On the Prevention and Therapy of Prostate Cancer by Androgen Administration

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Abstract

It has been widely suggested that elevated androgen levels may be critically involved in the genesis of prostate cancer. Despite the depend-ency of the normal prostate and of most prostatic cancers upon androgens and the fact that tumors can be produced in some rodent models by androgen administration, I will argue that, contrary to prevalent opinion, declining rather than high levels of androgens probably contribute more to human prostate carcinogenesis and that androgen supplementation would probably lower the incidence of the disease. I will also consider the possibility that the growth of androgen-independent prostate cancers might be reduced by the administration of androgens.

Introduction

It seems to be the prevailing opinion that the stimulation of prostatic tissue growth by higher than usual levels of androgen in aging human males provides an increased opportunity for mutation and so leads to an increased risk of prostate cancer (1). It is certainly true that the prostate will not develop without androgens and the gland will atrophy if androgen support is withdrawn. In some animal models, prostatic cancer can be produced and/or accelerated by androgen administration (2, 3). Furthermore, most prostatic cancers are, at least early in their progression, dependent upon androgens and regress if the patient is castrated. For these reasons, it is natural to suspect excessive androgen stimulation of the prostate to be a causative factor in prostatic carcinogenesis. However, despite extensive study, the data correlating the occurrence of prostate cancer in humans with increased androgen levels remain contradictory, and some studies have failed to detect any correlation (4). Bloods drawn at the time of tumor appearance tend to show low, not high, testosterone levels (5), and it has been reported that close relatives of prostate cancer patients tend to have testosterone levels that cluster at the low end of the normal range (6). However, in the largest and perhaps most convincing study favoring a role for high androgen levels in the etiology of human prostate cancer, Gann et al. (7) used stored bloods that had been drawn as much as 10 years prior to tumor appearance. Although their study showed "no clear associations between the unadjusted levels of individual hormones...and the risk of prostate cancer," there was a significant increase in prostate tumor incidence if the circulating testosterone had been above the mean, albeit within normal limits, whereas, in the same blood, the serum hormone-binding protein had been somewhat low (7).

The relationships of androgenic hormones to prostatic tissue growth are complex. It has long been known, as reviewed by Davies and Eaton (8), that androgen fails utterly to stimulate prostatic DNA synthesis and cell proliferation in vivo if the prostate is of normal size and unatrophied. To quote Bruchovsky et al. (9) "...a vital factor determining the proliferative response of the prostate to androgens is the number of cells in the gland relative to normal. When this number is normal, ...a proliferative response to androgens is not observed, although androgen is able to induce a large increase in tissue weight due to stimulation of secretory activity. Tissues that contain fewer than the normal number of cells respond to hormone administration by proliferating rapidly, but once the number of cells has returned to normal the rate of proliferation declines sharply." How this regulation is mediated is not clear (8), but, whatever the mechanisms may be, it seems, given these facts, doubtful that moderate androgen excess per se, even over a long adult lifetime, would provide, in the normal prostate, a greater opportunity for the occurrence of cancer-causing mutations.

A different hypothesis, that I shall put forward in this paper, is that declining androgen levels play a causative role in prostatic carcinogenesis. The hypothesis is based, in large part, upon the fact that prostatic-tumor incidence is the most age dependent of any tumor incidence: the incidence rises as the 9th or 10th power of age (10, 11). Simultaneously, as individuals age and the risk of prostate cancer rises, the androgen levels fall (12-14). Thus, the older the individual, the greater is the risk of prostate cancer and the lower is the level of androgen, a relationship that argues that an unusually high androgen level may not be a causative factor in the origin of a prostate cancer. This relationship between prostate cancer and aging suggests that it may be a falling rather than an elevated level of androgen that facilitates prostate oncogenesis. The mechanism by which a falling androgen level may be instrumental in the genesis of prostate cancers probably involves compensatory hyperplasia.

