

Why Offer Testosterone Therapy After Treatment of Prostate Cancer?

Abraham Morgentaler, MD, FACS

Founder, Men's Health Boston

Associate Clinical Professor of Urology

Beth Israel Deaconess Medical Center

Harvard Medical School

WHY HAS PROSTATE CANCER BEEN AN ABSOLUTE CONTRAINDICATION TO T THERAPY?

- Raising T believed to increase rate of growth of PCa cells
- Like “pouring gasoline on a fire”
- Current data fail to support this view



Testosterone

Origin of the T Prohibition

- Castration caused PCa regression and T administration caused “enhanced rate of growth” of PCa

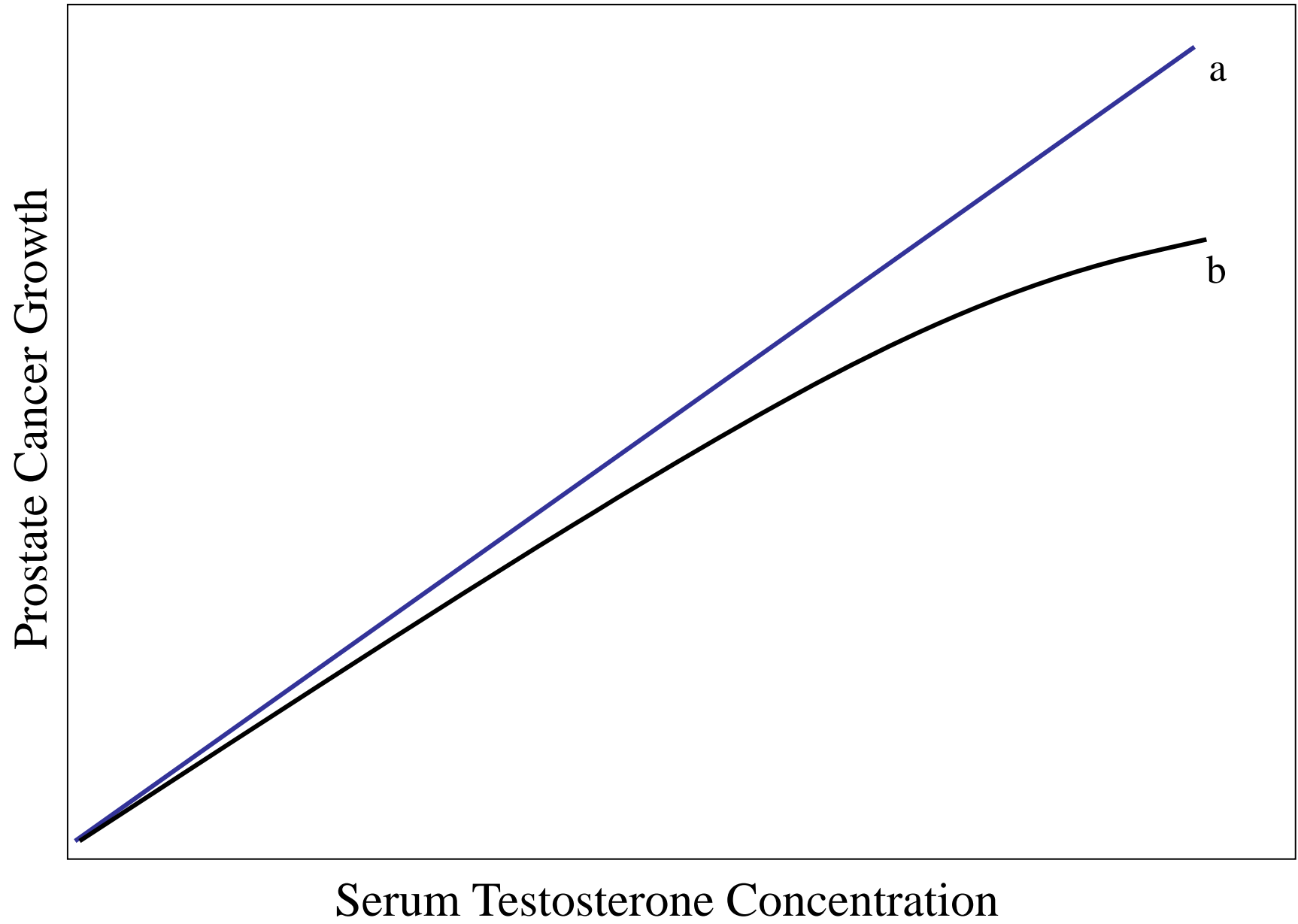
Huggins C, Hodges CV *Cancer Research* 1941; 1:293-7

- T administration caused progression or death within several weeks in 5/10 men with recurrent disease after castration

Prout GR, Brewer WR. *Cancer* 1967; 20:1871-8

- T admin caused “unfavorable response” in 45/52 men with metastatic PCa, most within 30 days

Fowler JE, Whitmore WF, Jr *J Urol* 1981; 126:372-5



Huggins and Hodges 1941

- Stated that 3 men received T injections
- Results given for 2 men
- One previously castrated- androgen-deprived
- Conclusion that testosterone caused “enhanced rate of growth” of PCa was based on a single patient

