available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Re: Hendrik Isbarn, Jehonathan H. Pinthus, Leonard S. Marks, et al. Testosterone and Prosate Cancer: Revisiting Old Paradigms. Eur Urol 2009;56:48–56

Isbarn et al. [1] noted that there is a correlation between lower levels of testosterone (T) and more aggressive prostate cancer (PCa). This correlation is further evidence that the saturation model is an improvement over the previous model of PCa growth being dependent on serum T levels. The saturation model, however, offers no insight as to why this correlation exists. Understanding the mechanism behind this correlation is a key to understanding the relationship between T and PCa.

Intracellular androgen receptors (iAR) and membrane androgen receptors (mAR) tend to act in opposition to each other [2], with iAR downregulating strongly antiapoptotic proteins such as Bcl-2 and strongly proapoptotic proteins such as Fas and with mAR upregulating both Fas and, to a lesser degree, Bcl-2. Assuming that the correlation between higher levels of T and less aggressive PCa is caused by an increase in the rate of apoptosis, then there are three possible explanations. First, the key factor might be that increased T causes an increase in Fas. In this case, natural selection would favor those PCa cells with more iAR to lower the level of Fas. Next, the key might be the decrease in Bcl-2. In this case, PCa cells with more mAR would be favored. Finally, there might be no causality on the part of T, and the aggressiveness of the PCa or some independent mechanism might be the causal factor. In this case, there should be no major change in the number of androgen receptors. In fact, there are typically so many more mAR in PCa than in normal prostate epithelial cells that it has been suggested that the presence of significant numbers of mAR might be used as a diagnostic tool [3].

Assuming during the initial stages of PCa development that higher levels of T result in lower levels of Bcl-2 and that the more mAR present, the more Bcl-2 present, then it would be logical to assume that the highest levels of mAR would correlate with more aggressive PCa. In fact, this is exactly what was observed [4]. However, the relationship between increased mAR and increased PCa growth is nonlinear, so if there is too much agonism of mAR in relationship to iAR, such as can be created when T is used in conjunction with finasteride (a drug that blocks the conversion of T to dihydrotestosterone), then the PCa growth will decrease. This was observed in the LNCaP cell line [5].

All of the above suggests that if T is used early enough in the treatment of PCa, then high enough levels just might have the potential to eradicate the PCa. However, due to the increased levels of mAR observed when PCa is typically diagnosed, it is doubtful that the entire PCa population would be vulnerable to the proapoptotic effects of T at that time. Early diagnostic tools that enable PCa to be detected before evolution produces the increase in mAR may allow T to be utilized as an effective therapeutic agent.

Conflicts of interest: The author has nothing to disclose.

References

[1] Isbarn H, Pinthus JH, Marks LS, et al. Testosterone and prostate cancer: revisiting old paradigms. Eur Urol 2009;56:48–56.
[2] Friedman AE. Can a single model explain both breast cancer and prostate cancer? Theor Biol Med Model 2007;4:28.
[3] Stathopoulos EN, Dambaki C, Kampa M, et al. Membrane androgen binding sites are preferentially expressed in human prostate carcinoma cells. BMC Clin Pathol 2003;3:1.
[4] Dambaki C, Kogia C, Kampa M, et al. Membrane testosterone binding sites in prostate carcinoma as a potential new marker and therapeutic target: study in paraffin tissue sections. BMC Cancer 2005;5:148.
[5] Eggener SE, Stern JA, Jain PM, et al. Enhancement of intermittent androgen ablation by "off-cycle" maintenance with finasteride in LNCaP prostate cancer xenograft model. Prostate 2006;66:495–502.

A. Edward Friedman*
Department of Mathematics, 5734 S. University Ave., Chicago, Illinois, 60076, USA

*Tel. +1 773 702 3716; Fax: +1 773 702 9787
E-mail address: ed@math.uchicago.edu

June 25, 2009
Published online on July 3, 2009

DOI of original article: 10.1016/j.eururo.2009.03.088
 doi:10.1016/j.eururo.2009.06.033