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Original article

Serum levels of chromogranin A are not predictive of high-grade, poorly differentiated prostate cancer: Results from an Italian biopsy cohort

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Abstract

Objectives: To explore the association of chromogranin A (CgA) levels and the risk of poorly differentiated prostate cancer (CaP) in men undergoing prostate biopsy.

Materials and methods: Between 2006 and 2012, we prospectively enrolled 1,018 men with no history of CaP undergoing prostate biopsy. The risk of detecting poorly differentiated CaP as a function of CgA concentration was evaluated using crude and adjusted logistic regressions. Further analyses were performed to determine whether CgA was a significant predictor of high-grade CaP in men with low PSA (<10 ng/ml).

Results: We found a significantly higher level of CgA in men with poorly differentiated CaP. CgA was however co-linear with age, and serum CgA levels were not significantly associated with the overall risk of CaP, and the specific risk of poorly differentiated CaP (OR 1.001 95% CI 0.99–1.01, $P = 0.74$). Moreover, in men with low PSA levels (<10 ng/ml), CgA was not a significant predictor of high grade-disease on univariate (OR 1.00; 95% CI 0.99–1.01; $P = 0.66$) and multivariate analysis ($P = 0.85$).

Conclusions: In our cohort of patients, the serum level of CgA is not a significant predictor of poorly differentiated CaP on initial prostate biopsy, even in men with low PSA levels (<10 ng/ml). According to our experience, CgA should not be considered a reliable marker to predict poorly differentiate cancer in the setting of initial prostate biopsy.

Keywords: Prostate cancer; Biopsy; Chromogranin A; High-grade; Neuroendocrine

1. Introduction

Prostate cancer (CaP) is a major health concern worldwide, being the second most common neoplasm and sixth cause of cancer-related death in the entire world [1]. Today, a crucial clinical need is the rapid identification of men harboring high-grade, poorly differentiated CaP, which are those at higher risk of progression, to provide a quick and efficacious local treatment for these aggressive neoplasms. PSA is considered the standard marker to identify patients at risk of CaP. However, considering its limitations, especially in men with low PSA values, several markers have been investigated in particular to identify patients at risk of high-grade, poorly differentiated CaP [2]; nevertheless, to date, none of the markers investigated have been found to be sufficiently accurate to enter routine clinical practice.

Chromogranin A (CgA) is an acidic protein encoded by the CHGA gene, commonly expressed in all neuroendocrine cells [3]. The levels of CgA are increased in patients affected by neuroendocrine tumors [4], such as pheochromocytoma and gastrointestinal neuroendocrine neoplasms, while the extent to which the circulating level of this protein increases in prostate cancer is object of debate [2,5–13]. Some investigators have reported a possible link between elevated CgA levels and poorly differentiated CaP [10]. As such, the measurement of circulating CgA has been proposed to identify patients with poorly differentiated CaP with low PSA values [3–5,7,8], and could aid in establishing which men truly need a biopsy, reducing the number of unnecessary procedures. However, these hypotheses have

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not been validly tested, and evidence on the role of CgA in the initial management of prostate cancer is lacking.

The purpose of our study was to evaluate the association of serum CgA concentrations and the risk of detecting high-grade, poorly differentiated CaP in a cohort of Italian men undergoing transrectal ultrasound (TRUS) guided prostate biopsy. Secondary aim was to evaluate the influence of CgA concentrations in men with low PSA values.

