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European Association of Urology

Prostate Cancer

Dihydrotestosterone Levels and Survival in Screening-Detected Prostate Cancer: A 15-yr Follow-up Study

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Article info

Article history:
Accepted April 18, 2007
Published online ahead of print on April 26, 2007

Keywords:
Dihydrotestosterone
Prognosis
Prostate cancer

Abstract

Objectives: It has been hypothesized that dihydrotestosterone (DHT), the main intracellular androgen in the prostate, affects prostatic tumour progression. In this study, we evaluated serum DHT levels at the time of prostate-cancer diagnosis in relation to survival.
Methods: Sixty-five screening-detected patients diagnosed in 1988–1989 were followed for 15 yr. DHT levels at the time of diagnosis were determined through radio-immuno assay. Subjects were followed up through the nationwide tax register. Medical records of all dead subjects were reviewed, and cause of death was established by an endpoint committee. Data were analyzed through Kaplan-Meier estimation and Cox proportional-hazards regression.
Results: Seventeen of 41 deaths in the cohort during follow-up were attributed to prostate cancer. Patients with DHT above the median had a significant better prostate-cancer-specific survival than those with DHT below the median (log rank $p = 0.0075$). In the univariate analyses, one unit increase in DHT was associated with a hazard ratio (HR) of 0.14 (95% CI = 0.02–0.93). In the multivariate model, including prostate-specific antigen level, the association between DHT and prostate-cancer-specific survival was not significant (HR = 0.18; 95% CI = 0.02–1.6). DHT level below the median remained significantly associated with decreased survival in the multivariate model (HR = 0.23; 95% CI = 0.06–0.90). No association was found between DHT level and hazard of dying from causes other than prostate cancer.
Conclusions: Although the prognostic value of DHT levels at diagnosis remains unclear, these results provides evidence of an association between low DHT and decreased survival in prostate cancer patients.

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1. Introduction

With a growing number of patients diagnosed with prostate cancer, more men are receiving surgery or radiation therapy with curative intent. Both methods are considered effective but have side effects that may negatively affect the quality of life [1,2]. Studies have demonstrated that many cases of prostate cancer have a low risk of progression, even when left untreated [3–5]. To prevent unnecessary side effects of treatment as well as to increase cost-effectiveness, there is a need for markers with higher predictive value to distinguish those who would benefit from treatment from those who would not. An increased knowledge of the etiology of prostate cancer is also important to develop effective primary and secondary prevention measures.

Androgens are instrumental in the differentiation and maturation of the male reproductive organs and the development of male secondary sex characteristics [6]. There is established evidence that androgens promote the development of prostate cancer [7,8]. This relationship is not explained by a simple dose-response pattern, but instead a saturation model is more adequate. In such a model, a certain amount of androgen is needed for cancer growth, but higher levels do not contribute to cancer development and can even have the opposite effect [9]. In vitro androgens have been shown to increase the production of insulin-like growth factor-I (IGF-I), having a potential paracrine effect on prostate epithelial cells [10]. Several studies have assessed the potential association between serum levels of androgens and the risk of developing prostate cancer, but no simple mechanistic relationship has yet been found [11]. Other studies have tried to establish a correlation between the androgen level and the pathological stage of the cancer [12].

Testosterone is the principal androgen in the circulation, and the main intracellular androgen in the prostate is dihydrotestosterone (DHT) [13]. DHT arises primarily from intraprostatic conversion of testosterone by 5α-reductase and binds to the intracellular androgen receptor with an affinity several-fold higher than testosterone. The DHT androgen-receptor complex seems to be the main regulator of fundamental prostatic function [14,15]. In one theoretical model, DHT was suggested to protect the cell from apoptosis by binding to the intracellular androgen receptor [16].

