Do Diet and Androgens Alter Prostate Cancer Risk via a Common Etiologic Pathway?

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Among the numerically most important cancers in the United States, prostate cancer was until recently by far the least studied epidemiologically, and there were few clues as to etiology and pathogenesis. Even now, the only widely accepted risk factors for prostate cancer are age (among all cancers, prostate is the most strongly related to aging) and race–ethnicity (African-American men have by far the highest prostate cancer rates in the world, whereas Japanese and Chinese men native to those countries have the lowest; there is a roughly 30-fold difference in risk between these two extremes) (1). The past 2 years have seen a flurry of activity in this field, however, so that now we are positioned to further our understanding of the etiology of this disease on several fronts. The strong familial component to risk has recently been much better characterized (2) and will likely lead to serious efforts among molecular geneticists and genetic epidemiologists to identify a prostate cancer gene—similar to the efforts under way to identify and characterize genes predisposing to colon and breast cancer. A number of ongoing studies are attempting to better understand the reproducible association between vasectomy and prostate cancer risk. A recent report (3) has suggested a strong inverse relationship between circulating levels of the active form of vitamin D, 1,25-dihydroxyvitamin D, and prostate cancer development. Further studies of this relationship are ongoing, and, if confirmed, future studies likely will focus on determinants of 1,25-dihydroxyvitamin D levels, which seem largely unrelated to diet or to sunlight exposure. The molecular genetics of prostate cancer development are also now being vigorously pursued. The high prevalence of allelic loss of the short arm of chromosome 8 in prostate cancer tissue has suggested that a tumor suppressor gene might be located there (4). However, no areas of current research have generated greater interest or have greater implications for understanding strategies to prevent prostate cancer than do those of the relationships between hormonal and dietary factors and prostate cancer risk.

Harvard epidemiologists have contributed greatly during the past decade to improving methods for assessing diet and measuring the relationship between dietary factors and chronic disease development. Two reports (5,6) from Harvard investigators, including one in this issue (6), have together provided the most detailed evaluation to date on the relationship between dietary fat and components of fat and prostate cancer risk. These studies are not the first to link prostate cancer to fat intake. This link has been one of the most consistently reproducible findings in the diet and cancer epidemiologic literature (7). Despite this consistency, the association, to date, has not been totally convincing because these studies have varied in attention to methodologic detail. Not all investigators have selected an appropriate comparison group; others have had an insufficient sample to accurately estimate risk; and many have inadequately measured individual diet histories.

Both new studies (5,6) suggest a relationship between prostate cancer and animal fat consumption (especially from red meat) and, independently, an association with the essential fatty acid, α-linolenic acid. Despite the general consistency in results between the studies, many important issues are unresolved in establishing either association as causal. In particular, neither study provides evidence of a clear dose–response relationship between the increasing intake of either component of fat and the increasing risk of prostate cancer; in both studies the associations with fat seem limited to very advanced disease. Most importantly, we have no established mechanism to explain how these components of fat might contribute to prostate cancer etiology.

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See "Notes" section following "References."
There are compelling reasons to believe that androgens are also intimately involved in prostate cancer pathogenesis. Advances in molecular biology have demonstrated that for a cell to change from normal to a malignant phenotype requires the activation of one or several proto-oncogenes and/or the inactivation of one or several tumor suppressor genes. Activation of proto-oncogenes and inactivation of tumor suppressor genes can occur through a number of mechanisms, but all require cell division. Cell division in the prostate is controlled by testosterone after intracellular conversion to its reduced form, dihydrotestosterone. This conversion is metabolically controlled by a single enzyme, 5-alpha reductase. Some evidence suggests that the racial-ethnic variation in prostate cancer is due, in part, to underlying differences in androgen secretion and metabolism. Young adult African-American men have at least 10% higher circulating testosterone levels than young adult white men, a difference that, if sustained over an extended period, is probably sufficient to explain the 60%-70% higher prostate cancer rates in older adult African-Americans compared with whites (8). Both native Japanese and native Chinese men appear to have substantially lower 5-alpha reductase activity than U.S. whites or African-Americans, a difference that could explain a substantial part of the very low prostate cancer rates observed in these populations. The epidemiological evidence that variation in expression of 5-alpha reductase explains some population differences in prostate cancer incidence provided an important rationale for the ongoing national prostate cancer chemoprevention trial using finasteride, a 5-alpha reductase inhibitor.

At face value, the hormonal and dietary fat relationships with prostate cancer seem disparate and without a common etiologic pathway. However, as noted by the two Harvard investigative teams (5,6), there are several common threads that might tie together these two distinct etiologic hypotheses. In considering the roles of hormones and diet, it is important to recognize that the marked racial-ethnic differences in prostate cancer incidence are already apparent for men in their early 40s (when prostate cancer incidence begins to increase), therefore the etiologic factors responsible for these differences must begin early in life. There is no dramatic shift in prostate cancer incidence among those who migrate to the United States from low-risk areas; on the contrary, rates gradually shift toward those of U.S. whites and African-Americans over a series of generations. This pattern contrasts with that for colon cancer (another cancer related to animal fat consumption) for which rates shift rapidly even when migration occurs in adulthood. Rather than supporting a strong and rapidly acting promoting effect of diet, these demographic characteristics suggest far more gradual influences.

In our model illustrated in Fig. 1, we propose that diet can alter steroid hormone profiles and thereby modify prostate cancer risk throughout life. The model suggests that diet-regulated hormonal influences first occur in utero. We have demonstrated that African-American women have much higher first-trimester testosterone levels than do white women (9). We have speculated that these high testosterone levels contribute to the high rates of prostate cancer in their male offspring, possibly by their impact on the hypothalamic-

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**Fig. 1.** Model of prostate cancer pathogenesis. T = testosterone; DHT = dihydrotestosterone.
pituitary–testicular feedback system, the gonadostat, such that higher circulating levels of testosterone occur in African-Americans compared with whites. A closely related event, the onset of puberty, is also earlier in African-American females (and presumably males) than in their white counterparts (10), and native Japanese and Chinese women have a delayed menarche (11). Dietary factors (increased ratio of energy intake to expenditure) may well further accelerate the onset of puberty in males as well as females.

There is some evidence that reduction in dietary fat in adulthood will reduce circulating testosterone levels, therefore low dietary fat in adulthood might further alter prostate cancer incidence. Our model suggests that altered expression of 5-alpha reductase will also modify prostate cancer risk, and Gann et al. (6) suggest that this may be yet another target of dietary fat. Finally, our model allows for the possibility that some other dietary component, such as fiber, might be the important component that alters risk rather than fat per se. Fiber can reduce reabsorption of steroid hormones excreted through the biliary tract.

Cross-cultural studies that can exploit and refine the relationship between diet (whether total calories, animal fat, or fiber) and the cumulative lifetime production of testosterone and dihydrotestosterone should provide valuable insight into the issues we have addressed. Although pharmacologic intervention in adult life is a reasonable approach to prostate cancer prevention at this stage of our knowledge, dietary interventions early and continuously in life may well hold the greatest hope for reducing the risk of prostate cancer.

References

Notes
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