Prout and Brewer 1967

- 5/10 men with metastatic PCa progressed or died with T administration- all previously castrated
- 0/20 men if no castration or 6 with recent castration

RESPONSE OF MEN WITH ADVANCED PROSTATIC
CARCINOMA TO EXOGENOUS
ADMINISTRATION OF TESTOSTERONE

GEORGE R. PROUT, JR., MD, AND WALTER R. BREWER, MD*

Response to T injections:

“Most of these individuals experienced an increase in sense of well being and some noticed vague diminution of pain”

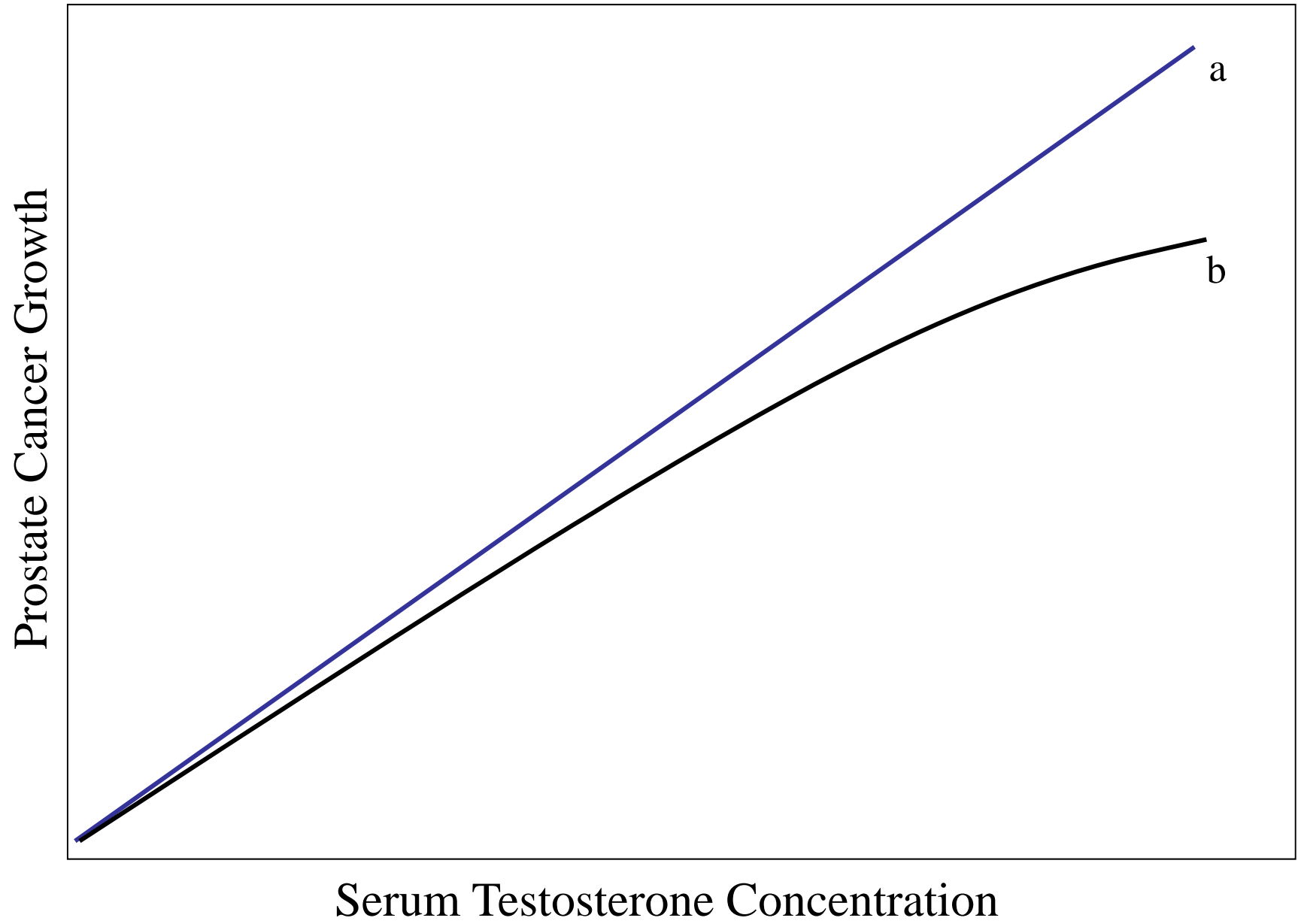
Prout and Brewer, Cancer. 1967; 20:1871

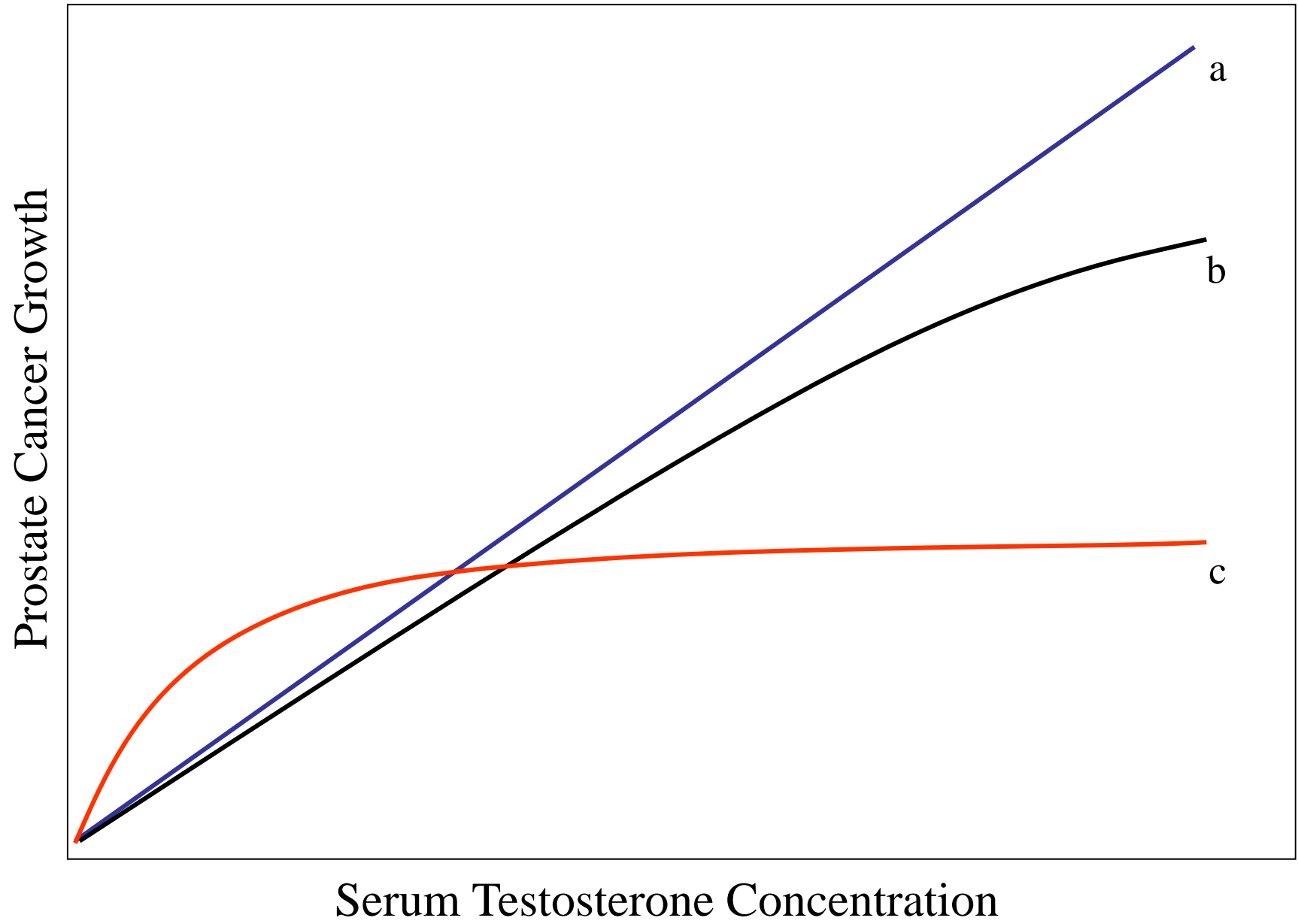
Fowler and Whitmore 1981

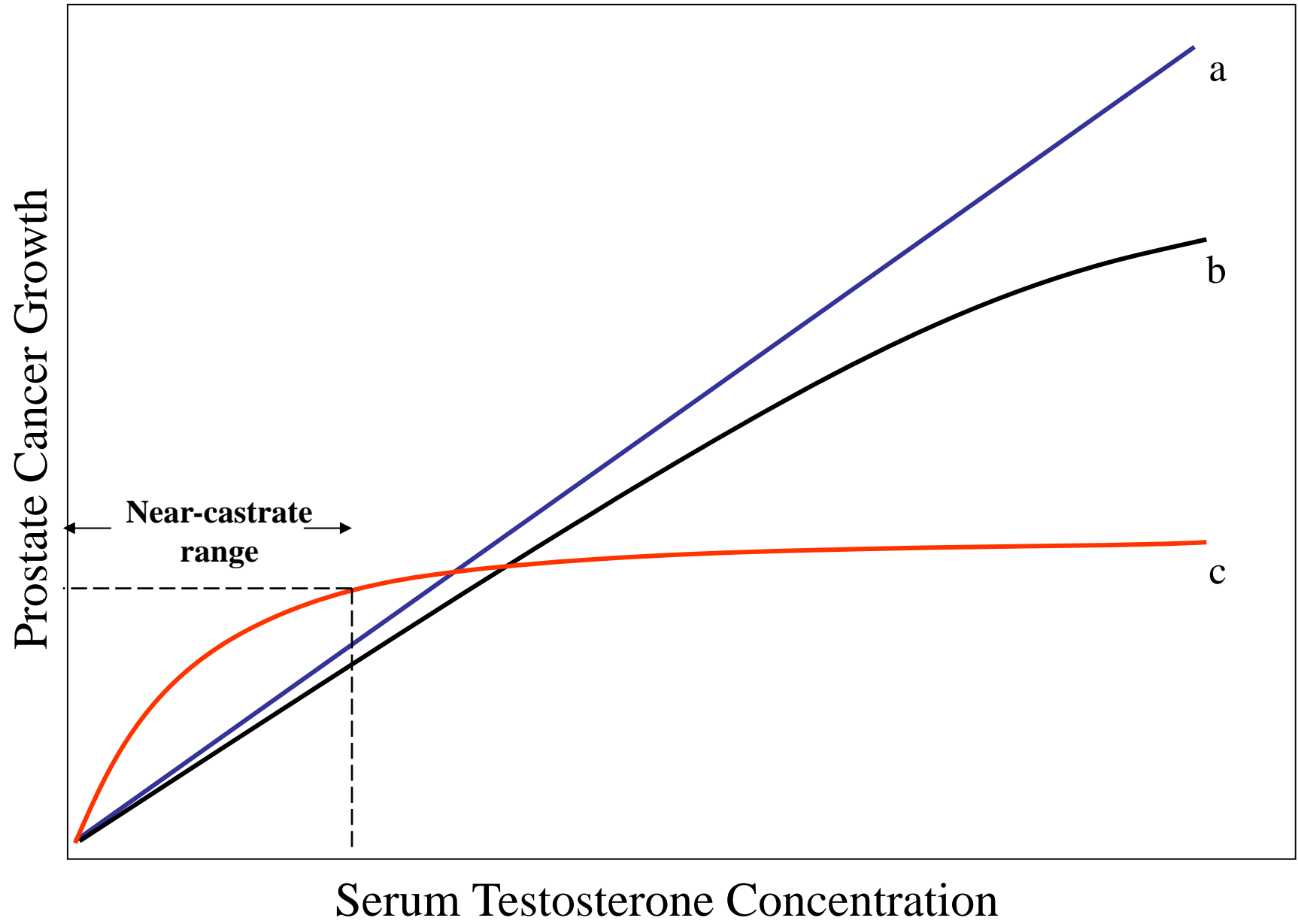
- 45/52 men with metastatic PCa with “unfavorable response” to T administration, most within 30 days
- All androgen deprived (castration or estrogen Rx) except 4 men
- 1/4 had “unfavorable response” within 30 days
- Remaining 3 received daily T injections for 52, 55, and 310 days, without negative effects

