Original Article

Correlation Between Immunohistochemical Expression of PSA and PHP in Different Gleason Grades of Prostate Cancer

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ABSTRACT

Introduction: Among the Palestinian population, lung cancer was the most common cause of death among cancer patients (22.8%) followed by prostate cancer (9.5%).

Aim of the Work: The aims of this study were to examine the expression of prostate specific antigen (PSA) and parathyroid hormone-related protein (PTHrP) in prostatic adenocarcinoma.

Materials and Methods: Fifty-eight prostatic tissue sections: 6 benign prostatic hyperplasia (BPH) and 52 prostatic carcinomas were stained with hematoxylin and eosin for grading identification. Moreover, tissue blocks were immunohistochemically stained for PSA and PTHrP using specific monoclonal antibodies, including anti-PSA and anti-PTHrP. Area and intensity of staining for PSA and PTHrP were quantitatively analyzed and correlated with the documented seven forms of Gleason scores.

Results: Generally, PSA and PTHrP expressions were positive in all specimens. In those specimens with positive staining, the expression varied between cells. PSA expression was positively ($P < 0.001$) correlated to the expression of PTHrP among all investigated specimens. It is obvious that the area (μm^2) of immunoexpressed PSA and PTHrP was positively ($r = 0.274$ and $r = 0.474$, $P < 0.001$) correlated with the various grades of prostate cancer. However, the intensity displayed a negative correlation ($r = - 0.619$ and $r = - 0.359$, $P < 0.001$) between the immunoexpressed PSA and PTHrP and the various grades of prostate cancer, respectively. Thereby, the immunoreactivity for PSA is related to PTHrP expression in prostatic tissue.

Conclusion: The counteract behavior of area and intensity of expressed PSA and PTHrP has to be considered during diagnosis. This immunophenotypic characteristic should be focused on advanced scores of Gleason scores..

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Key Words: Gleason grade, immunohistochemistry, prostate cancer, PSA, PTHrP.

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INTRODUCTION

Prostate cancer is the most common cancer in males. The incidence rate increases with age where 70% of men carry the malignancy by 75 years of age. Prostate cancer remains undetected without generating symptoms throughout the life of affected men. The incidence of prostate cancer is different among different populations and countries. Prostate cancer occurred in the Middle East more frequently in Lebanon (37.2 out of 100,000), Jordan (15.3 in 100,000), and Palestine (15.2 in 100,000) than in Asian countries[1]. Currently, diagnosis and management of prostate cancer rely mainly on the measurement of prostate specific antigen (PSA).

PSA is a serine protease member of the human kallikrein family. The PSA protein is totally produced by the acinar secretory cells of the prostate[2]. Most of the PSA produced remains in the gland while only a small portion is released into the bloodstream. PSA test is used for the detection and management of the pathology of prostate cancer. The PSA test is commonly measured and used for monitoring recurrence of the disease and response to therapy. Since PSA is specifically present in normal and prostate cancer, immunohistochemical PSA analysis can be used to identify and diagnose metastatic adenocarcinoma. However, cellular PSA levels are drastically reduced or absent in poorly differentiated adenocarcinoma. Therefore, negative immunohistochemistry staining of PSA is correlated with poor differentiation, widespread metastasis, poor prognosis, and very low serum PSA levels[3].

The parathyroid hormone-related protein (PTHrP) is a multifunctional protein that has diverse effects on the behavior of tumor cells. This function is usually mediated after posttranslational processing which results in the formation of several biological domains and isoforms. PTHrP can stimulate the growth, invasion, and metastasis

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of prostate cancer cells, through paracrine/autocrine pathways[4]. Studies have suggested that although PTHrP can inhibit tumor progression during the early stages, it functions the opposite by promoting the development and metastasis of tumor during advanced stages resulting in reducing the patients' survival[5]. In addition, numerous studies have shown that PTHrP has the potential to regulate tumor dormancy, tumor cell proliferation, apoptosis, and survival[6].

PTHrP among other factors such as growth factors, neuroendocrine peptides, and cytokines play important roles in the normal development and functions of prostate gland[7]. PTHrP is expressed by both neoplastic and normal prostate epithelia[8]. It is expressed by benign and malignant prostate cells. However, its expression is elevated in malignant tissue and drastically increased with higher tumor grade[9].

