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Induction of Prostate-Specific Antigen expression by synthetic progestins in patients with prostate and breast cancer

[Letters to the Editor]
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To the Editor: In the October 1997 issue of the Mayo Clinic Proceedings (pages 932 to 934), Wehbe and associates reported an interesting phenomenon of a patient with prostatic carcinoma whose serum prostate-specific antigen (PSA) level decreased precipitously after discontinuation of megestrol acetate (MA) treatment. The same phenomenon was described previously by Dawson and McLeod. [1] In an effort to explain this phenomenon, Wehbe and coworkers speculated that these prostate cancers may have acquired a mutation in the androgen receptor that results in its activation by nonandrogens, including the synthetic progestin MA. There is no proof or literature supporting the view that an androgen receptor mutation was responsible for the phenomenon observed in these patients, however.

Recently, my colleagues and I identified PSA expression by breast cancer cells. [2] Using a tissue culture system and breast carcinoma cell lines, we have shown that PSA can be up-regulated by progestins and androgens as well as by glucocorticoids and mineralocorticoids. [3] Furthermore, we have shown that breast tumors can be stimulated to produce PSA by the administration of MA at doses approximating those reported by Wehbe and associates. Serum PSA levels increase significantly in approximately 50% of women with metastatic breast cancer who receive MA treatment. [4] Similar to the data reported by Wehbe and colleagues and others [1] for prostate cancer, withdrawal of MA results in significantly decreased serum PSA levels in patients with breast cancer. These data demonstrate that MA can stimulate PSA production in both prostate and breast tumors by an as yet unknown mechanism. The phenomenon is certainly common, occurring in about 50% of patients with breast cancer. Our study with breast carcinoma cell lines shows that many other progestins, including cyproterone acetate, can stimulate PSA production. [3] We speculated that in patients who receive the antiandrogen-progestin cyproterone acetate for management of prostate cancer, measurement of serum PSA may be a misleading parameter of clinical response because cyproterone acetate may up-regulate PSA as a progestin and, at the same time, down-regulate PSA as an antiandrogen. [3]

We conclude that PSA regulation is not simply mediated through androgens alone but is likely a complex process involving the androgen, progesterone, and estrogen receptors. [3] The stimulating effects of MA on prostate cancer cells should not be regarded as unique or rare because they have also been noted in about 50% of breast cancer cells. Serum PSA concentrations should always be evaluated in light of the patient's treatment with steroid hormones, including progestins. An increasing PSA level in such patients may represent stimulation by the steroid hormones and have no correlation with the clinical condition of the patient.

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References

1. Dawson NA, McLeod DG. Dramatic prostate specific antigen decrease in response to discontinuation of megestrol acetate in advanced prostate cancer: expansion of the antiandrogen withdrawal syndrome. J Urol 1995;153:1946-1947

2. Diamandis EP, Yu H. New biological functions of prostate-specific antigen? [editorial]. J Clin Endocrinol Metab 1995;80:1515-1517

3. Zarghami N, Grass L, Diamandis EP. Steroid hormone regulation of prostate-specific antigen gene expression in breast cancer. Br J Cancer 1997;75:579-588

4. Diamandis EP, Helle SI, Yu H, Melegos DN, Lundgren S, Lonning PE. Prognostic value of plasma prostate specific antigen following megestrol acetate treatment in patients with metastatic breast cancer [submitted for publication].