Compensatory Hyperplasia

The declining level of androgen as the male ages is correlated with varying degrees of atrophy in the prostate (9), which may or may not be causally related to the common lesion of older men called benign prostatic hypertrophy or hyperplasia. Benign prostatic hypertrophy seems to be unrelated to the genesis of prostate cancer because it occurs in areas of the gland not usually subject to cancer. However, and directly related to cancer, there is probably, as a result of the atrophy associated with aging, selection throughout the prostate for surviving cell populations that are less dependent upon androgens; foci of these surviving cells probably undergo a form of compensatory proliferation. The factor whose loss in the atrophic prostate gland is compensated by the new and better adapted cell populations has not been identified, but the discovery of that factor would seem to be of the utmost urgency. Continued and ever-increasing selection pressure in an environment of declining androgen levels can be expected to result in hyperplastic foci more resistant to atrophy, increasingly less dependent upon androgens to support their growth, and more susceptible to oncogenic changes. The end of this process is seen in the progression of prostate cancers from androgen dependency to androgen independency, accompanied by greater malignancy. The thesis that declining levels of androgen may contribute to the growth of prostatic carcinoma suggests that prostatic cancers that are associated with severe testicular atrophy and the consequent severe fall in testosterone levels might have an unusually poor prognosis. This prediction has recently been confirmed by Daniell (15), who reported that men whose testes were severely atrophic at the time of therapeutic orchectomy for prostate cancer generally had a bad prognosis (15).
The probability that cancer may often originate in an area of “clonal adaptation” (16, 17) and compensatory hyperplasia is not a new idea, although it may not have been emphasized in the case of prostate cancer (18, 19). There is much evidence, for example, concerning the role of clonal adaptation in the evolution of cancer of the liver (16) and the principle may be quite general (20). Toxicity appears to be a common attribute of chemical carcinogens so it may be that most cancers arise in tissues damaged by age and/or by toxic agents; i.e., they usually arise under those conditions in which one might expect compensatory hyperplasia (21) and, thus, an increased risk of mutation and perhaps of eventual development of a mutator phenotype (22).

One question related to the role of androgens is to what extent the growth of a clinically evident prostate cancer is still driven by the same mechanisms of compensatory hyperplasia that I postulate were instrumental in its origin. In the normal prostate, compensatory growth that is dependent upon androgen proceeds until normal size (presumably function) is restored and then stops (9). A tumor, at least early in its progression and, in some cases, even after many transplant generations, retains the property of slowing its growth as its mass increases and the unknown functions, which are presumably compensated by the tumors growth, are elevated (23). If the prostate is still available to respond to exogenous androgen administration, the restored normal gland plus whatever function the tumor may still supply might be sufficient to remove the stimulus to compensatory tumor cell proliferation. This control mechanism, if it exists, would not be compromised even if the tumor were divided by metastasis into many parts; the tumor would still function as a single organ (24). However, because a tumor responds to normal growth controls imperfectly and the normal gland cannot enlarge beyond its normal size, it might take an immense tumor mass to produce enough excess function to stop compensatory tumor growth (23). Consequently, androgen supplementation with the goal of eliminating this compensatory type of stimulation to tumor growth may not be practical. Nonetheless, as I will explain shortly, androgen supplementation may still have a place in therapy.

**Biphasic Action of Androgen**

Not only is the oncogenic process begun in an environment of falling androgens, but tumor growth can apparently be inhibited by androgen excess. According to Sonnenschein et al. (25), androgen may not be directly stimulatory to prostatic growth; rather, physiological levels of androgen are thought to block a serum inhibitor of the prostates intrinsic proliferative potential. However, high levels of androgen are themselves inhibitory and, apparently, shutoff this proliferative mechanism. These authors concluded that “the development of an androgen-dependent tumor is probably due to a defective shutoff mechanism; this will allow proliferation to occur in the presence of androgen concentrations otherwise sufficient to trigger the shutoff mechanism in normal cells” (25). A study of the genes involved in the shutoff of proliferation by excess androgen has begun (26), and current evidence suggests that the shutoff mechanism is mediated through the androgen receptor (27). Other authors have also described the inhibition of prostate cancers by excess androgen under experimental conditions (28–31). The biphasic response of prostate cancer to androgen is but one of the many intriguing analogies between prostate and breast (32); in the breast, estrogen also may either promote or inhibit tumor growth, depending upon dosage (32).

