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Immunohistochemical Expression of Estrogen Receptor-α and Progesterone Receptor in Patients with Papillary Thyroid Cancer

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Keywords
Thyroid cancer · Estrogen receptor · Progesterone receptor · Sexual hormone receptors

Abstract
Background: Papillary thyroid cancer (PTC) prevalence is nearly 3 times higher in females than in males. This gender difference suggests that growth and progression of PTC might be influenced by female sex hormones. ***Objectives:*** To analyze the expression of both estrogen receptor (ER)-α and progesterone receptor (PR) by immunohistochemistry in 203 PTC patients. ***Methods:*** ER-α and PR expression was evaluated in paraffin-embedded tumor tissue samples of 45 males and 158 females followed up for 7.2 ± 3.7 years. ***Results:*** ER-α was expressed in 52 (25.6%) patients (41 females and 11 males) and PR in 94 (46.3%) patients (75 females and 19 males). ER-α and PR were coexpressed in 31 (15.3%) patients (27 females and 4 males). ER-α expression correlated significantly with tumor size in the whole sample (ER-α positive 22.8 ± 11.8 mm vs. ER-α negative 15.1 ± 12.4 mm; $p = 0.02$) and in the subgroup of women (ER-α positive 18.8 ± 12.8 mm vs. ER-α negative 14.9 ± 12.3 mm; $p = 0.048$). In addition, ER-α expression significantly correlated with remission of the disease. In fact, of the 192 patients followed up, 50/153 (32.7%) disease-free patients were ER-α positive, in contrast to only 3/39 (7.7%) with evidence of disease persistence/recurrence ($\chi^2 = 8.5$, $p = 0.0036$). PR expression was not associated with any of the parameters analyzed. ***Conclusions:*** The present study confirmed recent data indicating that ER-α and PR expression is a common finding in thyroid tumor tissue. However, in contrast to previous reports, we observed an association between ER-α expression and a more favorable outcome in PTC patients.

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Introduction

The incidence of differentiated thyroid cancer (DTC) is about 3 times higher in women than in men [1, 2] and decreases after menopause [3]. The age-standardized (per 100,000) incidence of thyroid cancer ranges from 2 to 10 in females and from 1 to 3 in males in different populations. The higher prevalence in females, particularly dur-

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ing the reproductive period, is observed in all regions and in all ethnic groups [4]. Since thyroid cancer and most benign thyroid diseases (Graves disease, endemic goiter, and Hashimoto thyroiditis) are significantly more frequent in women of childbearing age [5], many studies have been designed to examine the influence of reproductive and hormonal factors on the etiology of thyroid diseases [3, 6–8]. Epidemiological reports demonstrate gender differences in the development of thyroid cancer, thus suggesting that sex hormones, particularly estrogens, may be somewhat involved in its growth and progression [6–9]. Some studies showed the use of oral contraceptives to be associated with a moderately increased risk of thyroid cancer, although other studies did not confirm this association [10–12]. Also, an increased risk of thyroid cancer has been reported in women using estrogens for gynecological impairments, but not in women given low-dose estrogen therapy for menopausal hormone replacement [11, 13, 14].

Despite the higher incidence of DTC in females, women generally show a more favorable outcome than males. Indeed, different cohort studies reported a better "overall" and "disease-specific" survival, and fewer relapses in women than in men. Specifically concerning papillary thyroid carcinoma (PTC), although the overall outcome seems comparable in the two sexes, analysis of subgroups aged under and over 55 years indicates a more favorable prognosis in females at a younger age [13, 14].

All the above suggests a possible role for estrogens in the development and progression of DTC, and several studies have investigated the expression of estrogen receptor (ER) subtypes in thyroid cancers. However, results are not consistent yet, likely because of the existence of confounding factors in the populations selected [15, 16].

The purpose of our study was to determine the immunohistochemical expression of ER-α and progesterone receptor (PR) in a large series of PTC patients, and to correlate the above expressions with epidemiological and clinical features.

Patients and Methods

The study included 203 consecutive patients diagnosed with the classical variant of PTC between 2000 and 2009 who underwent total thyroidectomy, radioiodine ablation (^{131}I) of postsurgical residual thyroid tissue (whenever deemed necessary), and levothyroxine (LT_4) treatment at TSH-suppressive or -semisuppressive doses. For the purpose of this study, patients were divided into 2 groups according to tumor size: the PTC group (113 patients with PTC >10 mm) and the micro-PTC group (90 patients with PTC ≤10 mm).