Weihua et al. [17] hypothesized that DHT protects the prostate from development of high-grade cancer. The mechanism behind this somewhat paradoxical idea is that oestrogen receptor β (ERβ), which inhibits epithelial growth in prostatic tissue, is activated by 3-β-androstanediol (3βAdiol), a metabolite of DHT. Low levels of DHT would thus lead to low levels of 3βAdiol and less binding to ERβ, which in turn leads to loss of growth inhibition and tumour progression. To assess these hypotheses, we evaluated serum-DHT levels at the time of prostate-cancer diagnosis in relation to survival in a cohort of screening-detected patients with 15 yr of follow-up.

2. Methods

The study was approved by the local ethical committee at Karolinska Institutet. A population-based screening study of 1782 men aged 55–70 yr was undertaken from 1988 through 1989 [18]. Participants were examined with digital rectal examination (DRE), transrectal ultrasonography (TRUS), and prostate-specific antigen (PSA). If they had abnormal findings on DRE and/or TRUS, they underwent TRUS-guided biopsies. If PSA level was over 7 ng/ml, a new TRUS was performed. If the PSA level was over 10 ng/ml, randomized quadrant biopsies were taken. With this protocol, 65 (3.6%) patients with prostate cancer were diagnosed among all the screened men. None of the men were undergoing hormonal treatment at the time of examination.

Blood samples were drawn from all men between 08:00 and 11:00 to reduce the distortion by diurnal variation. Two venous blood samples were drawn: one for PSA-measurement and the other was immediately stored at −70 °C. The blood samples were analyzed for DHT, testosterone, and sexual-hormone binding globulin (SHBG) in 1993. DHT was analyzed through radio-immuno assay using an antiserum against 15β-carboxyethylmercapto-5α-DHT-bovine serum albumin (Code X-140 [5-24-76]; Southwest Foundation for Biomedical Research, San Antonio, TX, USA). Testosterone was analysed with the DPC Coat-A-Count method (Diagnostic Products Corp., Los Angeles, CA, USA) for which the intra- and interassay coefficient of variation was <8%. The minimal detectable dose of testosterone was 0.14 nmol/l, and the cross-reactivity for 5α-DHT was 3.3%. SHBG was analyzed with the $^{I-125}$-SHBG Immunoradiometric Assay Kit (Orion Diagnostica, Espoo, Finland) for which the intra- and interassay precisions were 3.2% and <10%, respectively. The practical assay range was 6.25–100 nmol/l.

Through the use of the subjects' national registration number, a 10-digit unique personal identifier used in all medical records and population registries, we were able to follow up all subjects in the cohort until 31 December 2003, 15 yr after the initiation of the study. Vital status was verified using the population register of the Swedish Tax Authority. If a subject had died, his medical record was retrieved. No subjects were lost to follow-up. Three independent senior urologists reviewed the records separately and designated the cause of death. In case of disagreement between the reviewers (one case), the majority ruled.

Follow-up time was calculated by summing the period from diagnosis to death from prostate cancer, death from other causes, or end of follow-up, whichever came first. We analyzed survival until death from prostate cancer as well as death from other causes. Because we had no prior knowledge of a relevant cut off for DHT levels, we analyzed this variable as continuous as well as dichotomized into above and below the median value. We used the log rank test to compare survival between groups. Data were modelled through Cox proportional hazards regression. In the final multivariate model, we retained variables that contributed significantly to model fit as well as prognostic or confounding factors. Data were analyzed using Intercooled Stata 8.1 for Windows (Stata Corp., College Station, TX, USA). All p values are two-sided, and statistical significance was set at $p < 0.05$.

3. Results

The median age at diagnosis was 65 yr (range: 55–71 yr). Median follow-up time of subjects was 12.8 yr (range: 1.1 to 15.3 yr). Among the 65 men with prostate cancer, 41 had died by the end of follow-up. Seventeen of the 41 deaths were attributed to prostate cancer. Table 1 presents univariate characteristics of the cohort.

