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Hormonal Balance and the Risk of Prostatic Cancer

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Multiple malignant steps are necessary for a normal cell to give rise to a fully malignant cancer cell. With regard to prostatic carcinogenesis, it is known that androgens have at least a permissive role in this malignant process since: (1) prepubertal orchiectomy prevents the clinical development of prostatic cancer, and (2) clinically established prostatic cancers often respond to androgen ablation. In an intact adult male, the supply of androgens regulates a balance between prostatic cell death and proliferation, so that neither overgrowth nor involution of the gland normally occurs. Organ homeostasis is achieved by the balancing of two distinct processes, one responsible for initiating DNA synthesis and cell proliferation (*i.e.*, agonistic effect of androgen), and the other responsible for inhibiting prostatic cell death (*i.e.*, antagonistic effect), with both processes being under androgenic control [1]. Thus, observation that androgen is chronically required for prostatic carcinogenesis does not establish whether or not, besides maintaining these cells, androgens have additional carcinogenic abilities for prostatic epithelial cells.

Regardless of this uncertainty, theoretically it should be possible to reduce the possibility (*i.e.*, the risk) of prostatic epithelial cells undergoing both the initiation and promotional stages of carcinogenesis by lowering the androgenic influences on these cells. Usually such reduction in androgenic effects is achieved by reducing the blood levels of testosterone by either surgical or medical means. Unfortunately, such a systemic reduction in the circulating testosterone level has undesirable side effects including sterility, impotence, decreased libido, hot flashes, increased breast tenderness and loss of the anabolic effect of androgen upon muscle mass. Based upon these quality of life issues, systemic reduction of blood testosterone is unlikely to be very useful as an approach to chemoprevention of prostatic cancer.

Within the prostate, testosterone is rapidly converted irreversibly to 5α-dihydrotestosterone (DHT) by the membrane bound NADPH-dependent Δ^4-3-ketosteroid 5α-oxidoreductase (*i.e.*, 5α-reductase). A series of studies by a large variety of independent investigators has demonstrated that the major intracellular mediator of androgen action in the prostate is DHT rather than testosterone, and that 5α-reductase conversion of testosterone to DHT functions as a means of amplifying androgenic stimulation in the prostate. Recently a series of 5α-reductase inhibitors (*e.g.*, finasteride, SKF-105657) has been synthesized which can effectively inhibit the *in vivo* production of DHT and thereby lower its intraprostatic concentration without lowering serum testosterone. In experimental rodent models, treatment with such 5α-reductase inhibitors lowers prostatic tissue DHT which results in inhibition of prostatic cell proliferation and activation of prostatic cell death leading to involution of the normal prostate [2]. Such 5α-reductase inhibitor treatment does not result in a lowering of serum testosterone. Treatment with 5α-reductase inhibitors does not produce, however, as rapid or as extensive an involution of the normal rat prostate as surgical orchiectomy [2]. One explanation for this difference is that, unlike castration which reduces all androgens in the prostate (*i.e.*, testosterone, DHT, and their metabolites), treatment with 5α-reductase inhibitors reduces DHT and its metabolites while increasing

testosterone within the normal prostate. These results suggest that testosterone itself (without conversion) can have androgenic effects if the tissue levels are high enough.

Based upon these and other experimental studies of the *in vivo* response of the normal prostate, the potential of 5α-reductase inhibitors as chemopreventive agents for prostatic carcinogenesis warrants testing. Additional support for such a potential is also provided by recent studies of the *in vivo* response of two androgen-sensitive rat prostatic cancers (*i.e.*, Dunning R-3327 H and G sublines) and one androgen-sensitive human prostatic cancer (*i.e.*, PC-82) to 5α-reductase inhibitors. The rat R-3327 G tumor and the human PC-82 tumor have a low to undetectable level of tissue 5α-reductase activity and both responded to 5α-reductase inhibitors with a reproducible inhibition of tumor growth [3]. Associated with this antitumor effect is a major decrease (*i.e.*, >70%) in tissue DHT content in both tumors. In contrast, the rat R-3327 H prostatic cancer has a much higher level of tissue 5α-reductase activity and neither tumor DHT content nor growth of the tumor was inhibited by treatment with 5α-reductase inhibitors [3]. Drug treatment of rats bearing R-3327 H tumors resulted in a similar reduction in the DHT content, wet weight, and DNA content of the ventral prostate to that produced in R-3327 G tumor-bearing rats which experienced an antitumor response. These results suggest that 5α-reductase inhibitors can produce antitumor effects if a substantial reduction in tissue DHT is achieved. Such reduction in DHT, secondary to inhibition of the tissue 5α-reductase enzyme, appears to be more difficult to achieve in tumors than in the normal prostate.

REFERENCES

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