Although immunohistochemistry has been routinely used in histopathological diagnosis, several issues need further clarification. If immunohistochemistry can determine the PSA level and prognosis, then it has enough potential to be clinically useful. The expression of PSA and PTHrP were analyzed in benign and malignant prostate tumor tissues, and the correlation between each marker expression and the grading system was determined as well.

MATERIALS AND METHODS

Patients

This retrospective study included tissue sections from 58 patients enrolled in Al-Makassed Islamic Charitable Hospital (Palestine) from 2017 to 2020. The work is ethically approved, and prostate specimens were included irrespective of the history or stage of patients. All paraffin blocks were prepared, and 4µm thick sections were stained by hematoxylin and eosin (H&E). All slides were evaluated microscopically by two independent experienced pathologists and graded according to the Gleason grading system[10].

Immunohistochemistry

For immunohistochemistry, sections were taken on poly-L-lysine coated slides. The slides were deparaffinized, rehydrated, rinsed in distilled water, and incubated in 3% H_2O_2 to quench the endogenous peroxidase activity. Rinsing in 0.01M phosphate buffer saline (PBS) (pH 7.4) for 5 minutes. The nonspecific binding sites were blocked by incubation with horse serum (1.0% in PBS) for 20 minutes. Slides were stained by PSA monoclonal anti-human (dilution 1: 200, Clone BSB-7, Bio SB, USA), and PTHrP polyclonal anti-rabbit antibodies (dilution 1: 200, Cat. No.: 10817-1-AP, proteintech, USA), using the streptavidin-biotin-peroxidase technique in the fully automated Ventana BenchMark GX slide preparation system (Ventana BenchMark GX, Roche Diagnostics), and the DAB detection kit (Ventana), tissue preparation and staining instrument (Ventana BenchMark GX, Roche Diagnostics).

Image analysis

Morphometric image analysis was done by Leika Qwin 500 Image analyzer (Leica, Imaging Systems, Ltd, Cambridge, England), which is composed of Leica DM-LB microscope with JVC color video attached to a computer system Leica Q. The count and area (μm^2) of positive cells as well as the intensity of immunostaining for PTHrP and PSA were quantified in 5 random microscopic fields (magnification, x400) with the assistance of the software program.

Statistical Analysis

Statistical analyses by using the non-parametrical Kolmogorov–Smirnov test. The data were expressed as means ± standard error of the mean (SEM). One-way analysis of variance (ANOVA) was used to compare more than two groups. In this study, all parameters were analyzed using SPSS software (version 22, IBM, Chicago, IL, USA) and all analyses were two-tailed tests, where $P < 0.05$ was considered statistically significant.

RESULTS

This retrospective study included 58 prostatic tissue specimens: 6 benign prostatic hyperplasia (BPH) and 52 prostatic carcinomas. Both bilirubin and creatinine showed higher concentrations in benign patients compared to prostate cancer patients; however, the creatinine displayed significant differences ($P < 0.05$). All Gleason scores were presented in the study as shown in (Table 1). Cancerous tissues were subdivided into seven Gleason grades; 3+3, 3+4, 4+3, 4+4, 4+5, 5+4, and 5+5.

Intensive cytoplasmic reactivity for PSA immunostaining and mild nuclear reactivity of PTHrP were documented in BPH cases (Figure 1). The different patterns of Gleason scores (Table 2) and representative photos for each Gleason score were demonstrated in the prostate cancerous specimens stained by H&E (Figures 1,2). Immunohistochemical staining for PSA and PTHrP was assessed in the cytoplasm of tumor cells (Figures 1,2). As shown in figure 2, PSA and PTHrP cytoplasmic immunoreactivity of strong intensity was detected in most epithelial cells. In this score (4+5), immunoreactivity to PSA was strong while PTHrP was intermediate. Most of the specimens in this grade (5+4) revealed moderate staining for PSA and intense reactivity toward PTHrP.