Impact of T Injections In Men With Metastatic PCa

- Castrated men- Bad outcomes
- Hormonally intact men- Benign outcomes

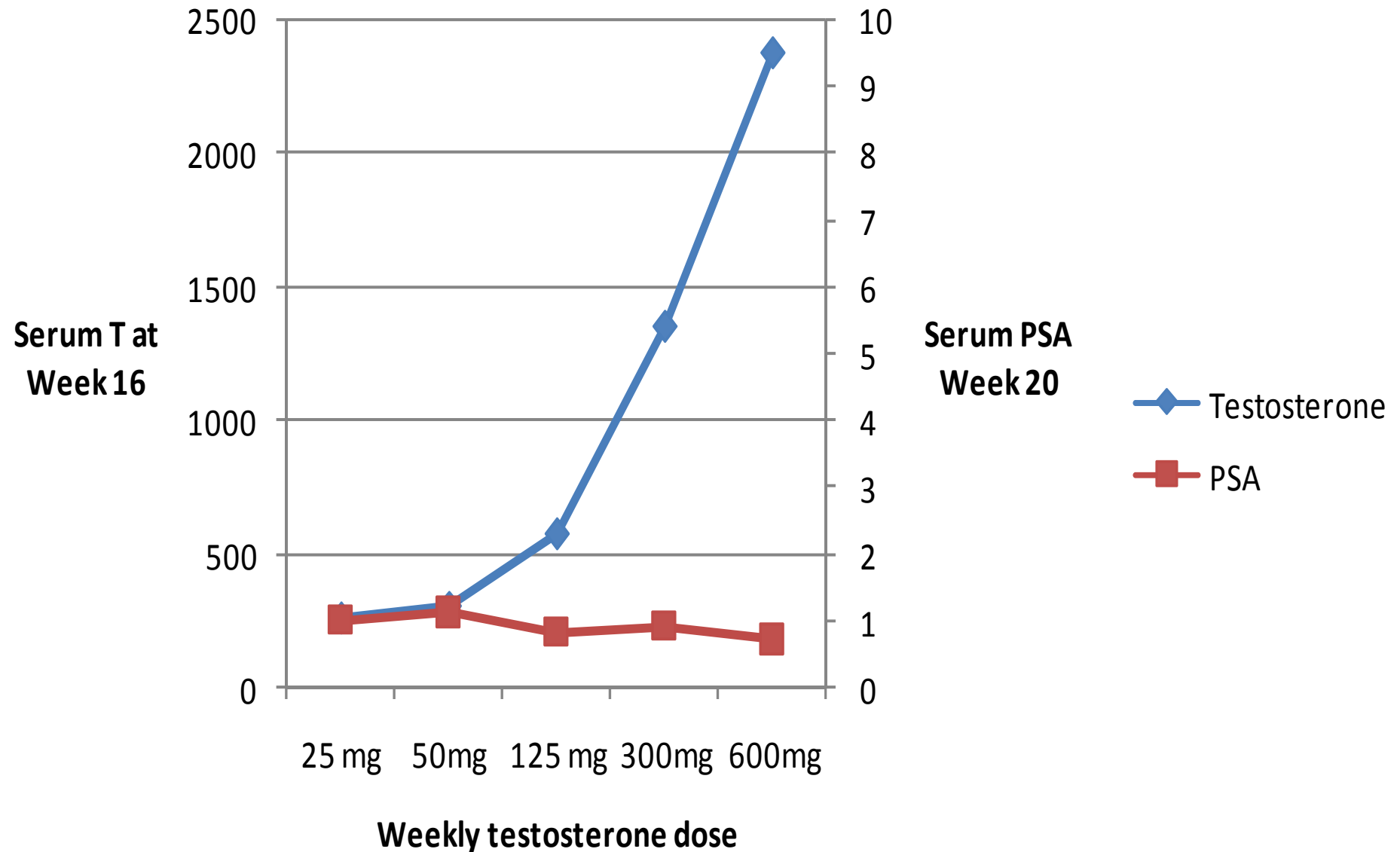




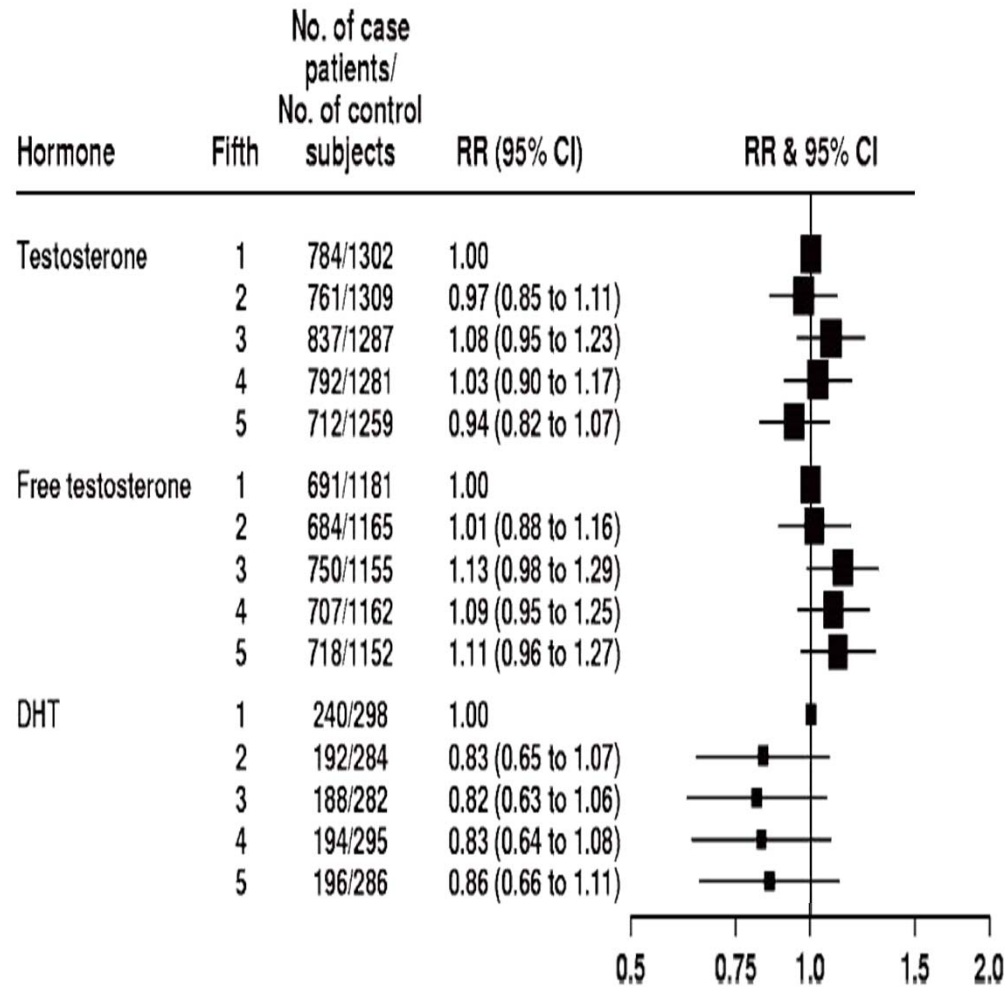


Serum testosterone and PSA in young men

From Bhasin et al Am J Physiol Endocrin Metab 281:e1172,2001



Global Pooled Longitudinal Study of Hormones and PCa Risk



- 3886 men with PCa
- 6448 age-matched controls
- No significant relationship between androgens and PCa
- Highest 20% T vs lowest 20%- no difference

T AND PROSTATE CANCER IN PLACEBO ARM OF REDUCE TRIAL

- 3255 men
- Prostate biopsies at 2y and 4y
- PCa risk NOT associated with serum T or DHT
- Men with high T no greater PCa risk