Suspicious nodules were identified at intraoperative histopathology and then treated in formalin for 24 h. Cutting and selection of tissue specimens were performed, followed by histological evaluation of paraffin-embedded tissue. The diagnostic protocol included the assessment of: (i) histotype; (ii) tumor size; (iii) tumor margins; (iv) multifocality; (v) level of lymph node metastases, if any; and (vi) TNM staging.

Tissue-Arrayer was used for all tumor samples by coring tissue from the paraffin-embedded block in order to obtain tumor specimens with a diameter of 0.6–1.5 mm. Tumor sections were then transferred to a paraffin block for immunohistochemical studies.

Immunohistochemical determination was performed using automated protocols on a Ventana BenchMark Ultra Immunostainer. For antigen retrieval, buffer CC1 was used for 28 and 20 min for ER and PR determination, respectively. The sections were incubated with the following monoclonal primary antibodies: ER-α: clone SP1, Ventana-Roche, incubation for 28 min; PR: clone 1E2, Ventana-Roche, incubation for 16 min. A section of breast tissue was used as a positive control in all the samples. As described for breast cancer, the sections were assessed semiquantitatively using the system of the *H-score*, which measures both percentage of positive cells and intensity of expression [17].

Disease free was defined as follows: (i) no clinical evidence of tumor; (ii) no imaging evidence of tumor by radioactive iodine (RAI) imaging and/or neck US; and (iii) serum Tg levels <0.2 ng/mL during TSH suppression or <1 ng/mL after stimulation in the absence of interfering antibodies [18].

Quantitative variables are expressed as means ± SD and categorical variables as frequencies and proportions. Quantitative variables were compared using the Student *t* test; qualitative variables were analyzed by χ^2 test. $p < 0.05$ was considered to be statistically significant. Statistical analyses were performed using the SSPS statistical package (SPSS, Chicago, IL, USA).

Informed consent was obtained from the subjects, and the study protocol was approved by the institute's committee on human research.

Results

Epidemiological and Clinical Features

The main clinical and epidemiological characteristics of the 203 patients, either as a whole or as subgroups (PTC group and micro-PTC group), are reported in Table 1. The mean age at diagnosis, the percentage of subjects younger than 45 years, and gender distribution were not different in the two subgroups. As expected, the disease was confined to the thyroid in the vast majority of patients from the micro-PTC group, with evidence of extrathyroidal extension in 4/90 patients only. Conversely, almost one-third (32/113) of the patients in the PTC group showed extrathyroidal extension (minimal in 29/113 and beyond the thyroid capsule in 3/113). In addition, a significantly higher rate of patients from the same group had multifocal disease and lymph node metastases at presentation. Finally, 10/113 patients

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Table 1. Epidemiological and clinical features of the study patients

Characteristics	Whole sample (n = 203)	PTC group (n = 113)	Micro-PTC group (n = 90)	p value
Mean age at diagnosis ± SD, years	48.2±14.3	47.2±15.1	49.5±13.1	0.13
Range	20–85	22–85	20–79	
Age <45 years, n (%)	90 (44.3)	52 (46)	38 (42.2)	0.59
Females, n (%)	158 (77.8)	85 (75.2)	73 (81.1)	0.31
Female/male ratio	3.5:1	3:1	4.3:1	
Mean tumor size ± SD, mm	16.97±13.93	26.35±12.65	5.92±2.88	<0.0001
Range	1–80	11–80	1–10	
Tumor extension				
T1a, n (%)	86 (42.4)	–	86 (95.5)	–
T1b, n (%)	51 (25.1)	51 (45.1)	–	–
T2, n (%)	30 (14.8)	30 (26.5)	–	–
T3, n (%)	32 (15.7)	29 (25.6)	3 (3.3)	<0.0001
T4a, n (%)	4 (1.9)	3 (2.6)	1 (1.1)	0.78
T4b, n (%)	–	–	–	–
Multifocality, n (%)	75 (36.9)	49 (43.3)	26 (28.8)	0.034
Lymph node metastases				
NX, n (%)	127 (62.6)	57 (50.4)	70 (77.7)	0.0001
N0, n (%)	28 (13.8)	19 (16.8)	9 (10)	0.161
N1, n (%)	48 (23.6)	37 (32.7)	11 (12.2)	0.0006
^{131}I ablation, n (%)	141 (69.4)	94 (83.2)	47 (52.2)	<0.0001
Staging				
I, n (%)	150 (73.9)	66 (58.4)	84 (93.3)	<0.0001
II, n (%)	8 (3.9)	8 (7.1)	0	
III, n (%)	13 (6.4)	12 (10.6)	1 (1.1)	0.014
IVa, n (%)	21 (10.3)	17 (15)	4 (4.4)	0.014
IVb, n (%)	0	0	0	
IVc, n (%)	11 (5.4)	10 (8.8)	1 (1.1)	0.035
Follow-up, years	7.2±3.7	7.7±3.9	6.7±3.2	0.02
Disease persistence/recurrence, n (%)	39 (20.3)	33 (29.2)	6 (6.7)	0.0001