One-way ANOVA demonstrated that the count of positive cells for either PTHrP or PSA was significantly affected ($P < 0.001$) by the various grades of cancerous tissues. The mean count of positive PSA immunostained prostate cancer specimens with grades (3+3, 3+4, 4+4, 4+5, and 5+5) was (6.54±0.47, 7.26±0.54, 8.34±0.55, 5.42±0.41, and 8.79±0.55) higher than those mean count of BPH (4.55±0.38) respectively, while count (3.08±0.31 4.46±0.37) of grades 4+3 and 5+4 was lower than BPH (4.55±0.38) respectively (Figure 3A). In contrast, the mean area (μm^2) of PSA immunoreactive cells in sections

of all grades (3+3, 3+4, 4+3, 4+4, 4+5, 5+4, and 5+5) was significantly ($P < 0.01$) decreased compared to BPH sections (4.55±0.38) respectively (Figure 3B). The intensity of immunostained PSA revealed significantly higher levels ($P < 0.001$) (141.63±0.95, 105.06±0.98, 120.64±1.54, and 134.02±1.54) in tissue sections of Gleason scores (3+3, 3+4, 4+4, and 4+5) respectively, while showed significantly lower levels ($P < 0.001$) (80.63±1.60 and 78.37±0.65) in specimens of Gleason scores 5+4 and 5+5 than those benign tumor sections (89.17±1.50) respectively. While mean (141.63±0.950) of grade score 3+3 did not demonstrate any significant difference compared to benign sections (89.17±1.50) (Figure 3C).

For PTHrP expression, the mean count (6.05±0.49, 3.78±0.35, 4.11±0.37, 4.40±0.31, and 4.81±0.38) of positive cells in tissue sections (3+3, 3+4, 4+5, 5+4, and 5+5) was significantly higher ($P < 0.001$) than benign tissue samples (3.75±0.34), respectively (Figure 4A). Mean of immunostained area (µm2) of PTHrP (7.72±0.36, 10.18±0.76, 11.73±0.63, 11.36±0.84, 10.33±0.47, 9.32±0.45 and 21.37±1.03) were significantly decreased ($P < 0.001$) in all documented Gleason score grades (3+3, 3+4, 4+3, 4+4, 4+5, 5+4, and 5+5) of prostate cancer specimens compared to benign tissue sections (218.42±14.91) respectively (Figure 4B). Mean intensity (147.33±1.35, 128.64±2.62, 124.23±1.90) of grades 3+3, 4+4, and 5+5 were significantly higher ($P < 0.001$) than those of benign group (108.37±2.42) while other grades (3+4, 4+3, 4+5, and 5+4) were significantly lower ($P < 0.001$) than those of benign sections (108.37±2.42) (Figure 4C).

A positive correlation was observed between the expression of PSA and PTHrP regarding both area (µm^2) ($r = 0.450$, $P < 0.001$) and intensity ($r = 0.579$, $P < 0.001$) (Figure 5). The relation between Gleason grades and the expression of either PSA or PTHrP were significantly ($P < 0.001$) positively correlated in relation to area (µm^2) ($r = 0.274$ or $r = 0.244$) respectively (Figure 6). On the other hand, the intensity of either PSA or PTHrP was significantly correlated ($P < 0.001$) and displayed an inverse relation with the Gleason grades ($r = - 0.619$ or $r = - 0.359$) respectively (Figure 6).

