Getting Over Testosterone: Postulating a Fresh Start for Etiologic Studies of Prostate Cancer

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Assessing progress in our understanding of prostate cancer etiology is difficult, although it is certainly clear that we have much to learn. Despite a substantial research investment spanning dozens of years, prostate cancer remains as enigmatic as it is burdensome. We know that increasing age, African American race, residence in a Western nation, and family history are associated with increased prostate cancer risk, although we have yet to identify risk factors that are of substantial magnitude and are amenable to preventive intervention. This is not due to a lack of candidates, including a multitude of environmental, lifestyle, or nutritional factors (1).

Among endogenous factors, elevated androgen levels have been persistently associated with prostate cancer despite previous literature reviews pointing to a dearth of supportive epidemiologic evidence (2,3). The intense and sustained interest in confirming an androgen-driven hypothesis likely arises from the key role that androgens play in normal prostate development and from Huggins’ Nobel Prize–winning observation that suppression of testosterone in men with advanced prostate cancer can lead to dramatic regression of the disease (3,4). An androgen etiology of prostate cancer would have immediate implications for prevention, such as screening for higher androgen levels and, if elevated, subsequent use of more systematic or intensive screening and possibly specific strategies or medications to lower androgen levels.

Dihydrotestosterone-suppressing 5α-reductase inhibitors remain a tantalizing possibility for effective prostate cancer chemoprevention, even without a link between prostate cancer and androgen level. However, results from the Prostate Cancer Prevention Trial temper potential preventative benefits with possible perils for men using finasteride. This prevention trial of 18,882 men found an association between finasteride and a 25% reduction in prostate cancers, although it also found a simultaneous increase in high-grade prostate cancers (5). Ironically, the hypothesis that provided the theoretical foundation for the Prostate Cancer Prevention Trial has been convincingly debunked in the accompanying article by the Endogenous Hormones and Prostate Cancer Collaborative Group (6). The group’s findings suggest an underappreciated difference between excess prostate cancer risk conferred by elevated endogenous androgen levels and prostate cancer risk reduction from drug-induced suppression of androgens among men who may have low or normal androgen levels.

In this issue of the Journal, the Endogenous Hormones and Prostate Cancer Collaborative Group (6) presents an impressive pooled analysis examining the widely hypothesized link between circulating levels of sex hormones and prostate cancer risk. Analyzing 18 prospective studies of 3886 men with prostate cancer and 6438 control subjects, the authors use conditional logistic regression to determine that there are no associations between prostate cancer risk and serum concentrations of testosterone, calculated free testosterone, dihydrotestosterone, dehydroepiandrosterone sulfate, androstenedione, androstanediol glucuronide, estradiol, or calculated free estradiol and that there is a modest inverse association for sex hormone–binding globulin. This collaborative research project is commendable on a number of levels.

The study is an impressive example of collaboration and coordination among 18 research groups and dozens of research centers spanning the globe—a heartening display of scientific collaboration. By combining the data from their unique efforts, they are able to examine an important issue to a degree that extends beyond the capability of any one study. Lending strength to its findings, this analysis examines only studies including prediagnostic serum samples from case patients with prostate cancer. Because prostate cancer can influence hormone levels in men, the exclusion of studies of men already diagnosed with the disease helps to prevent confusion between the cause and effect of higher hormone levels and prostate cancer.

Perhaps related to the issue of excess risk from elevated hormone levels vs reducing risk through hormone suppression among those with low-to-normal levels, the factors that promote localized or nonaggressive prostate cancer may be entirely different than those that promote fast-growing, high-grade prostate cancers. Because most of the cancers included in these studies were localized and low grade, pooling data from many studies allowed a sample size that was large enough to perform subanalyses of advanced and high-grade cancers and the power to investigate interactions among hormones and sex hormone–binding globulins.

This study is not without limitations. The main analysis presented pooled data from these 18 different studies. To standardize the data, participants in each study were divided into quintiles that were assigned values of 0, 0.25, 0.5, 0.75, and 1. Such categorization and subsequent analysis of the data as if it were continuous may have underestimated the error in their models. The analysis also assumes that the association between the androgens and

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prostate cancer incidence is the same across the studies—that the extra risk associated with being in the top quintile vs the bottom quintile is the same among men in Washington County, MD, in 1974 and in Japanese men in 1990 (7,8). However, the authors also performed a meta-analysis (see their online supplementary figures), in which individual study results were summarized and similar results were found.

What is most intriguing about prostate cancer is the evidence of modifiable environmental factors that exert a potentially strong effect on risk. Despite the concerted efforts of so many, we are still searching for the framework with which to understand this risk. Perhaps it is time for research efforts to focus instead on developing more sophisticated hypotheses and novel study designs that can be simultaneously comprehensive, meaningful, acceptable, and practical.

This study’s methodology provides a good example of how we might pursue the development and examination of these new hypotheses, which may be especially important now that we have exited the era of budget doubling for the National Institutes of Health (NIH). Through the NIH Roadmap and National Cancer Institute–specific initiatives, we are developing information technology infrastructure and biospecimen banking systems enabling research to maximize the potential contribution of any one participant or research site. These systems may facilitate pooled analyses similar to that performed by the collaborative group, thus allowing the efficient and expeditious preliminary exploration of a broad array of novel hypotheses while reserving use of large, expensive primary data collection efforts for the evaluation of potential prostate cancer risk factors with strongly suggestive preliminary data.

The international collaborative effort by this group represents progress in our understanding of prostate cancer epidemiology and introduces an opportunity. By confirming the lack of evidence to support an androgen–prostate cancer hypothesis, the study obliges the scientific community to move past a seductive, clinically relevant, and biologically plausible hypothesis and get on with the difficult task of exploring, analyzing, and characterizing modifiable risk factors for prostate cancer.

References