To assess disease persistence/recurrence, 192 patients were followed up in the total group, and 106 and 86 patients in the PTC and micro-PTC groups, respectively. p values: PTC vs. micro-PTC.

from the PTC group and 1 patient from the micro-PTC group presented distant metastases (pulmonary in all cases).

Overall, 11 patients were lost to the follow-up. Of the remaining 192 patients (148 females and 44 males), 39/192 (20.3%; 33 from the PTC group and 6 from the micro-PTC group) showed persistent or recurrent disease.

Immunohistochemical Expression of ER-α and PR

Table 2 summarizes data on ER-α and PR expression in the whole sample and in the 2 subgroups. In particular, ER-α expression was found in 52/203 (25.6%) cases (Fig. 1a–c), whereas PR expression was found in 94/203 (46.3%) cases (Fig. 1d–f).

ER-α expression was found to be similar in both sexes (41/158 females vs. 11/45 males, p = 0.83), and no differences were observed in mean ages of ER-α-positive or -negative patients (45.9 ± 14.8 vs. 49.1 ± 13.9, p = 0.087). Similar results were found when the PTC and micro-PTC groups were analyzed, either separately or comparatively.

Conversely, ER-α expression significantly correlated with tumor size, either in the whole sample (ER-α positive 22.8 ± 11.8 mm vs. ER-α negative 15.1 ± 12.4 mm; p = 0.02) or in the subgroup of women (ER-α positive 18.8 ± 12.8 mm vs. ER-α negative 14.9 ± 12.3 mm; p = 0.048). When the 2 groups (PTC and micro-PTC group) were considered for analysis, the correlation between ER-α expression and tumor size could not be further confirmed in the PTC group (ER-α positive 26.7 ± 12.6 mm vs. ER-α

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Table 2. Immunohistochemical expression of ER-α and PR in the study patients

	ER-α+	PR+	ER-α–PR+
Whole group (n = *203)*			
Patients, *n* (%)	52 (25.6)	94 (46.3)	31 (15.3)
Females, *n* (%)	41 (20.2)	75 (36.9)	27 (17.1)
Males, *n* (%)	11 (5.1)	19 (9.3)	4 (8.9)
Mean age ± SD, years	45.9±14.8	47.3±14.5	42.7±13.1
Range	20–85	20–80	20–67
Mean tumor size ± SD, mm	22.8±11.8	16.7±13.7	19.03±11.2
Range	3–50	2–80	3–50
Disease persistence/recurrence, *n* (%)	3 (1.6)	16 (8.3)	2 (1.04)
PTC group (n = 113)			
Patients, *n* (%)	34 (26.5)	56 (46.3)	24 (21.2)
Females, *n* (%)	27 (23.8)	42 (37.2)	21 (18.6)
Males, *n* (%)	7 (6.2)	14 (12.4)	3 (8.9)
Mean age ± SD, years	44.6±14.3	45.4±15.2	40.9±11.4
Range	22–85	22–80	22–62
Mean tumor size ± SD, mm	26.7±12.6	24.4±13.6	22.7±10.4
Range	11–50	11–80	11–50
Disease persistence/recurrence, *n* (%)	3 (2.8)	13 (12.3)	2 (1.9)
Micro-PTC group (n = 90)			
Patients, *n* (%)	18 (20)	38 (42.2)	7 (7.8)
Females, *n* (%)	14 (15.6)	33 (36.7)	6 (6.7)
Males, *n* (%)	4 (4.4)	5 (5.5)	1 (1.1)
Mean age ± SD, years	49.3±15.8	50.2±13.1	49.1±17.4
Range	20–79	20–73	20–67
Mean tumor size ± SD, mm	7.05±2.6	6.4±2.7	7.6±2.7
Range	3–10	2–10	3–10
Disease persistence/recurrence, *n* (%)	0	3 (3.5)	0

To assess disease persistence/recurrence, 192 patients were followed up in the total group, and 106 and 86 patients in the PTC and micro-PTC groups, respectively.

negative 26.2 ± 12.7 mm; $p = 0.41$), whereas it was significant in the micro-PTC group (ER-α positive 7.05 ± 2.6 mm vs. ER-α negative 5.6 ± 2.9 mm; $p = 0.031$).