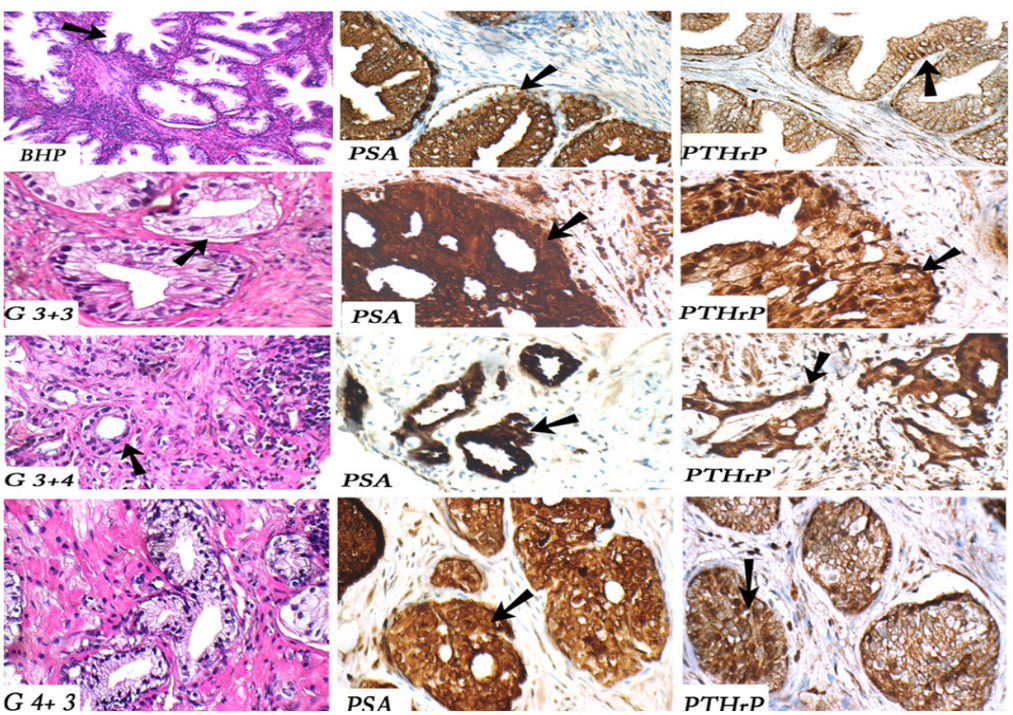

Fig. 1: BPH: hyperplastic acini with hyperplastic epithelial lining, intra-luminal infoldings (black arrow), in the hypertrophied fibromuscular stroma with moderate lymphocytic infiltrate (black arrow), PSA; strong cytoplasmic reactivity (+++), PTHrP; mild nuclear reactivity (+). G 3+ 3: infiltrating tumor composed of separate small-sized acini with the single-cell lining with large vesicular nuclei with prominent nucleoli (black arrow), PSA; strong cytoplasmic reactivity (+++), PTHrP; strong nuclear reactivity (+++). G 3+ 4: infiltrating tumor composed of separate small-sized acini with single-cell lining showing large vesicular nuclei with prominent nucleoli (black arrow), PSA; strong cytoplasmic reactivity (+++), PTHrP; strong nuclear reactivity (+++). G 4+ 3: infiltrating tumor composed of separate and fused acini with single lining showing large vesicular nuclei with prominent nucleoli (black arrow), PSA: moderate cytoplasmic reactivity (++), PTHrP strong nuclear reactivity (+++) (H&E, and immunostain x 400).

