Re: Endogenous Sex Hormones and Prostate Cancer: A Collaborative Analysis of 18 Prospective Studies

Steroid hormone concentrations do not appear to be associated with the risk of prostate cancer (1). A parallel disconnect between the laboratory and the disorder itself exists for acne, and a further parallel may extend to etiology. The link between dairy foods and acne, which was made originally by Bulkley in 1885 in 1500 patients, was confirmed by Fisher (2) in his 1965 study of 1000 patients. Recent work (3,4) links acne with diet in two ways—through its association with skim milk and dairy products (presumably by supplying exogenous androgen precursors) and through high glycemic load diets (presumably by inducing supraphysiological levels of insulin-like growth factor 1 and thus raising testosterone availability). Darling et al. (5) identified testosterone, progesterone, and two 5α-reduced dihydrotestosterone precursors (5α-androstanedione and 5α-pregnanedione) in cow milk. Associations between prostate cancer and dairy have been reported (6), but what thread links all four—that is, prostate cancer, acne, dairy, and exogenous precursors and stimulators of androgen?

The enzymes that convert dairy precursors to dihydrotestosterone are located in both the pilosebaceous unit and prostate gland. Dihydrotestosterone appears to be the principal androgen responsible for both prostate and pilosebaceous growth. Some experts, however, consider that an age-related decline in the production of testosterone is responsible for loss of prostate homeostasis, which allows dihydrotestosterone to act as a carcinogen. I suggest that the chronic stimulation by dihydrotestosterone further destabilizes prostate homeostasis and thus increases the risk of prostate cancer.

Dietary androgens may have two roles. The first is as pathogens. The human prostate evolved in the absence of exogenous dairy androgens, and the negative feedback loop that controls endogenous glucocorticoids has no parallel inhibitory feedback loop for ingested 5α-reduced hormones and precursors (Figure 1). Their unopposed impact on pilosebaceous and prostate glands may explain the epidemiological associations of dairy with acne, prostate cancer, and even breast cancer. Androgens' second role may be to effect the persistence or recurrence of prostate cancer. The hypothesis of androgen-driven prostate cancer has led to use of specific strategies and medications to lower androgen levels, including orchi(d)ectomy and treatment with finasteride and dutasteride. However, metastatic prostate tumor cells contain enzymes that mediate intracrine production of dihydrotestosterone from precursors derived from dairy products; this dihydrotestosterone may support the survival of the tumor. Patients with metastatic prostate cancer often consume dairy products as an increasing percentage of the diet, and this practice may thus be more detrimental than beneficial.

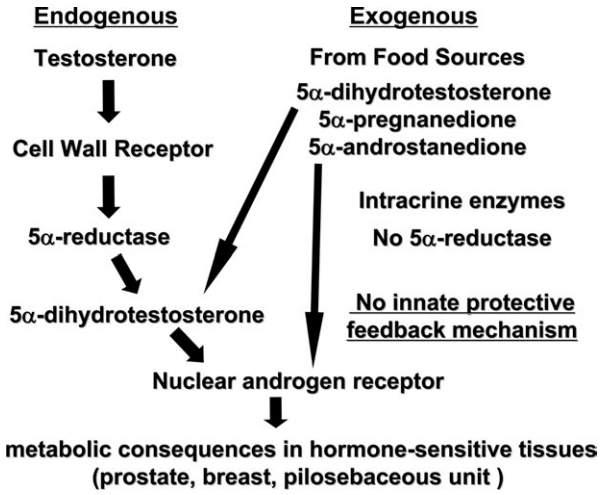

Figure 1. Pathways of androgen impact on prostate cells. Note absence of negative feedback mechanism.

We simply do not know which hormones, and how much, are in the food that we ingest. More effort has been directed at the investigation of illicit use of designer steroids by Olympians and ballplayers than to the investigation of the effect of dietary hormones on cancer and other diseases that affect millions.

Carpenter et al., in an editorial in the Journal (7), stated that they supported "reserving use of large, expensive primary data collection efforts for the evaluation of potential prostate cancer risk factors with strongly suggestive preliminary data." Consequently, I propose the establishment of a National Reference Laboratory for Hormones in Food to monitor levels of steroid and other hormones and growth factors in all dairy and meat-containing foods. Such a facility, funded as a national priority, will provide the capability to progress further in this field.

F. WILLIAM DANBY

References

1. Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst.* 2008;100(3):170–183.
2. Fisher JK. *Acne Vulgaris; A Study of One Thousand Cases.* 1966. Available from: http://www.acnemilk.com/fisher_s_original_paper.
3. Adebamowo CA, Spiegelman D, Danby FW, Frazier AL, Willett WC, Holmes MD. High school dietary dairy intake and teenage acne. *J Am Acad Dermatol.* 2005;52(2):207–214.
4. Smith RN, Mann NJ, Braue A, Makelainen H, Varigos GA. The effect of a high-protein, low glycemic-load diet versus a conventional, high

glycemic-load diet on biochemical parameters associated with acne vulgaris: a randomized, investigator-masked, controlled trial. *J Am Acad Dermatol.* 2007;57(2):247–256.
5. Darling JA, Laing AH, Harkness RA. A survey of the steroids in cows' milk. *J Endocrinol.* 1974;62(2):291–297.
6. Kurahashi N, Inoue M, Iwasaki M, Sasazuki S, Tsugane AS. Dairy product, saturated fatty acid, and calcium intake and prostate cancer in a prospective cohort of Japanese men. *Cancer Epidemiol Biomarkers Prev.* 2008;17(4):930–937.
7. Carpenter WR, Robinson WR, Godley PA. Getting over testosterone: postulating a fresh start for etiologic studies of prostate cancer. *J Natl Cancer Inst.* 2008;100(3):158–159.

Notes

Affiliation of author: Adjunct Assistant Professor of Medicine (Dermatology), Dartmouth Medical School, Hanover, NH.

Correspondence to: F. William Danby, MD, FRCPC, 721 Chestnut Street, Manchester, Hanover, NH 03104-3002 (e-mail: fwdljm@tds.net).

DOI: 10.1093/jnci/djn287