No relationship was found between ER-α expression and lymph node metastases, either when analysis was performed in the whole sample or when the subgroups were considered.

Finally, ER-α expression significantly correlated with remission of the disease. In fact, of the 192 patients followed up, 50 of 153 (32.7%) disease-free patients were ER-α positive, in contrast to only 3 of 39 (7.7%) patients with evidence of persistence/recurrence ($\chi^2 = 8.5$, $p = 0.0036$). The same result was confirmed when the outcome of the PTC group patients was considered. Thus, of a total of 106 PTC patients followed up, 30 of 74 (40.5%) disease-free patients and 3 of 32 (9.4%) patients with evidence of persistent or recurrent disease were ER-α positive ($\chi^2 = 8.72$, $p = 0.0031$). When analyzed by gender, ER-α expression was found to be significantly associated with remission in females only in the whole sample ($\chi^2 = 7.05$, $p = 0.0079$) and in the PTC group ($\chi^2 = 7.45$, $p = 0.0063$).

Concerning PR expression, no correlation was found between PR positivity and gender, patient age, tumor size at diagnosis, presence of lymph node metastases, and risk of disease progression or recurrence in both sexes.

Finally, both ER-α and PR were coexpressed in 27 of 158 (17.1%) women and 4 of 45 (8.9%) males ($p = 0.26$). Among females, coexpression was significantly associated with a younger age at diagnosis (ER-α+PR+ positive 42.1 ± 12.5 years vs. ER-α+PR– 48.5 ± 13.8 years; $p = 0.013$). Moreover, a nonstatistically significant trend towards a lower risk of progression or recurrence was observed in women with ER-α and PR coexpression ($\chi^2 = 3.79$, $p = 0.051$).

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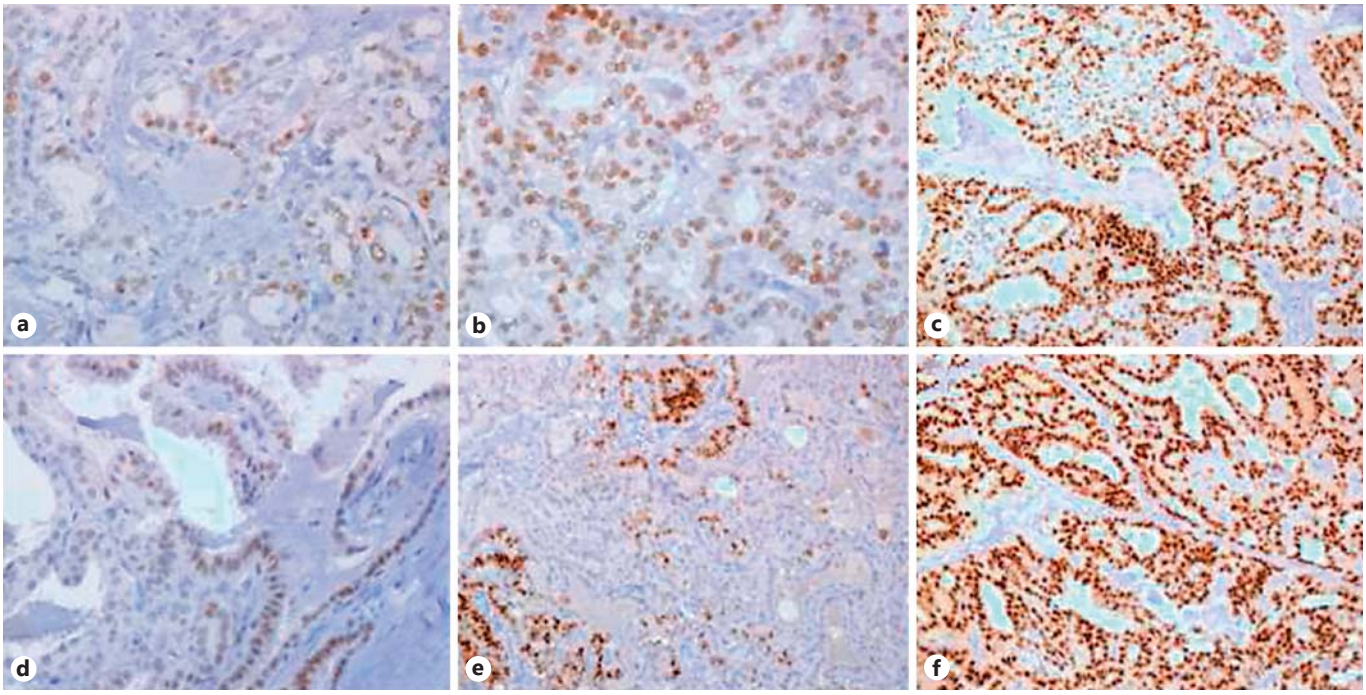

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Fig. 1. Immnunohistochemical ER-α (**a–c**) and PR (**d–f**). The intensity of expression (brown color) progressively increases from the right to the left panel.