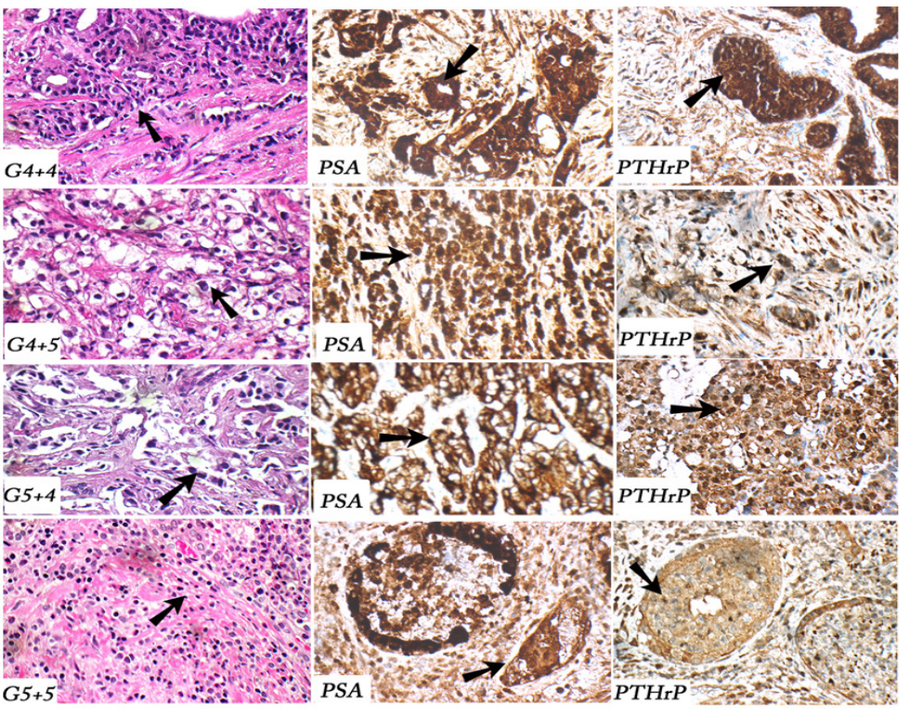

Fig. 2: G 4+ 4: infiltrating tumor composed of fused and irregular small-sized acini with single-cell lining (black arrow), in desmoplastic stroma, PSA: strong cytoplasmic reactivity (+++), PHP: strong nuclear reactivity (+++). G 4+ 5: infiltrating tumor composed of solid sheets of markedly pleomorphic malignant cells with clear cytoplasm, PSA: strong cytoplasmic reactivity (+++), PHP: mild nuclear reactivity (+). G 5+ 4: infiltrating tumor composed of small groups of pleomorphic malignant cells with amphophilic cytoplasm, some arranged in Indian file pattern(black arrow), PSA: moderate cytoplasmic reactivity (++), PHP; strong nuclear reactivity (+++).G 5+ 5: infiltrating tumor composed of solid sheets of markedly pleomorphic malignant cells (black arrow), in desmoplastic stroma, PSA: moderate cytoplasmic reactivity (++), PHP; mild nuclear reactivity (+). (H&E, and immunostain x 400).

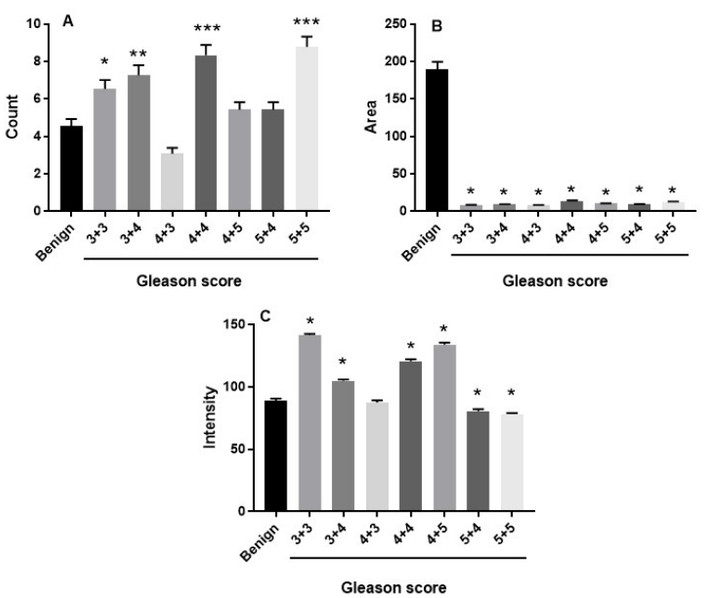

Fig. 3: Histogram of PSA immunostaining data obtained from benign and prostate tissue sections. The number of positive cells (A), the area (μm^2) of immunoreactive staining (B) and the intensity of immunostained cells (C) was quantitatively determined by image analysis. Data were expressed as a mean ± SEM. *: ($P < 0.05$) significant difference compared to benign group, **: ($P < 0.01$) significant difference compared to benign group, ***: ($P < 0.001$) significant difference compared to benign group.

