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Circulating testosterone and prostate cancer. A brief review

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ABSTRACT

***In vitro* and *in vivo* studies show that androgens stimulate prostate cancer. However, evidence from epidemiological studies of an association between circulating levels of androgens and prostate cancer risk has been inconsistent, but most studies have likely been undersized given that the association may be relatively weak.**

We review prospective studies on the association of serum levels of free and total testosterone, the principal androgen in circulation with risk of prostate cancer.

No significant association between total or free testosterone and risk of prostate cancer was found in studies that together included 1,525 cases of prostate cancer and 4,349 controls.

No support was found for the hypothesis that high levels of circulating testosterone within a physiological range stimulate development and growth of prostate cancer. Intraprostatic androgen metabolism may still be of importance for prostate cancer development.

Key words *: prostate cancer, androgens, testosterone, epidemiology, prospective studies*

I. INTRODUCTION

The hypothesis that androgens play a role in the pathogenesis of prostate cancer in men is mainly based on a large body of evidence from studies of tumor models [4]. *In vitro*, androgen response is observed in most well-differentiated cancer cell lines of prostatic origin [18, 35], and *in vivo*, androgens consistently stimulate induction and promotion of prostate tumors and prostate tumor xenografts in rodent models, whereas androgen ablation causes tumor regression [19, 3]. In humans, an increased risk of prostate cancer may depend on an increase in testicular production of testosterone resulting in high levels of circulating androgens, and/or to tissue-specific alterations within the prostate increasing androgen stimulation only in the prostate [4].

At least ten modest-sized prospective studies have investigated the former relationship, i.e. the association between circulating levels of androgens with prostate cancer risk, for recent reviews see [7, 17, 15]. Overall, the results from these studies have been inconclusive, some studies have shown a mildly increased risk [14, 8, 13, 12] whereas other studies have demonstrated a mildly decreased risk [31, 6], but none of these studies have shown a statistically significant association between absolute levels of circulating testosterone, the principal androgen in the circulation, and prostate cancer risk.

The biologically most active form of testosterone is considered to be bioavailable or free testosterone. Bioavailable testosterone is the fraction of testosterone that is not bound to sex hormone binding globulin (SHBG) - the dominant binding protein for testosterone in circulation - and free testosterone is the fraction not bound to any protein.

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Given that albumin levels are constant between individuals, these two measures will be highly correlated. A few studies have investigated the association between serum levels of free testosterone and risk of prostate cancer. No significant association was observed in any of the three studies in which free testosterone was directly measured [12, 6, 25].

Circulating levels of testosterone are inversely correlated to obesity, which has been inconsistently associated with a weak increase in risk of prostate cancer [17, 2, 5]. This paper presents a brief review of the two largest studies [7, 27] on the association between total and free testosterone and risk of prostate cancer, also taking obesity into account.

II. STUDY GROUPS AND RESULTS

The paper by Eaton and al. is a meta-analysis of eight prospective studies published until 1999, and included 817 cases and 2,107 controls analysed for total testosterone [7]. The study by Stattin and co-authors is a pooled analysis with 708 cases and 2,242 controls from three Nordic biobanks ; The Janus Serum bank in Oslo, Norway, The Helsinki Heart Study in Helsinki, Finland, and the Northern Sweden Health and Disease Cohort in Umeå, Sweden [27]. The number of cases included from Norway was 537, from Finland 84, and from Sweden 87, and from each country four controls per case was selected matching for age and date of blood collection.

In the paper by Stattin and co-authors, there were strong, direct correlations between total and free testosterone (r = 0.78) and between total testosterone and SHBG (r = 0.51), whereas the correlation between SHBG and free testosterone was very weak (r = -0.08). In the same paper, BMI was inversely correlated to SHBG (r = -0.33) and total testosterone (r = -0.28), and less strongly to free testosterone (r = -0.14) (Figure 1).

Levels of total and free testosterone and risk of prostate cancer

In the meta-analysis by Eaton and al. [7], no significant association between levels of total testosterone and prostate cancer risk was found when analyzing all cases and controls combined (Figure 2). Essentially the same pattern of risk was found in the pooled Nordic study [27], (Figure 3). For free testosterone both the meta-analysis and the pooled study basically had the same findings, namely that there were no significant association between levels of free testosterone and risk, (Figures 4a and 4b ; Figures 5a and 5b). The risk estimates remained almost unchanged in the pooled study by Stattin et al. when analysis included adjustment for BMI [27]. Similarly, the risk estimates remained essentially the same when analyses were done in subgroups according to age and lag time.