Patients with DHT above the median had a significantly better survival rate than those with DHT below the median (log rank $p = 0.0075$; Fig. 1). No such association was found between DHT and death from other causes (log rank $p = 0.82$; Fig. 2). In the Cox regression analysis, one unit increase in DHT was associated with a hazard ratio (HR) of 0.14 (95% CI = 0.02–0.93; Table 2). The analysis of DHT dichotomized into above and below the median remained significant in a multivariate model (including PSA level and tumour stage; HR = 0.23; 95% CI = 0.06–0.90), whereas the evaluation of the continuous DHT variable did not (HR for one unit increase = 0.18; 95% CI = 0.02–1.6; Table 2). In the multivariate analysis, one unit increase in PSA was associated with decreased survival (HR = 1.02; 95% CI = 1.00–1.04). No other variables were significantly associated with survival (Table 2).

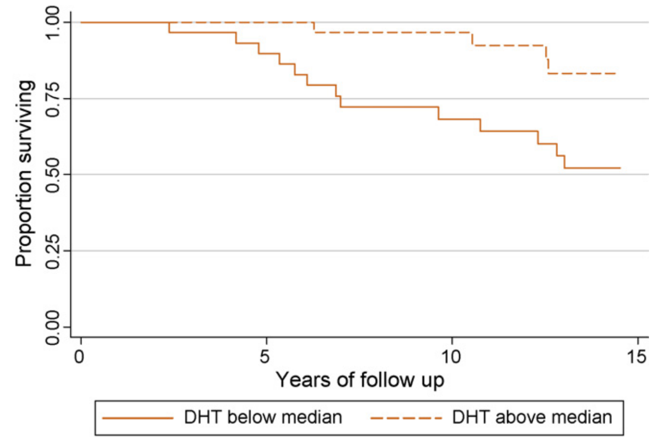

Fig. 1 – Prostate-cancer-specific survival for the 65 prostate cancer patients divided into two groups with dihydrotestosterone (DHT) level above and below the median. There is a significant improved survival in the group with DHT above the median (log rank $p = 0.0075$).

Table 1 – Univariate characteristics of the cohort

Characteristic	Total	Dead of prostate cancer	Dead of other causes	Alive at end of follow-up
Number of subjects	65	17	24	24
Median (range) age at diagnosis, (yr)	65 (55–71)	65 (61–70)	65 (55–71)	63 (56–70)
Tumour stage at diagnosis				
≤T2	32 (100%)	5 (16%)	13 (41%)	14 (44%)
≥T3	31 (100%)	11 (35%)	11 (35%)	9 (29%)
Tumour grade at diagnosis				
G1	16 (100%)	1 (6%)	9 (56%)	6 (38%)
G2	41 (100%)	12 (29%)	13 (32%)	16 (39%)
G3	8 (100%)	4 (50%)	2 (25%)	2 (25%)
Median (range) PSA value (ng/ml)	8.3 (1.3–100)	24 (1.5–100)	7.8 (1.3–46)	5.8 (1.3–25)
Median (range) DHT value (ng/l)	0.67 (0.23–1.9)	0.54 (0.28–1.3)	0.72 (0.36–1.9)	0.79 (0.23–1.5)
Median (range) testosterone value (nmol/l)	13 (8–35)	13 (8–30)	14 (8–34)	13 (8–35)
Median (range) sex-hormone binding globulin (nmol/l)	32 (3–120)	33 (18–57)	33 (3–120)	30 (8–71)
Treatment				
Prostatectomy	11 (100%)	0 (0%)	3 (27%)	8 (73%)
Radiation treatment*	30 (100%)	10 (33%)	10 (33%)	10 (33%)
Symptomatic/palliative	24 (100%)	7 (29%)	11 (46%)	6 (25%)

Nonadditivity due to missing values.
* The radiation category includes four subjects treated with a curative intent with laser.