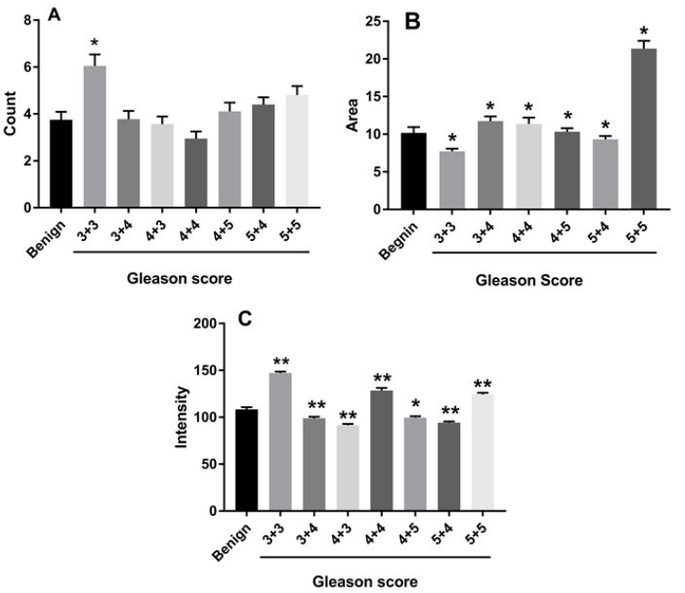

Fig. 4: Histogram of PHP immunostaining data obtained from benign and prostate tissue sections. The number of positive cells (A), the area (µm²) of immunoreactive staining (B) and the intensity of immunostained cells (C) were quantitatively determined by image analysis. Data were expressed as a mean ± SEM. *: ($P < 0.01$) significant difference compared to benign group, **: ($P < 0.001$) significant difference compared to benign group.

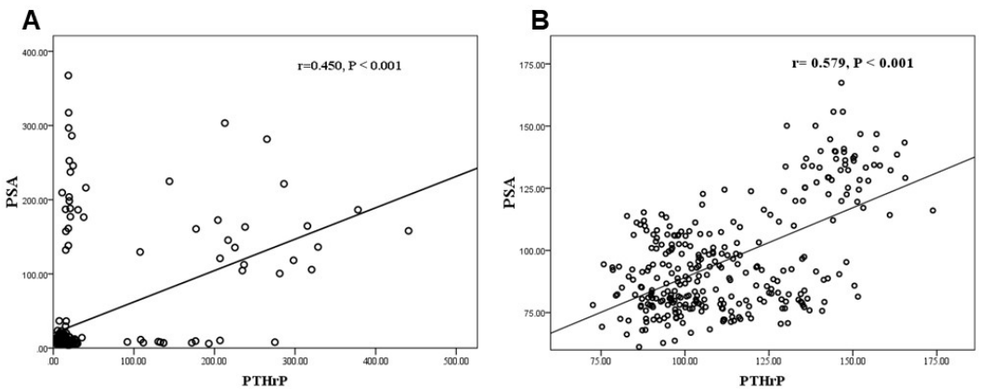

Fig. 5: Relation between the expression levels of PSA and PTHrP regarding their area (µm2) and intensity of staining in all 52 patients. R: Spearman correlation coefficient.

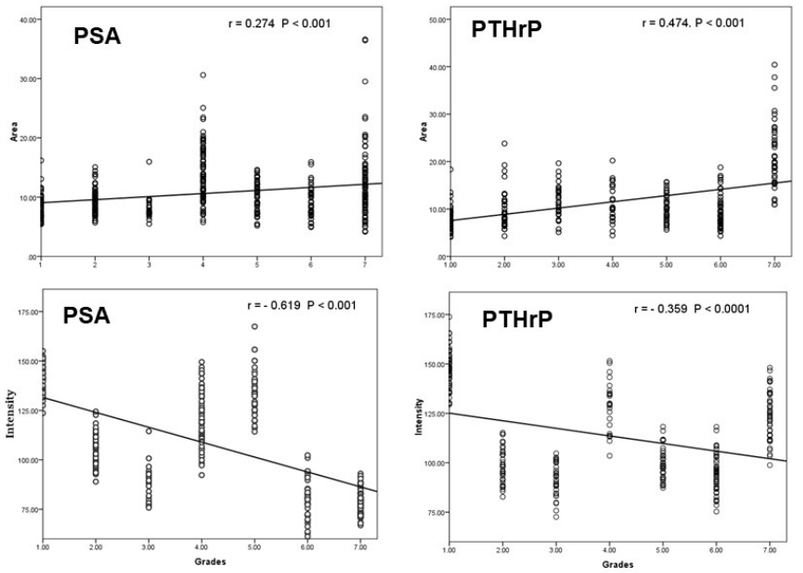

Fig. 6: Correlation between the area (µm2) of the expressed PSA or PTHrP and the various grades of prostate carcinoma as well as the intensity of immunostained PSA or PTHrP and the various grades prostate carcinoma among 52 patients. r = correlation coefficient.

