笔者推测,在单纯的甲状腺肿瘤患者中,更高的睾酮水平可能会抑制肿瘤细胞的增殖并提高预后,其具体的相关性需要更多的研究进行验证。

美国癌症数据库中的有关数据表明,与单纯患有甲状腺癌的患者相比,同时患有乳腺癌的患者有更高的淋巴结转移率,但是肿瘤的直径相对较小[13]。本研究中,单纯癌与合并癌组肿瘤直径均以≥0.5 cm 为主,分别占比为 79.07%、79.27%;同时,单纯癌组 58 例为单叶乳头状癌(67.4%),合并癌组为 64 例(77.1%),相比之下较双叶乳头状癌高,但本研究尚未发现两组在肿瘤大小与淋巴结转移间的差异,可能由于病例数量较少,需大量临床数据进一步验证。

有研究表明,BMI 指数与罹患甲状腺恶性肿瘤的风险呈正相关[14],同样在乳腺癌相关研究中发现患乳腺癌的风险随着 BMI 的增长以线性趋势增加,本研究结果发现,BMI 在两组间无统计学差异,但进一步分析可得,单纯癌组的超重患者其甲状腺癌肿瘤直径大于合并癌组的超重患者,其差异有统计学意义。因此笔者推断,甲状腺癌合并乳腺癌患者较单纯甲状腺癌患者相比,当 BMI>24 kg/m^2,往往伴随肿瘤直径更小、侵袭性更高的可能,但本研究因数据质量及方法,尚未进行肿瘤侵袭性研究。

综上所述,与单纯甲状腺癌患者相比,合并乳腺癌患者血清 T4、孕酮、雌三醇水平升高,睾酮水平下降;上述指标的检测对于单纯性甲状腺癌的诊断及评估病情进展具有重要意义。两组不同 BMI 者的患临床病理特征未发现明显差异性,但超重组合并癌患者其病理特征表现为肿瘤直径更小,因此临床上要加强肥胖患者健康宣教及疾病筛查,必要时定期行甲状腺及乳腺超声检查。

利益冲突　无

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(上接第 369 页)

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