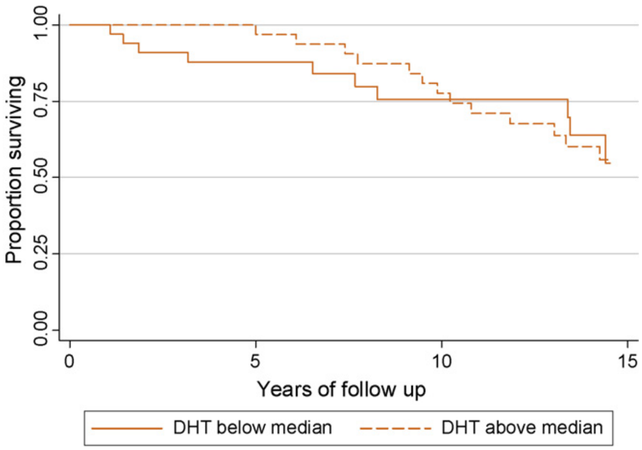

Fig. 2 – Survival until death from other causes than prostate cancer, divided into two groups with DHT above and below the median. There is no significant difference in survival between the groups (log rank $p = 0.82$).

When we stratified the analysis by treatment category, the point estimates remained qualitatively similar for the radiation group and the palliative group, whereas in the radical surgery group, the model could not be estimated due to lack of events (data not shown).

We also investigated the study variables in relation to risk of dying from causes other than prostate cancer. In those analyses, neither DHT (Table 2) nor PSA were associated with survival, whereas age at diagnosis was associated with survival (data not shown).

4. Discussion

To our knowledge, there is no previous study on the outcome for screening-detected prostate cancer patients related to hormone levels. The results indicate that a low DHT level may be a promoting factor in the progression of prostate cancer. Our data also suggest that serum DHT may be a prognostic factor in prostate cancer, although it remains to be elucidated whether DHT has any prognostic value beyond that of PSA.

Although statistical power was low in this study due to small numbers of patients, several strengths decrease the likelihood that our findings are generated by chance or represent an artefact. First, we had a strong a priori hypothesis built on knowledge of the hormonal regulation locally in the prostate gland. Second, in this cohort study we had no losses to follow-up in a study spanning 15 yr. Third, the patients in our study had not been subject to treatment with 5α-reductase inhibitors or any other hormonal treatment at the point of recruitment, thus confounding by use of hormonal drugs was not an issue. Nevertheless, sampling constraints

Table 2 – Hazard ratios and 95% confidence intervals for death from prostate cancer and other causes

Variable	Prostate cancer death		Death from other causes	
	Crude HR (95% CI)	Adjusted* HR (95% CI)	Crude HR (95% CI)	Adjusted† HR (95% CI)
DHT (continuous)‡	0.14 (0.02–0.92)	0.18 (0.02–1.6)	1.5 (0.46–4.8)	1.7 (0.49–5.6)
DHT (dichotomized)§				
Above median	0.24 (0.08–0.75)	0.23 (0.06–0.89)	0.91 (0.41–2.04)	0.89 (0.38–2.07)
Below median	1 (ref)	1 (ref)	1 (ref)	1 (ref)
PSA‡	1.03 (1.02–1.05)	1.02 (1.00–1.04)	1.00 (0.97–1.03)	0.99 (0.96–1.02)
Testosterone‡	0.99 (0.93–1.07)	–	1.04 (0.98–1.09)	–
SHBG‡	1.01 (0.98–1.04)	–	1.01 (0.99–1.03)	–
Tumour grade				
G1	1 (ref)	–	1 (ref)	–
G2	4.3 (0.56–33)		0.57 (0.24–1.3)	
G3	7.8 (0.87–70)		0.53 (0.11–2.5)	
Tumour stage				
≤T2	1 (ref)	1 (ref)	1 (ref)	1 (ref)
≥T3	3.8 (0.43–34)	1.8 (0.54–6.1)	1.4 (0.50–3.7)	1.6 (0.66–4.1)
Age (per yr increase)	1.14 (1.00–1.31)	–	1.15 (1.02–1.29)	1.2 (1.03–1.3)

HR, hazard ratio; CI, confidence interval; DHT, dihydrotestosterone; PSA, prostate-specific antigen; SHBG, sexual-hormone binding globulin.
* Adjusted for DHT, PSA, and tumour stage.
† Adjusted for DHT, PSA, tumour stage, and age.
‡ HR for one unit increase in test value.
§ Included in the model as an alternative to the continuous DHT variable.

hinder detailed evaluation of the association and conclusive inference.