III. DISCUSSION

In these two studies, one meta-analysis [7] and one pooled study [27], which together encompasses 1,525 cases of prostate cancer, no significant association between total or free testosterone and risk of prostate cancer was found.

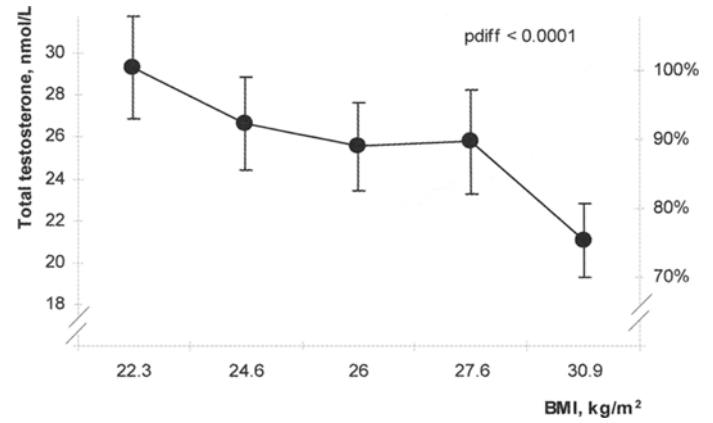
With regard to levels of androgen exposure, there was an approximately two-fold difference in serum testosterone in the highest *versus* the lowest exposure groups, in both studies. An equally large increase in androgen administration has produced substantial increases in induction and promotion of prostate tumors in rodent tumour models [4]. However, short-term administration of androgens in rodent models may not be equivalent to chronic exposure to mildly elevated endogenous androgen levels in men.

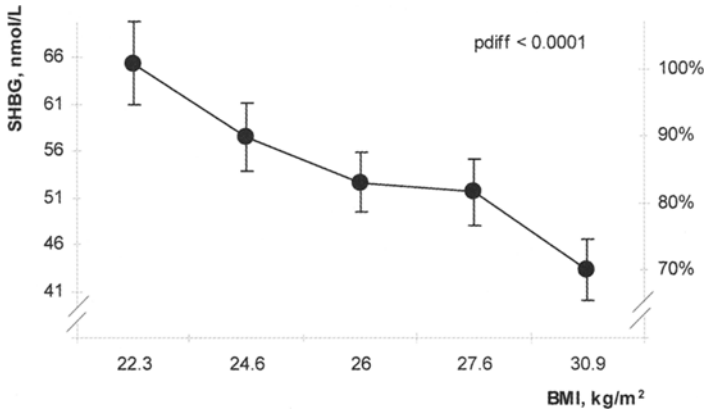
Most sex steroids are fairly robust in cryopreserved samples even for relatively long periods [28, 23], but some degradation cannot be ruled out in these studies in which some samples had been cryopreserved for a very long time. However, as the cases and controls had been closely matched for date of blood collection, degradation would affect samples from cases and controls non-differentially and would only tend to attenuate an association to risk. Serum levels of testosterone are relatively constant over time in an individual, with reported correlation coefficients ranging from 0.7 to 0.9 between levels in samples taken about three years apart [23, 9, 33, 30]. However, if one single blood sample is representative for longer time periods is unknown.

Concentrations of free testosterone, the biologically most active form of testosterone, is most accurately directly measured by a dialysis method, which has been used rather infrequently in epidemiological studies due to the requirements of large sample volumes and time-consuming methodology. However, such direct measurements have been shown to correlate well with indices of free testosterone calculated from total testosterone and SHBG levels as used in these studies [23, 1, 34].

Total testosterone linearly adjusted for SHBG can also be used as a calculated index of biologically active testosterone, and one often-cited paper by Gann et al. in the Phycian´s Health Study reported a significant increase in prostate cancer risk for total testosterone linearly adjusted for SHBG [8]. In contrast, in the pooled study by Stattin and co-authors [27] a non-significant *decrease* in risk was found for testosterone after adjustment for SHBG as done by Gann et al. [8]. A bell-shaped pattern of risk, with weakly increased risk for intermediate level and decreased risk for the highest level was for an index of free testosterone calculated from total testosterone and SHBG was seen in the same study.