Table 1: Clinicopathological characteristics of benign and prostate cancer specimens.

Parameter	Prostatic cancer (n=52) (Mean±SEM)	Benign (n=6) (Mean±SEM)	Significance
Age (years)	68.90±1.72	69.67±3.42	$P \geq 0.05$
PSA (ng/ml)	586.79±259.92	15.96±5.47	$P \geq 0.05$
Bilirubin	20.19± 1.62	30.28± 10.40	$P \geq 0.05$
Creatinine	1.05± 1.05	1.52± 0.28	$P < 0.05$

Table 2: Gleason grading distribution among prostate cancer specimens.

Type of grade	n (%)
3+3	7 (11.53%)
3+4	6 (6.61%)
4+3	12 (23.07%)
4+4	8 (13.46%)
4+5	7 (6.61%)
5+4	8 (19.23%)
5+5	5 (13.46%)

DISCUSSION

Several pathological processes result in the destruction of glandular architecture of BPH and prostate cancer. Abnormal growth of prostate epithelial cells may lead to the secretion of PSA. Adenocarcinoma of the prostate, similar to many epithelial malignancies, initiates in the secretory epithelial cells which are terminally differentiated[11]. The Gleason grading system relies on H&E-stained tissue sections showing the histologic pattern of carcinoma cells. Specifically, this method allows the categorization of various histologic patterns at low magnification (X10–40) relying on the extent of differentiation and growth pattern of the tumor glands in the prostatic stroma[12]. Because of concerns regarding over-diagnosis and over-treatment, PSA monitoring for prostate cancer has lately dropped. Several recent tests are commercially available, but none were frequently utilized due to a lack of evidence that they were superior to standard care in the general population[13]. Herein, the serum level of total PSA showed a non-significant difference between PHB and prostatic cancer. Several new tests became commercially available, but none were routinely used due to limited evidence of their benefits[13]. Thereby, evaluation of the PSA expression in the different scores of Gleason grade as a prognostic marker is the main objective. The present investigation localized immunoreactivity of PSA in most BHP cases as well as the moderately and well-differentiated prostatic cancer. The immunostained intensity of PSA was significantly decreased by increasing Gleason grade as reported by other studies[14,15].

The present work showed an inverse correlation between the immunostained intensity of PSA protein and the up-grading of the Gleason score ($P < 0.001$). The reduced PSA expression in high aggressive tumors needs to be clarified. PSA may have a tumor-protective effect, according to some scientists. The explanation for this inverse correlation can rely on other studies, for example, PSA inhibits angiogenesis by converting Lys-plasminogen to physiologically active angiostatin-like fragments[15]. Moreover, PSA inhibits the motility of PC-3 prostate cancer cells, according to Gkika *et al*. (2010) via stimulating a specific ion channel at the plasma membrane[16]. Moreover, PSA therapy inhibited the growth of prostate tumor xenografts in mice by modulating the expression of growth factors[17].

PSA can be used to identify the poorly differentiated adenocarcinomas of the prostate[18,19]. Considering PSA-positive cancers are all invasive, patients with tumors that express high PSA have a worse prognosis[18]. The present investigation localized immunoreactivity of PSA in most BHP cases as well as the moderately and well-differentiated prostatic cancer. The present study showed a positive correlation between the area of PSA immunostaining and the Gleason score upgrading system. This means that the area of the immunostained PSA might be seen enlarged by grading increase. However, the immunostained intensity of PSA was significantly decreased by increasing Gleason grade as reported by other studies[20,21].