Muller et al, European Urology, 2012

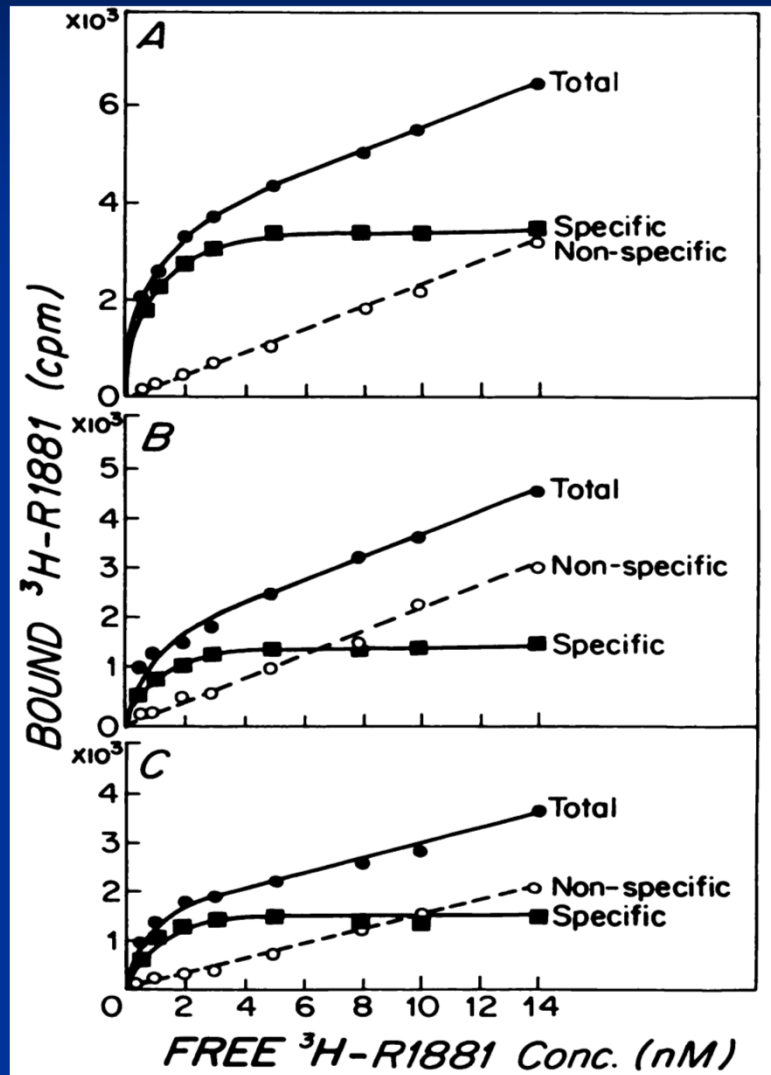
T THERAPY DOES NOT INCREASE PCa RATES

- Meta-analysis of 22 RCTs
- Eleven studies: < 12 mo duration
- Eleven studies: 12-36 mo duration
- 2351 men