2. Materials and methods

2.1. Study population and biopsy procedure

After an Internal Review Board approval, between 2006 and 2012, 1,177 Italian men with no known history of CaP were referred to our department to undergo initial prostate biopsy because of an abnormal finding on digital rectal examination (DRE) and/or an elevation of serum PSA (≥4 ng/ml). On the day of biopsy, after obtaining a dedicated informed consent, blood specimens were drawn before the procedure at 8:00 AM (all men were fasting from the night before) and processed by our laboratories: PSA and CgA were measured. CgA was calculated using a solid phase, competitive chemiluminescent enzyme immunoassay and measured in ng/ml. Patients had been asked to interrupt any treatment with proton pump inhibitors or H-2 antagonists, if present, 3 weeks before the prostate biopsy, as these drugs may determine a significant modification of CgA serum concentrations [14]. DRE was performed by a senior staff urologist and judged positive if suggestive of cancer; prostate volume was estimated by TRUS. Body mass index (BMI) was calculated as kg/m^2. Every patient underwent 12-core TRUS biopsy with the same scheme, following our department's protocol [15]. All biopsies were performed and pathologically reviewed in the same institute. Fifty-five patients with diabetes and 14 men affected by autoimmune disease (rheumatoid arthritis, inflammatory bowel disease, chronic gastritis) were excluded from final analysis because of the alteration that these diseases may cause in CgA levels [14]. This resulted in a final study population of 1,018 men.

2.2. Statistical analysis

Serum CgA concentration was examined as a continuous variable. Patients diagnosed with CaP were categorized in men with poorly differentiated (Gleason score ≥8) or non-poorly differentiated CaP (Gleason score ≤7). PSA, prostate volume, and CgA levels were logarithmically transformed attributable to nonparametrical distribution. A Mann-Whitney or χ^2 test, as appropriate, was performed to determine whether age, PSA, DRE, prostate volume, BMI, and CgA significantly differed across outcome groups (cancer vs. no cancer; poorly differentiated vs. non-poorly differentiated CaP). We conducted univariate and multivariate logistic regressions to assess the association between CgA and the overall risk of CaP diagnosis and the specific risk of poorly differentiated disease (Gleason score ≥8). Each multivariate analysis was adjusted for age, PSA, DRE, and prostate volume, all known predictors of high-grade disease [16,17]. These were all considered as continuous variables except for DRE (negative vs. positive). Finally, crude and adjusted logistic regressions were performed to assess the association of CgA levels with the overall risk of detecting poorly differentiated prostate cancer in men with a low PSA concentrations (PSA <10 ng/ml). Data are presented as median (range). An alpha value of 5% was considered as threshold for significance. All statistical analyses were performed using Stata 11.1 (StataCorp, College Station, TX).

3. Results

Table 1 illustrates the clinical characteristic of our cohort. After TRUS prostate biopsy, CaP was detected in 421 (41%) men, of whom 78 (19%) had a diagnosis of poorly differentiated CaP (Gleason ≥8). More specifically, 14 men had a Gleason score 3 + 5, 15 men a Gleason 4 + 4, 29 a Gleason 4 + 5, 14 a Gleason 5 + 4, and 6 a Gleason 5 + 5. Neuroendocrine histology was not reported in any patients.

Known predictors of CaP (age, PSA, DRE, prostate volume) significantly differed across men with and without CaP and across men with non-poorly and poorly differentiated CaP (Table 2). Moreover, median CgA concentration was significantly higher in men with CaP, especially in men with poorly differentiated CaP (Table 2). CgA was co-linear with age, with older men presenting with higher CgA levels (Spearman's $\rho = 0.33$, $P < 0.0001$). CgA levels were not significantly co-linear to the other variables tested (PSA, BMI, prostate volume).

When exploring the association between CgA and the overall risk of CaP, no significant association was observed on univariate and multivariate analysis (Table 3). In addition, when restricting the analysis to men diagnosed with CaP, CgA levels were not significant predictors of poorly differentiated CaP (Table 3). As expected, age, PSA, DRE, and prostate volume were all highly significant predictors of CaP and high-grade disease.

Finally, we evaluated the risk of detecting poorly differentiated CaP in men with a PSA <10 ng/ml. In this specific group, only age (OR 1.09; 95% CI 1.03–1.15; $P = 0.002$)

Table 1
Baseline characteristics of the cohort

Patients	1,177
Age (years)	68 (62–74)
PSA (ng/ml)	6.68 (4.64–9.80)
DRE	
Normal	781 (77%)
Abnormal	237 (23%)
BMI (kg/m^2)	26.8 (24.9–29.1)
Chromogranin A	61.9 (45.7–97.3)