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INVITED COMMENT

Possible Enhancement of Prostate Carcinogenesis by Some Chemopreventive Agents

Some of the most promising agents for chemoprevention of prostatic cancer, *i.e.*, 5α-reductase inhibitors and retinoids, may enhance rather than slow down the progression of prostatic cancer. I have summarized observations in the literature that form the basis for this troubling possibility below.

The proposition to use 5α-reductase inhibitors for chemoprevention of prostatic cancer is based on the assumption that these substances will prevent the predicted enhancing effect of endogenous androgens on progression of preneoplastic and early malignant lesions in the prostate. However, the studies summarized by Isaacs [1] indicate that the opposite effect may occur, perhaps due to a considerable increase of prostatic testosterone concentrations. Furthermore, it is possible that 5α-reductase inhibitors may actually select for androgen-independent cells by providing a selective growth advantage for these cells. A causal relation between androgens and prostate carcinoma development in man and animal models is very plausible. Male human populations that are at high risk for prostate cancer, for example African-Americans [2], often have slightly higher circulating testosterone levels than low risk populations [3,4]. Nevertheless, this may not be universally true in all high risk populations. Meikle and co-workers [5] found that circulating levels of testosterone and 5α-dihydrotestosterone were significantly *lower* in brothers (age 47–75) and sons (age 22–43) of prostate cancer patients than in unrelated control subjects of the same age ranges. Zumoff *et al.* [6] observed that circulating concentrations of testosterone, but not 5α-dihydrotestosterone, in prostate cancer patients were markedly lower in those younger than 65 years than in those 65 years and older; control subjects had similar testosterone levels to prostate cancer patients 65 years and older. These data indicate the possibility that the role of androgens in prostatic carcinogenesis is different depending on age, and different in men that are at high risk because of familial predisposition and those at high risk for racial or other reasons.

Epidemiologic data on the association between prostate cancer risk and dietary intake of vitamin A and/or carotenes are conflicting [3]. In approximately 40% of both case-control and cohort studies, negative associations were found between risk and intake of carotenes or foods rich in carotenes and/or vitamin A [7–11]. Forty percent of studies reported *positive* associations between risk and intake of (total) vitamin A [12–16], and in 20% of studies there was no association [17–19] (for summary see references 3 and 26). The prostate is, to my knowledge, the only human cancer site for which positive associations between risk and vitamin A intake have been found. Among the studies in which a positive association between risk and dietary vitamin A intake was found, there are two case-control studies in which the association was only present for men that were 70 years and older at the time of diagnosis, but not for younger men [12,15]. In a recent re-analysis of one of these studies, the positive association appeared due entirely to the consumption of papaya [18]. In one cohort study a positive association was only found for patients that were younger than 75 years [14]. In case-control and cohort studies on serum vitamin A levels, either no association [20–24] or an inverse relation with prostate cancer risk [25–27] was found, but never a positive correlation.

It is presently unclear whether the synthetic retinoids that are proposed for cancer chemoprevention act via the same molecular and cellular mechanisms as natural retinoids. Until this question is resolved, it is reasonable to assume that studies of cancer risk in relation to dietary intake of vitamin A have some significance for estimating the possible benefits and potential problems of cancer chemoprevention by synthetic retinoids. Thus, the epidemiologic data of prostate cancer risk and dietary vitamin A intake mentioned earlier raise the possibility that synthetic retinoids may enhance rather than inhibit prostatic carcinogenesis, although there is also evidence from *in vitro* studies suggesting a protective effect of retinoids. An enhancing effect of retinoids is not without precedent in experimental studies. Tumor promotion by retinoids, rather than inhibition, has been found in some animal models of liver and skin tumorigenesis [28,29] at dietary retinoid concentrations that were not toxic, but were effectively chemopreventive in other systems, such as models of bladder and mammary cancer [30,31]. The epidemiologic studies fur-

ther indicate the possibility that age may be a factor in modification of prostatic carcinogenesis by retinoids.

In conclusion, in this commentary the possibility is raised that 5α-reductase inhibitors and (synthetic) retinoids may enhance rather than inhibit prostatic carcinogenesis and prostate cancer progression under certain conditions. It is therefore imperative that such potential chemopreventive agents be thoroughly tested in animal and *in vitro* models of prostate carcinogenesis, not only for their efficacy but also for the direction of their effect. For reasons given elsewhere [32], it is desirable to use several different animal models of prostatic carcinogenesis for this purpose. Since basically only one animal model is presently available for chemoprevention studies [32] and there are no adequate *in vitro* models of prostatic carcinogenesis, further development and characterization of such models is highly warranted. Furthermore, it will be essential in human prostate cancer chemoprevention trials to consider separately such factors as age, race, and genetic (familial) predisposition, since it is possible that they may, in part, determine whether chemopreventive agents cause inhibition or enhancement of prostate carcinogenesis.

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