Results

- No difference in PCa rates for men who received T vs placebo

Androgen Binding and the Androgen Receptor

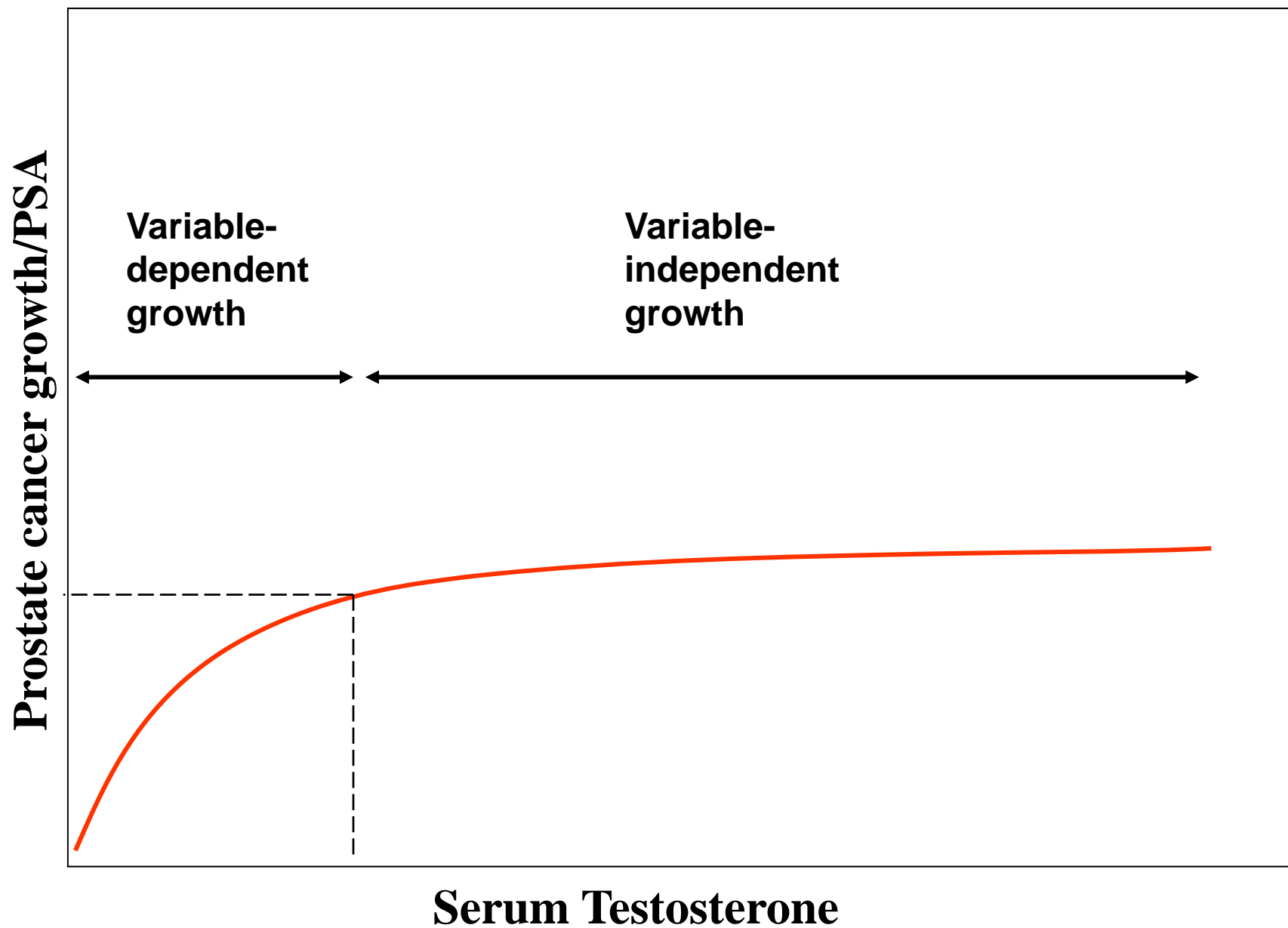


- Binding of androgen to AR in 3 lobes of Noble rat prostate
- AR has finite capacity to bind androgen
- Maximal binding (saturation of receptor) occurs at 2-3 nM (60-90ng/dl) in rat
- Max binding (in vitro) human 4 nM (120 ng/dl)