Discussion

Cellular signaling of estrogen is mediated classically via 2 nuclear soluble intracellular receptors: ER-α and ER-β. Other regulatory mechanisms include a nongenomic way and an independent ligand interaction [19].

Several human tissues, including the breast, ovary, prostate, lung, colon, pancreas, and thyroid, express both ER isoforms [19]. Specifically concerning the thyroid, ERs have been described in both neoplastic and nonneoplastic thyroid tissue, though the results are not consistent to date, likely because of differences in the sensitivity of the techniques employed [15, 16]. The role of estrogens in the development and evolution of DTC has been widely analyzed in several studies [20–28]. A recent meta-analysis including >5,000 patients reported that menopausal women had a reduced thyroid cancer risk, whereas increasing age at first pregnancy/birth was associated with a higher cancer risk [29]. Similar to other epithelial tumors, DTC also expresses both ER isoforms, with ER-α activation being associated with increased estrogen-dependent cell proliferation and, in contrast, ER-β likely promoting apoptotic actions and other suppressive functions in thyroid tumors [22, 30–33]. Overall, there is evidence that ER-α expression is greater in tumors than in normal thyroid tissues, whereas ER-β expression is significantly lower in neoplastic than in nonneoplastic thyroid tissue [28, 32].

Concerning PR, of the few studies which so far investigated its expression in thyroid tumors, most assessed PR in conjunction with ER [21–24, 34, 35].

In the present study, we evaluated the immunohistochemical expression of ER-α and PR in a large series of 203 classical PTC. In particular, the study sample included similar proportions of micro-PTC (<10 mm) and PTC (>1 mm). This balance allowed us to comparatively investigate differences, if any, in ER-α and PR expression in these two clinical entities, and to correlate the immunohistochemical findings to the disease outcome.

We found ER-α and PR to be expressed in 25.6 and 46.3% of the DTC patients, respectively, with 15.3% of tumor samples coexpressing both receptors. In particular, both ER-α and PR (either individually or in conjunction) were found to be expressed in PTC and micro-PTC to a similar extent, with no differences among sexes. When analyzed in the whole group, a positive correlation was found between ER-α expression and tumor size, a finding seemingly in line with the trend reported in the

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literature [34]. Unexpectedly, however, the above correlation could not be further confirmed when PTC and micro-PTC were analyzed separately, with a definite trend towards an increase in ER-α expression with increasing tumor size found in micro-PTC only. Moreover, a reverse relationship was found between ER-α expression and a poor clinical outcome, since a significantly higher proportion of tumors from disease-free patients, either in the whole sample or in the PTC group alone, proved to be ER-α positive. This finding is apparently inconsistent with current epidemiological and clinical evidence, overall suggesting that thyroid tumor development and progression may be influenced by estrogens. However, a study investigating the tissue expression of ER-α along with the coregulatory proteins SRC-1 (steroid receptor coactivator) and NCoR (nuclear corepressor) in different subtypes of thyroid cancers demonstrated that expression of ER-α and NCoR was significantly associated with well-differentiated tumors and a reduced incidence of disease recurrence. In contrast, the coactivator protein SRC-1, mostly expressed in poorly differentiated tumors, was associated with invasion, poor differentiation, tumor recurrence, and reduced disease-free survival [31].

In conclusion, presently available data strongly support the hypothesis that ER signaling plays a role in the development and progression of differentiated thyroid cancer. In our patients with micro-PTCs and PTCs of larger sizes, ER-α expression was found to be similar and was associated with a better outcome. The role of different patterns of ER isoform expression in thyroid tumor subtypes, along with ER-α and ER-β ratios, and the expression of coregulatory proteins modulating ER function should be further investigated to better understand the pathogenesis and the natural history of differentiated thyroid cancers.

Statement of Ethics

This research complies with the guidelines for human studies and animal welfare regulations.

Disclosure Statement

The authors have no conflicts of interest and any sponsorship or funding arrangements to disclose.

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