It is known that prostate carcinogenesis is characterized by an increase in PTHrP secretion[22]. Hypercalcemia is linked to PTHrP expression in cancer cells in patients with bone metastatic lytic lesions[23]. In the present study, the co-expression of PSA and PTHrP was evaluated in BHP and prostate cancer specimens. All Gleason grades were defined by histological examination of all prostate cancer specimens. These grades represented well-, moderately, and poorly differentiated cases, and were categorized into seven scores[13]. Quantitative digital image analysis for immunological marker changes until now has not been manipulated as a routine workflow, thus more studies needed to be done to confirm this issue. The expression of such markers might provide to grade in the prediction of the outcome[24]. The present findings indicated a significant positive correlation between the expression of PSA and PTHrP regarding their area and intensity. PTHrP expression in cancer cells is considered a risk factor for hypercalcemia in cancer patients with bone metastatic lytic lesions[25].

CONCLUSIONS

Quantification of PSA expression over a broader range could provide much more useful prognostic information. The data from the current investigation indicate that PSA measurement provides noticeable prognostic information in prostate cancer patients. Overall, these data show that the level of PSA expression in prostate cancer cells is one of the strongest prognostic features in this tumor entity. Prostate carcinoma histological grade is one of the most powerful predictors of clinical outcome in patients with this type of cancer.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

العلاقة بين التعبير الكيمونسيجومناعية للمستضد البروستاتي والبروتين المرتبط بالهرمون الجار درقي في درجات جليسون المختلفة لسرطان البروستاتا

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المقدمة: كان سرطان الرئة هو السبب الأكثر شيوعا للوفاة بين مرضى السرطان٪٢٢,٨)) يليه سرطان البروستات(٩,٥٪)، بين السكان الفلسطينيين.

الهدف من العمل: كانت أهداف هذه الدراسة هي فحص التعبير المناعي لمستضد البروستات النوعي (PSA) والبروتين المرتبط بهرمون الغدة الجار درقية (PTHrP) في سرطان البروستات.

مواد وطرق الدراسة: ثمانية وخمسون مقطعًا من أنسجة البروستات: ٦ حالات لورم البروستاتا الحميد (BPH) و٥٢ حالة لسرطان البروستاتا الخبيث. تم صبغ قطاعات الانسجة باستخدام الهيماتوكسيلين والإيوسين لتحديد درجات مقياس جليسون. وعلاوة على ذلك، تم تحضير قطاعات من نسيج البروستاتا وصبغها بالطريقة الكيمونسيجومناعية لكل من PSA و PTHrP باستخدام أجسام مضادة أحادية بما في ذلك مستضادات PSA وPTHrP. أجرى التحليل الكمي لعدد الخلايا المصبوغة والمساحة التي شغلتها وكذلك شدة الصبغة لكل الدلالات محل الدراسة وربطها بالدرجات السبعة على مقياس جليسون.

النتائج: بشكل عام، كانت تعبيرات PSA وPTHrP إيجابية في جميع العينات. في تلك العينات ذات الصبغة الإيجابية، كان تعبيرًا متفاوتاً لدلالات البحث بين الخلايا. كان تعبير PSA مرتبطًا طردياً بشكل معنوي ($P < 0.001$) مع تعبير PTHrP في جميع العينات التي تم التحقيق فيها. اوضحت النتائج أن مساحة(μm2) المناطق المصبوغة من PSA و PTHrP

($r= 0.274$ and $r= 0.474$, $P <0.001$) ترتبط طردياً مع الدرجات المختلفة من سرطان البروستاتا. ومع ذلك، أظهرت شدة وجود علاقة سلبية. ومن جانب آخر، كانت شدة الصبغة لـ PSA أو PTHrP مرتبطة معنوياً مع درجات جليسون

($r = - 0.619$, $P <0.001$ أو $r = - 0.359$) وأظهرت علاقة عكسية، على الترتيب. وبالتالي، يرتبط النشاط المناعي لـ PSA بتعبير PTHrP في أنسجة البروستاتا.

الخاتمة: لقد أثبتت الدراسة أهمية الاستعانة بقيمة مساحة الجزء المصبوغ داخل الخلايا وكذلك شدة الصبغة PSA و PTHrP أثناء تشخيص حالات البروستاتا . يجب التركيزعلى هذة الخاصية المناعية خصوصا الدرجات المتقدمة من مقياس جليسون.