Ho et al, J Androl 1985; 6:279-90

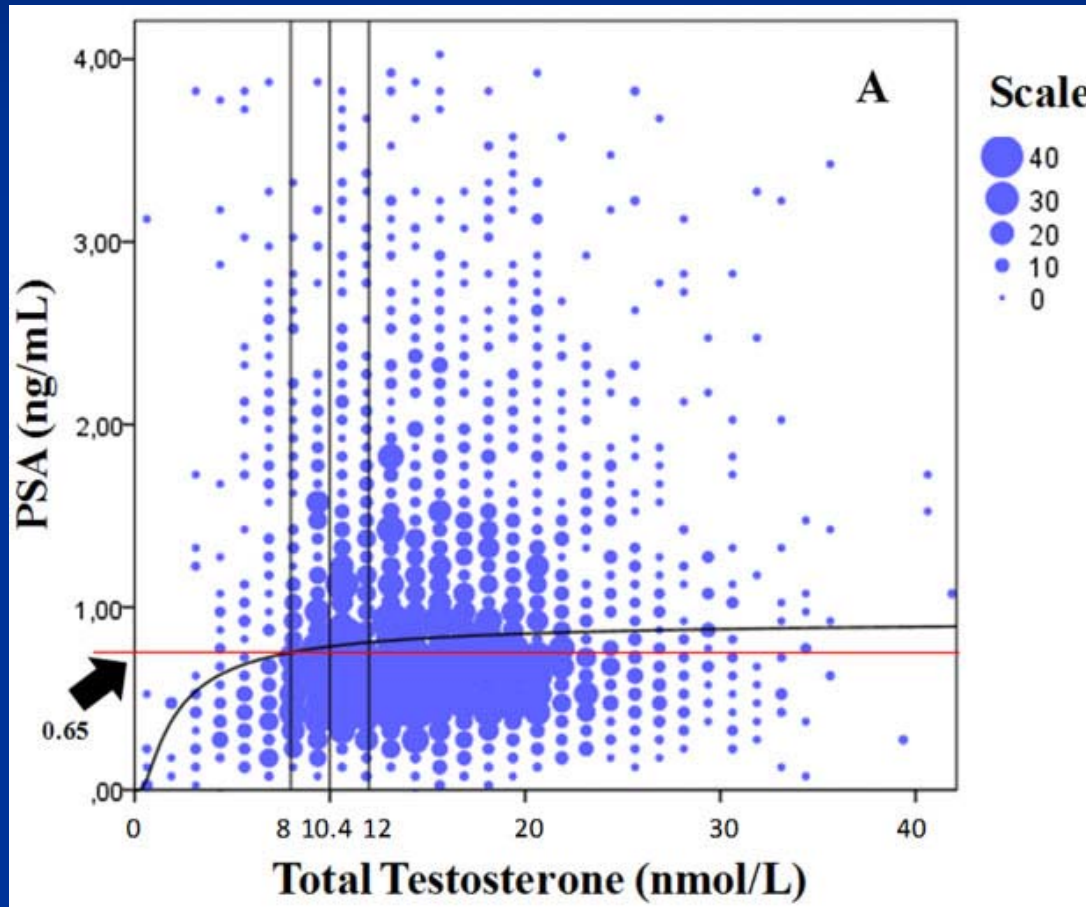
Traish A et al 1988 Prog Clin Biol Res

Saturation Model



PSA AND SATURATION

Rastrelli et al, J Sex Med 2013

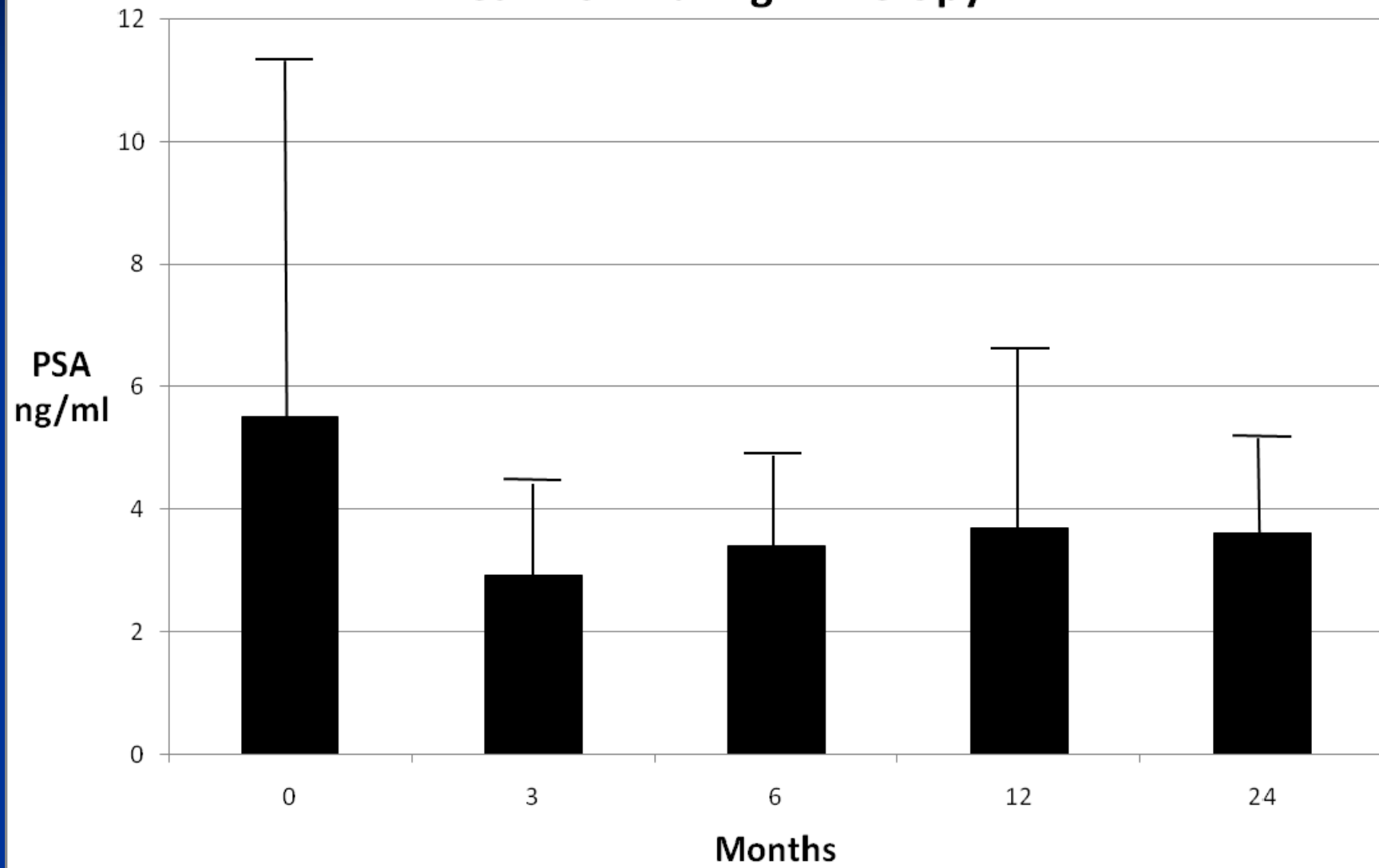


- 2967 men
- Seen for sexual dysfunction
- All with PSA < 4.0
- Saturation point ~ 8 nmol/L (250 ng/dl)

T THERAPY IN MEN WITH UNTREATED PCa

- T therapy in 13 men with untreated PCa (surveillance)
- Median duration T therapy 2.5y (1-8y)
- All with follow-up biopsies (avg 2/person)

Mean PSA During T Therapy



A thought experiment...

Imagine

- 2 brothers, identical twins, age 60
- Both s/p radical prostatectomy for Gleason 6 PCa
- PSA <0.1 ng/ml at 12 months
- Brother #1 happy, sexually active, T 600
- Brother #2 tired, absent libido, T 250
- Brother #2 requests T therapy

A thought experiment...

Brother #2:

- “Why is it alright for my brother to have a T of 600 ng/dl (20 nmol/L), but not me?”
- “If T of 600 (20 nmol/L) is unsafe, why don't you lower my brother's T?”

A thought experiment...

Our traditional unwillingness to offer T therapy to Brother #2 is illogical and unreasonable

Why Offer T Therapy To Men With Prostate Cancer?

- Because T therapy improves symptoms of T deficiency
- Because no known difference in risk between men who receive T therapy from men with endogenous normal T
- BUT: BE CAREFUL!
 - A percentage of men with PCa will have recurrences or progression
 - Will be blamed by patient or other MD on T therapy

WHY OFFER T THERAPY?

- Do the right thing for your patients
- Make decisions based on science, not by historical rules based on misunderstanding the literature