

## Androgen Receptor-Dependent Variation in PSA—Letter

Mark R. Goldstein<sup>1</sup> and Luca Mascitelli<sup>2</sup>

The observational study by Bentmar Holgersson and colleagues (1) of a cohort of 40- to 79-year-old Caucasian men from the European Male Ageing Study, without prostate cancer at baseline, demonstrated that the 16% of subjects carrying the A-allele androgen receptor (AR) polymorphism compared with the 84% of subjects carrying the G-allele AR polymorphism exhibited a nearly 2-fold risk of having a serum prostate-specific antigen (PSA) concentration greater than 3 and 4 ng/mL, and yet were only one third as likely to be diagnosed with prostate cancer after 4 years. We believe that this paradox is possibly explained by the antiangiogenic properties of PSA (2).

Prostate-specific antigen expression is regulated by the AR (3). The physiologic role of PSA is to liquefy the seminal fluid, and its concentration in the seminal fluid is 10<sup>6</sup>-fold that of the serum, because the normal prostatic architecture keeps the PSA tightly confined and only a minute portion leaks into the circulation (3). *In vitro*, PSA inhibits endothelial cell proliferation, migration, invasion, and endothelial cell responses to the proangiogenic molecules fibroblast growth factor-2 and vascular endothelial growth factor (2). Autopsy studies have shown that latent prostate cancer is present in about 70%

of men in their 60s; in contrast, the lifetime risk of prostate cancer is 17% in the United States (3). Angiogenesis is a critical step in the progression of prostate cancer from early to advanced disease, and it is plausible that the locally high concentration of PSA in prostatic tissue inhibits angiogenesis and in part explains the indolent features of localized prostate cancer (4).

Moreover, 5 $\alpha$ -reductase inhibitors inhibit the conversion of testosterone to dihydrotestosterone, the active androgen in the prostate, resulting in a 50% decrease in serum PSA concentrations (3). Disturbingly, prospective randomized trials testing the benefits of 5 $\alpha$ -reductase inhibitors to prevent prostate cancer demonstrated that they increased the risk of high-grade prostate cancer by 2-fold (5). Perhaps, this occurred because the drugs decreased prostatic PSA concentration, enabling angiogenesis and the progression of advanced tumors.

Therefore, the A-allele AR polymorphism resulting in higher serum PSA concentrations and likely higher prostatic tissue concentrations might promote a local environment in the prostate that limits angiogenesis and the subsequent progression of localized prostate cancer to a more advanced clinically apparent disease. Finally, studies are needed to determine whether pharmacologically "increasing" local prostatic PSA concentrations can prevent prostate cancer progression to advanced local and metastatic disease in men of various races.

<sup>1</sup>NCH Physician Group, Naples, Florida. <sup>2</sup>Comando Brigata Alpina "Julia," Multinational Land Force, Medical Service, Udine, Italy.

**Corresponding Author:** Mark R. Goldstein, NCH Physician Group, 1845 Veterans Park Drive, Suite 110, Naples, FL 34109. Phone: 239-566-2382; E-mail: markrgoldstein@comcast.net

**doi:** 10.1158/1055-9965.EPI-14-1133

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## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received October 3, 2014; accepted October 7, 2014; published online January 13, 2015.

## References

1. Bentmar Holgersson M, Giwercman A, Bjartell A, Wu FCW, Huhtaniemi IT, O'Neill TW, et al. Androgen receptor polymorphism-dependent variation in prostate-specific antigen concentrations of European men. *Cancer Epidemiol Biomarkers Prev* 2014;23:2048–56.
2. Fortier AH, Nelson BJ, Grella DK, Holaday JW. Antiangiogenic activity of prostate-specific antigen. *J Natl Cancer Inst* 1999;91:1635–40.
3. Lilja H, Ulmert D, Vikers AJ. Prostate-specific antigen and prostate cancer: prediction, detection and monitoring. *Nat Rev Cancer* 2008;8:268–78.
4. Goldstein MR, Mascitelli L. Regarding prostate specific antigen: let's not shoot the messenger. *Q J Med* 2012;105:207–10.
5. Theoret MR, Ning Y-M, Zhang JJ, Justice R, Keegan P, Pazdur R. The risks and benefits of 5 $\alpha$ -reductase inhibitors for prostate-cancer prevention. *N Engl J Med* 2011;365:97–9.