Indirect support for the hypothesis that high levels of circulating androgens is a risk factor for prostate cancer have included the dramatic regression of tumor symptoms in a majority of men with advanced prostate cancer after androgen ablation, which entails a total cessation of testicular production of testosterone [24]. However, the effects of the drastic reduction in androgen levels seen at a very late stage of cancer development may not be relevant to the effect of variations within a physiological range on early tumor events that takes place decades earlier.





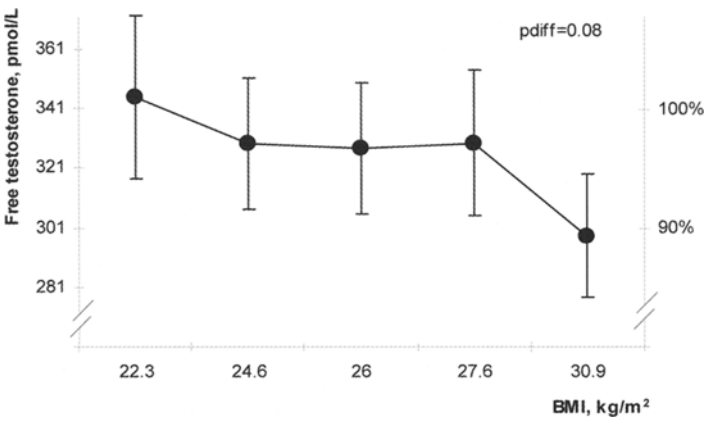


Figure 1 : Means of hormonal levels by quintile levels of body mass index (BMI) in the pooled Nordic study [27].

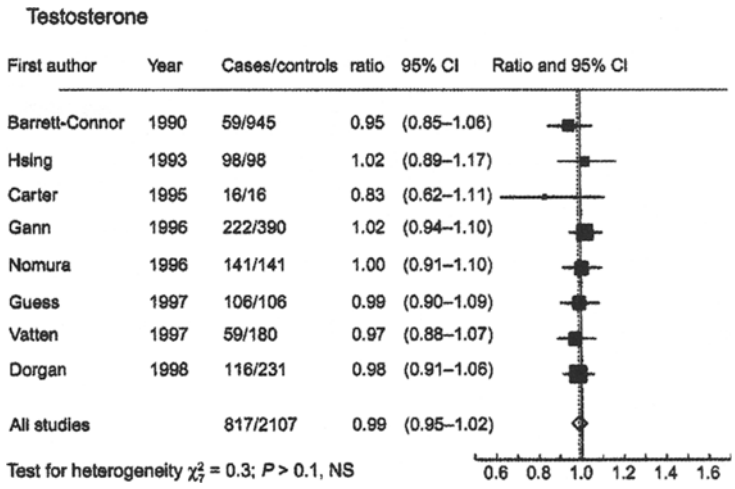


Figure 2 : Meta-analysis of prospective studies on the association between total testosterone and risk of prostate cancer [6].

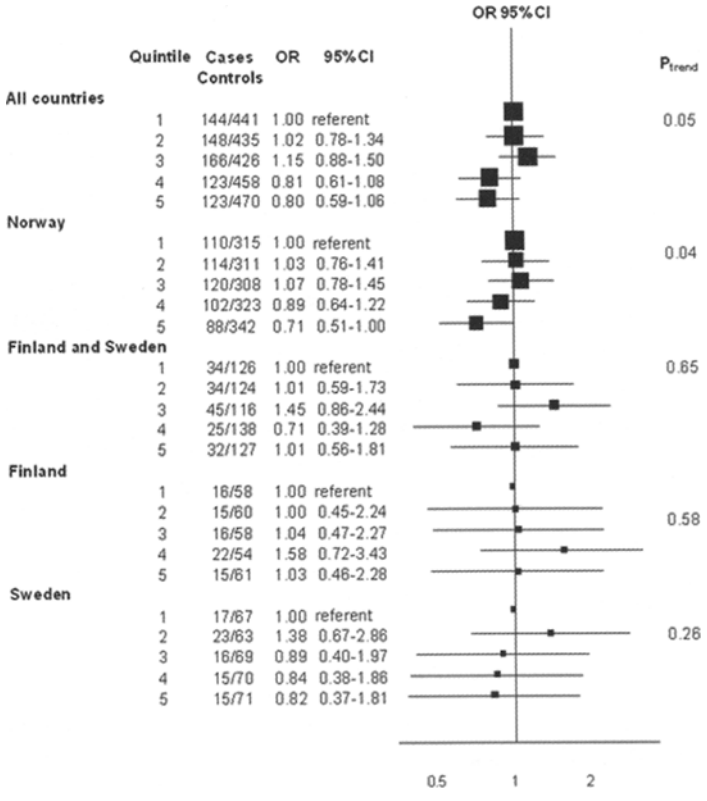


Figure 3 : Odds ratios of prostate cancer by quintile of testosterone levels in the pooled Nordic study [27].

