

# THE LANCET

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## **Hydroxyflutamide may not always be a pure antiandrogen**

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Reprinted from THE LANCET Saturday 22 March 1997  
Vol. 349 No. 9055 Page 852

## Hydroxyflutamide may not always be a pure antiandrogen

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Prostate cancer has become the most commonly diagnosed cancer in US men.<sup>1</sup> Today most prostate cancers from patients treated with androgen ablation progress from an androgen-dependent to an androgen-independent state. With the cloning of the androgen receptor cDNA<sup>2</sup> and the discovery that some mutant androgen receptors may be able to change steroid and antiandrogen specificity,<sup>3</sup> the hypothesis that mutations in androgen receptors may be the reason why hydroxyflutamide, the active metabolite of flutamide, can activate androgen receptor target genes and stimulate (rather than inhibit) prostate cancer growth, is becoming widely accepted. The same mechanism has been used to explain the flutamide withdrawal syndrome, in which patients who experience an increase in prostate-specific antigen (PSA) while taking flutamide, have a decrease in PSA after withdrawal of treatment. Since this syndrome often heralds the failure of androgen-ablative therapy, elucidating the mechanism by which hydroxyflutamide increases the expression of PSA may provide a new approach to delaying or reversing the emergence of androgen independence.

The discovery of ARA70, the first co-activator for androgen receptor, and the observation that higher concentrations of hydroxyflutamide may have weak agonistic activity in the presence of ARA70,<sup>4</sup> has allowed us to investigate this phenomenon further. We present evidence that hydroxyflutamide can activate androgen receptor target genes, such as PSA and MMTV-LTR, in the presence of ARA70. While AR877 mutation may increase potency of hydroxyflutamide (figure, B, 7; C, 7), a mutated androgen receptor alone has only a small capacity to mediate hydroxyflutamide induction of PSA in DU145 cells (figure, C, 1-4). Our data suggest that in the absence of androgens, a condition similar to some of the later stages of prostate cancer under maximal androgen ablative therapy, hydroxyflutamide may become an agonist by inducing PSA in the presence of ARA70 and normal/mutant androgen receptor. This suggests that in addition to the androgen receptor, another factor, ARA70, may be required to enhance the agonistic activity of hydroxyflutamide.

These findings may raise some concerns about treatment of prostate cancer with supposedly pure antiandrogens in maximal androgen ablative therapy.<sup>5</sup> Finding molecules that interfere with the interaction between the androgen receptor and ARA70 may be valuable in delaying the emergence of androgen resistance.

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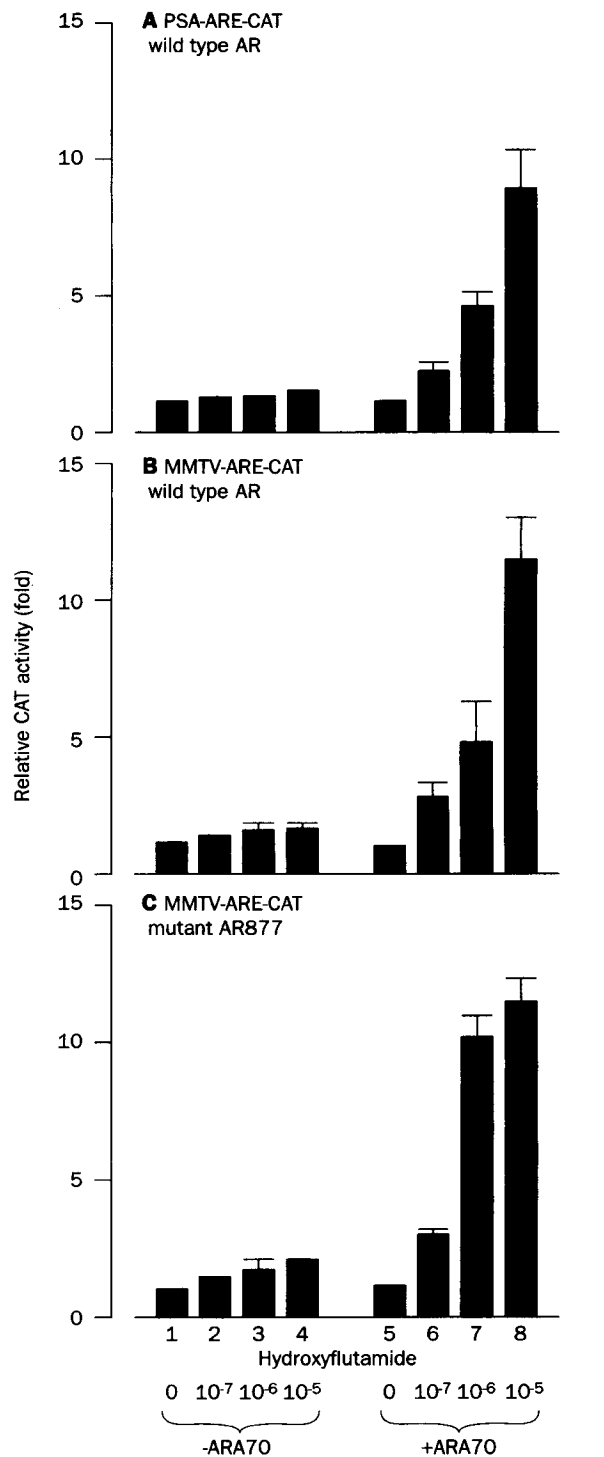
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4 Yeh S, Chang C. Cloning and characterization of a specific coactivator, ARA70, for the androgen receptor in human prostate cells. *Proc Natl Acad Sci USA* 1996; 93: 5517-21.

5 Chang A, Yeap B, Davis T, et al. Double-blind, randomized study of primary hormonal treatment of stage D2 prostate carcinoma—flutamide versus diethylstilbestrol. *J Clin Oncol* 1996; 14: 2250-57.

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### ARA70 and androgenic activity of hydroxyflutamide

A and B: 1.5  $\mu$ g wild-type hAR alone (columns 1, 2, 3, and 4) and co-transfected with 4.5  $\mu$ g ARA70 (5, 6, 7, and 8) in the absence or presence of 10<sup>-7</sup>, 10<sup>-6</sup>, 10<sup>-5</sup> mol/L of hydroxyflutamide. C the mutant AR877 was used to replace the wild-type AR to perform the same experiment on panel B. All experiments were performed in human prostate cancer DU145 cells cultured in DMEM with 5% charcoal-stripped fetal calf serum. In each transfection, 3.5  $\mu$ g of PSA-ARE CAT (A) or MMTV-ARE CAT (B and C) were used as a reporter. The mock treatment of lane 1 was counted as standard one-fold. Relative CAT activity was calculated by the quantitation of phosphorimager. Data represent an average of at least three experiments.