Thus far, I have emphasized the probable role of declining androgen levels. How can this hypothesis be reconciled with the evidence, derived from tests in rats, that androgen administration, can, in some genotypes, increase the incidence of prostate or seminal vesicle tu-

**Evolution of the Tumor Phenotype**

It follows from above that there may be two types of prostate cancer that can, perhaps, be distinguished by different phenotypes. Some tumors and probably most human tumors arise in an androgen environment that is below the level that had been normal for the individual with the tumor. Others, particularly those rodent tumors that are produced in animals subjected experimentally to exogenous androgen, arise in an environment that is high in androgen. The two types of tumor will, therefore, be subjected to different selective pressures, and this can be expected to produce different tumor phenotypes. Among the tumors arising in a declining androgen environment, the selective pressure should be toward an ever-increasing lack of dependency upon androgens for the tumors continued growth, but there would be no selection for cells better able to withstand the normal growth-inhibitory action associated with very high androgen levels. Conversely, tumor progression among tumors that evolve in a high androgen environment would be toward resistance to the inhibitory effects of excessive androgen, but there would be no selection toward an ability to grow in the absence of androgen.

Most human cancers seem to progress toward androgen independence. Indeed, they could hardly do otherwise, once therapy by castration and an androgen blocker such as flutamide is initiated, but the process probably starts with the declining androgen levels associated with aging. However, in those rodent models in which prostate cancer is produced or accelerated by testosterone administration, applications of DHT, a hormone that is twice as effective in stimulating prostate tissue as is testosterone (9), can, in the same system, prevent tumor appearance (2). This prevention occurs only if the DHT is given early in the oncogenic process before overt tumors have appeared (2). Therefore, tumor progression among these rodent tumors is demonstrably toward resistance to the inhibitory effect of excess androgen, in this case, DHT.

**Prevention and Therapy**

If my thesis that most human tumors originate as a consequence of the decline in androgen levels that occurs with aging were correct, androgen supplementation beginning early in the middle years might, among other possible benefits, largely prevent prostate cancer. Perhaps the biggest problem with the use of androgens as a preventive modality and especially as a therapeutic modality is finding the courage to study the possibility. Given the fear that androgens may accelerate the growth of prostate cancer, how can there be ethical studies? I think the problem, at least in the case of prevention, may be overcome now that the growth of most tumors can be monitored rather exactly by the change in PSA. Therefore, preventive androgen supplementation in an aging population that is carefully monitored by repetitive PSA determinations might be performed with little risk.

The tumor-inhibitory action of excess androgen in a variety of

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2 The abbreviations used are: DHT, dihydroxytestosterone; PSA, prostate-specific antigen.
experimental contexts suggests the possibility that exogenous androgen administration might at times be useful as therapy. The possible value of androgen as therapy has heretofore not been satisfactorily tested. However, in a very difficult to evaluate retrospective trial of low dosages of exogenous testosterone, 45 of 52 patients were reported to have had an “unfavorable” response, as judged in large part by subjective means or by a rising serum acid phosphatase (33), and another study noted considerable toxicity when androgen was given for 3 days prior to chemotherapy (34); thus, optimism must be tempered. Nonetheless, there exist a number of small clinical studies, performed before the days of PSA and usually with small dosages of androgen, that suggest that many prostatic tumors were not stimulated and at least some were definitely inhibited by treatment with exogenous androgen; the responses were extremely variable (35–39).

At least one experimental prostate cancer model beautifully supports the androgen as therapy concept (40); after culture of the LNCaP 401-S human prostate cancer cell line for over 100 passages in androgen-depleted medium, the line, whose growth in nude mice had originally been stimulated by physiological concentrations of androgen, was now repressed by even very low androgen levels. Thus, the possibility exists that the ultimate evolution of a prostate cancer in a severely androgen-deficient animal or human may be a tumor that requires little or no androgen for growth but that cannot grow if the androgen level is sufficiently high.