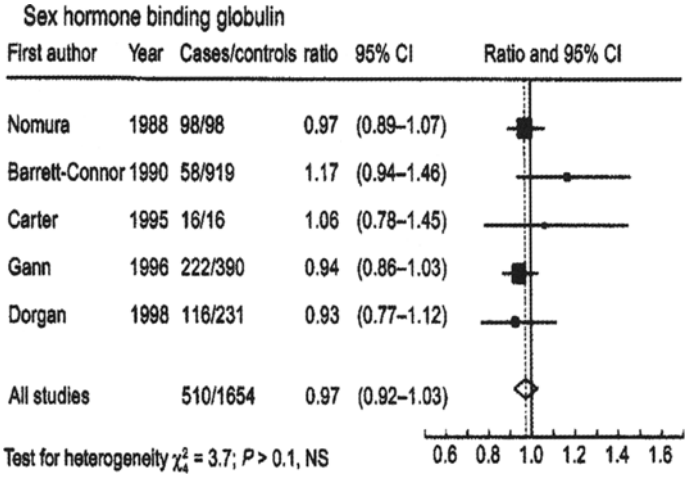


Figure 4a : Meta-analysis of prospective studies on the association between SHBG levels and risk of prostate cancer [6].

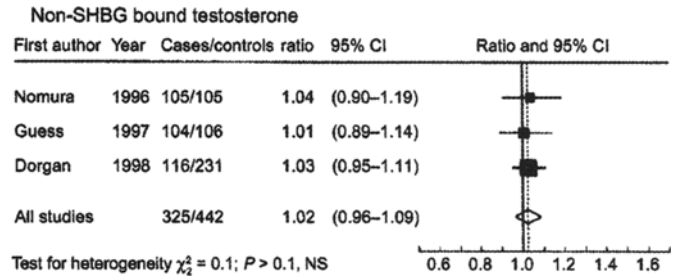


Figure 4b : Meta-analysis of prospective studies on the association between non-SHBG bound testosterone levels and risk of prostate cancer [6].

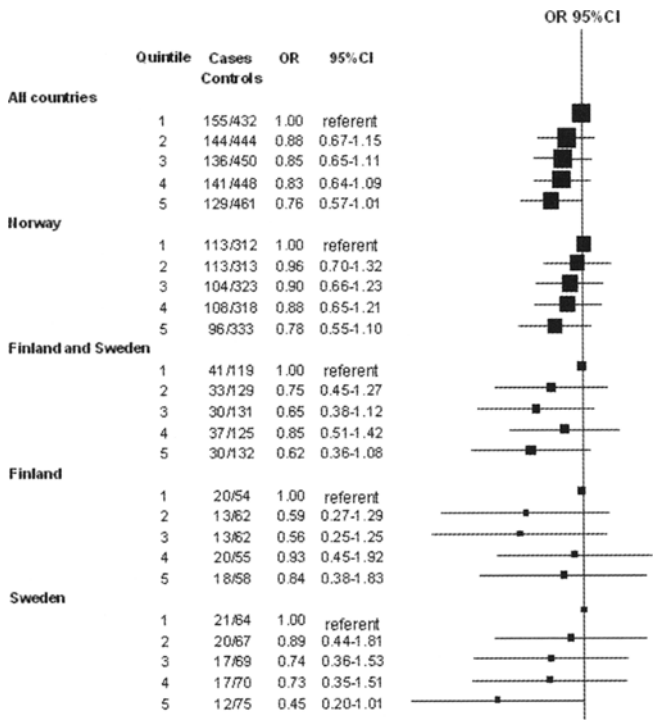


Figure 5a : Odds ratios of prostate cancer by quintile of SHBG levels in the pooled Nordic study [27].

