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Androgens and prostate cancer risk

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Androgens have been implicated in prostate tumourigenesis. However, no association between circulating levels of androgens and prostate cancer risk was found in a recent large pooled analysis of prospective studies. A decreased risk of prostate cancer among men treated with finasteride, a 5α-reductase inhibitor which reduces levels of dihydrotestosterone, was observed in the Prostate Cancer Prevention Trial (PCPT), a large clinical trial. In the PCPT, a higher number of high-grade tumours was found in the finasteride group than in the control group; the reason for this finding is still unclear. Treatment of symptoms of late-onset hypogonadism – such as decreased muscle and bone mass and decreased cognition and libido – has become more prevalent with the advent of new forms of administration of testosterone replacement therapy. One small placebo-controlled study showed no increase in incidence of prostate cancer after 6 months of testosterone therapy, but data on the safety of testosterone replacement therapy remain limited.

Key words: prostatic neoplasms; androgens; finasteride; testosterone; late-onset hypogonadism; testosterone replacement therapy.

TESTOSTERONE METABOLISM

Androgens have long been implicated in prostate carcinogenesis.[1–3] In animal models, high doses of androgens promote and stimulate prostate tumours[4–6]; in men, however, the association between circulating and intraprostatic levels of androgens and prostate cancer is less clear.[7]

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Testosterone, the main androgen in the circulation, is mainly protein-bound, either strongly to sex hormone binding globulin (SHBG), or loosely to albumin. Only about 2% is unbound; this is called free testosterone and is considered to be the most biologically active form of testosterone. In the target tissue testosterone can either bind directly to the androgen receptor (AR) or, if the tissue expresses the enzyme 5α-reductase, be converted to dihydrotestosterone (DHT). The AR is a ligand-dependent nuclear transcription factor which binds to androgen-response elements in the DNA and regulates transcription in androgen-regulated genes.[8,9] Due to its stronger affinity for the AR, DHT is two to ten times more potent as an androgen than testosterone, giving tissues expressing 5α-reductase a mechanism for local regulation of androgen activity.[8,10,11] The enzyme 5α-reductase exists in two forms: type 1, present mainly in the skin and to a lesser extent in the liver, and type 2, present mainly in the prostate and the genital skin.[12] Inhibitors of 5α-reductase can either inhibit type 2 selectively (e.g. finasteride), or both types 1 and 2 (e.g. dutasteride). Serum DHT is decreased more by dutasteride (94%) than by finasteride (73%).[13]

Androstanediol glucuronide (A-diol-g), a circulating end-product of DHT[14], is used as a marker for intraprostatic androgenicity. Although levels of A-diol-g reflect the activity of both types of 5α-reductase, selective inhibition of 5α-reductase type 2 lowers circulating A-diol-g by 86%, suggesting that most of the circulating A-diol-g comes from the prostate.[15]

PROSPECTIVE STUDIES ON ANDROGENS AND PROSTATE CANCER

To date, about 20 prospective studies have investigated the relationship between endogenous circulating levels of androgens and risk of prostate cancer.[16–35] Most of these studies have been case–control studies nested in prospective cohort studies. In these studies pre-diagnostic levels of androgens in men who after the blood draw were diagnosed with prostate cancer were compared with circulating androgen levels among matched controls that stayed cancer-free. Overall, these studies have not shown a consistent association between circulating levels of androgens and risk of prostate cancer.

Individually, these studies have had limited power due to a relatively modest number of study subjects. In 2008, a pooled analysis of 18 prospective studies on circulating levels of androgens and prostate cancer risk was published by the Endogenous Hormones and Prostate Cancer Collaborative Group.[36] The analysis included 3886 cases of prostate cancer and 6438 matched controls for whom plasma levels of testosterone and other androgens were available from prospectively collected blood samples. This study, the largest to date, reported no significant associations between high levels of any of the androgens under investigation and risk of prostate cancer (Figure 1). However, high levels of SHBG were significantly associated with a 14% reduction in risk of prostate cancer. Similar results have been reported in two very recent studies that were not included in the pooled analyses.[34,35]

Some studies have also investigated androgens in subgroups according to tumour aggressiveness, usually defined as high-grade tumour, i.e., Gleason score $\geq$7 and/or advanced stage. One study reported a non-significant increase in the risk of low-grade tumours and a significant decrease in the risk of high-grade tumours[30], while other studies have shown only weak, non-significant decreases in risk of aggressive tumours, with increasing levels of testosterone.[28,32,33,35] In contrast, one study reported a significant, linear increase in the risk of aggressive disease for an increased