Currently, the mainstay of therapy for prostatic cancers that cannot be removed is androgen ablation via chemical or physical castration and often supplemented by an androgen blocker such as flutamide. However, tumor progression, under this selective pressure, leads, following early remission, almost inevitably to a recurrent tumor that can grow in the near total absence of androgen. It is at this point that the possibility of therapy with exogenous androgen might be considered.

It has become the accepted practice to withdraw flutamide as soon as a rising PSA signals that cancer growth is recurring, despite maximally suppressed androgen levels. Some 20–30% of tumors undergo temporary regression in response to flutamide withdrawal (41). The mechanism of this effect may depend upon an alteration in the androgen receptor enabling the tumor to use flutamide itself as a growth-stimulating androgen (42). Alternatively, the possibility exists that, in analogy with the previously described LNCaP 104-R2 (40), some tumors may have reached a stage of progression at which even a slight rise in the effective levels of androgen, as might be produced by flutamide withdrawal, is directly inhibitory. At this point in the course of the disease the prognosis is already poor and a vigorous supplementation with androgen, added to the flutamide withdrawal, is directly inhibitory. At this point in the course of the disease the prognosis is already poor and a vigorous supplementation with androgen, added to the flutamide withdrawal, could probably be tried with little danger. Given the probability, especially after androgen ablation therapy, that most tumors will have evolved a phenotype that is not resistant to the inhibitory effects of excess androgen, the chance of a favorable response may be good. If the PSA did not respond as desired after a reasonable trial, the supplementation could be stopped and little, if any, harm would probably be done.

Conclusions

In sum, it seems reasonable to hypothesize that most human prostatic cancers are caused, at least in part, by the decline in androgen levels that are a by-product of aging and that the tumors might be prevented by a very modest androgen supplementation. This supplementation should probably not be permitted to raise the androgen levels above those found in normal young adults for fear of promoting tumors in men with unusually susceptible genotypes, as occurs in the androgen-treated Lobund-Wistar rat model (2), nor should administration be begun in older men in whom incipient cancers may already be present.

To the extent that racial differences in the incidence of prostate cancer (low in Japanese but high in blacks; Refs. 43 and 44) have a hormonal basis, the differences may be caused by the magnitude of the androgen decline with age. The thesis I have advanced here suggests that it may be the prostatic atrophy that results from a decline in androgen levels, and the resultant compensatory hyperplasia that increases the risk of cancer formation. It may not be the initial level of androgen that is important but rather the magnitude and/or the rapidity of the age-related decline. However, even if a somewhat higher than the mean free testosterone level, many years before the appearance of a tumor, were found to be associated with an increased risk of prostate cancer, as is suggested in the work of Gann et al. (7), it would not necessarily mean that the rate of androgen decline with age was not also important in determining the cancer incidence. The two hypotheses to explain a higher incidence of prostate cancer, i.e., the higher androgen levels hypothesis and the falling androgen levels hypothesis are not mutually exclusive. It is possible that, although the initial steps on the road to prostate cancer may be dependent upon falling androgen levels in an aging population, the resulting androgen-dependent tumors may grow faster in those individuals whose age-reduced androgen levels remain, nonetheless, somewhat higher than the age-specific norm.

Most importantly, androgen-independent tumors that have escaped the inhibition provided by androgen ablation therapy, might often be inhibited, at least temporarily, by high levels of androgen supplementation, the highest that can be maintained without unacceptable side effects. In the human LNCaP 104-R2 tumor line, which is inhibited by even low levels of testosterone, growth in the presence of androgen sometimes produces a slow reversion to a tumor type that is once again dependent upon androgen (40). Thus, it seems possible that many prostate cancers might be kept under control, perhaps indefinitely, by alternating androgen ablation and high androgen supplementation as the phenotype of the tumor adjusts to these opposite therapeutical extremes. Perhaps the time has come for courage and a definitive trial of high-dose DHT or other androgens in the treatment of those prostate tumors that are no longer inhibited by androgen deprivation.

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References

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