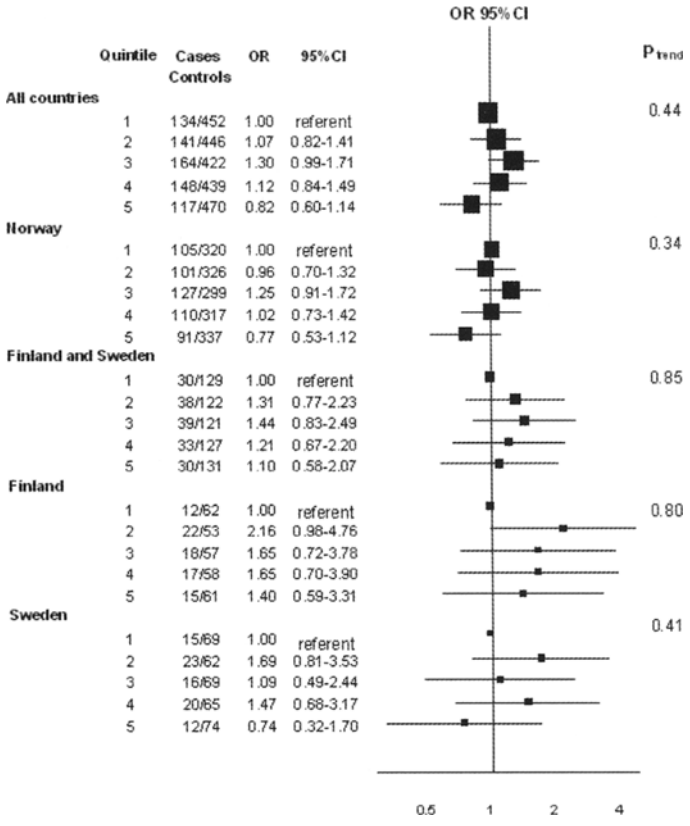


Figure 5b : Odds ratios of prostate cancer by quintile of free testosterone levels in the pooled Nordic study [27].

The association between obesity measured by BMI and prostate cancer risk have been somewhat inconsistent, but most prospective studies have shown a weak direct association [17, 2, 5]. In the pooled analysis there was a rather strong negative correlations between BMI, and SHBG and total testosterone, but less strong with free testosterone which fits with that an obesity-induced decrease in SHBG levels decreases testosterone levels through a feedback mechanism of free testosterone on the hypothalamic-pituitary-gonadal axis [17]. Thus, the fact that obesity is not a protective factor for prostate cancer supports the idea that circulating testosterone is not a major risk factor for prostate cancer [17].

Circulating androgen levels can be important for prostate cancer development only if they accurately reflect intraprostatic androgen signaling and little is known if they do. Intraprostatatic androgen signaling may depend more on the rate of conversion of testosterone by the 5α-reductase - II enzyme to dihydrotestosterone (DHT), the most potent androgen in the prostate, and on the propensity for androgen receptor activation than on circulating androgen levels [4, 20, 16, 10]. Polymorphisms affecting 5α-reductase activity and pharmacological blockade of 5α-reductase conversion of testosterone to DHT have been associated with prostate cancer risk in some studies [20, 16, 26]. Importantly, one very large randomized study recently demonstrated a 25% reduction in prevalence of prostate cancer in men treated with finasteride compared to men treated with placebo [29]. Furthermore, androstanediol glucuronide (A-diol-g), the main circulating metabolite of DHT, was the only androgen that was significantly increased in prostate cancer cases in the meta-analysis [7]. However, circulating A-diol-g levels only partially reflect intraprostatic DHT levels as A-diol-g is also produced by the 5α-reductase-I enzyme present in the skin. Finally, variations in the length of CAG repeats in the androgen receptor affects DNA transcriptional activity and may also possibly influence development of prostate cancer [10, 21].

A clinical implication of our results concerns androgen supplementation, which has been become easier to administer with the advent of transdermal patches and gels [11, 32]. Androgen supplementation has been suggested for treatment of mild hypogonadism, and reports have included benefical effects on erectile dysfunction, abdominal obesity, osteoporosis, muscle strength, and angina pectoris [32, 22]. There has been concern that androgen supplementation in the same order of magnitude as endogenous testicular production of testosterone (3-10 mg/24h) may promote prostate cancer but our results do not support this view. As SHBG levels are slightly decreased by androgen administration, levels of free testosterone proportionally increase more than levels of total testosterone [11]. Thus, whether the effect of variations within the physiological range of endogenous testosterone levels can be inferred to the effect of a constant exogenous supply of testosterone, by-passing the normal co-regulation of testosterone production is unknown.

IV. CONCLUSION

Taken together, data from all published prospective studies on circulating levels of total and free testosterone do not support the hypothesis that high levels of circulating androgens are associated with an increased risk of prostate cancer [7, 17, 27].

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