The ideal observational assessment of the hypothesis on DHT levels and prognosis in prostate cancer would have been to measure intraprostatic levels of DHT. Although inhibition of 5α-reductase leads to both lower intraprostatic and serum levels of DHT, there is no strong correlation between these concentrations [19,20]. Such misclassification should, however, be nondifferential between the comparison groups, leading to a dilution of the differences. Moreover, in our data set there was no difference in mortality from causes other than prostate cancer, and the fact that DHT is specifically associated with death from prostate cancer points to a true association between DHT and tumour progression in the prostate. Conclusive data in the assessment of this hypothesis will be difficult to obtain. However, follow-up for survival within the Prostate Cancer Prevention Trial (PCPT) study [21] would provide highly valuable information.

While we found a robust association between DHT and prognosis in the univariate analysis, the inclusion of PSA into the regression model diminished the effect of DHT, particularly in the analysis of DHT as a continuous variable. From the clinical perspective, it could be inferred that there is little prognostic value of DHT beyond that of PSA. From the etiological point of view, however, it may be more relevant to interpret the effect of DHT unadjusted for PSA, because DHT and PSA may be components in a causal chain where DHT comes first. Unfortunately, our sample size was too small to evaluate the effect of DHT stratified by PSA levels.

Our data could not reveal whether the association between DHT and prognosis in prostate cancer is explained by a true tumour-progressive effect of DHT, or whether the DHT level merely reflects a more aggressive tumour. In fact, the aggressiveness of prostate cancer may be determined very early in life, although there is evidence that manipulation of the DHT level at adult ages may affect tumour grade. In the PCPT [21], Finasteride, a 5α-reductase inhibitor that lowers DHT in serum by 70%, was given to prevent the development of prostate cancer. Although the number of cancers was reduced in the treatment arm, the proportion of high-grade tumours was increased. Several possible explanations have been proposed by the PCPT investigators and others to explain the finding of higher tumour grade among those treated [22], but the finding in our study is compatible with the hypothesis that DHT could influence the prognosis in prostate cancer.

A possible hormonal mechanism was described by Weihua et al. [17], who studied mice with and without ERβ and compared the proliferation in the prostate when the mice were given 3βAdiol. Mice without ERβ had a high proliferation rate in their prostates. In the group with intact ERβ, proliferation diminished when 3βAdiol was administered. In prostate-cancer cell lines it has been shown that lack of 3βAdiol, which binds to ERβ, could lead to loss of inhibition of cell migration [23]. In addition, single nucleotide polymorphisms in the genes *HSD3B1* and *HSD3B2*, encoding the enzyme 3β-hydroxysteroid dehydrogenase that converts DHT to 3βAdiol, could be associated with higher risk for prostate cancer [24].

5. Conclusions

This study provides evidence of an association between low DHT and decreased survival in prostate cancer patients. It remains unclear whether DHT at diagnosis has any prognostic value beyond that of PSA and PSA velocity. PSA levels merely reflect tumour stage and grade, whereas DHT may play an etiological role in the progression of the tumour.

Conflicts of interest

The authors have no conflict of interest in connection to this paper.

Acknowledgements

The authors thank Drs Michael Häggman, Hans Wijkström, and Lennart Öst for their contribution in evaluating causes of death. The study was supported by the Stockholm County Council, the Thure and Brita Grafström Foundation, and a grant from Odd Fellows 164 Södertälje.

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