

Controversies with Testosterone Therapy



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BPH

**Female Sexual
Dysfunction**


**Controversies with
TTh**

Prostate Cancer

CVD

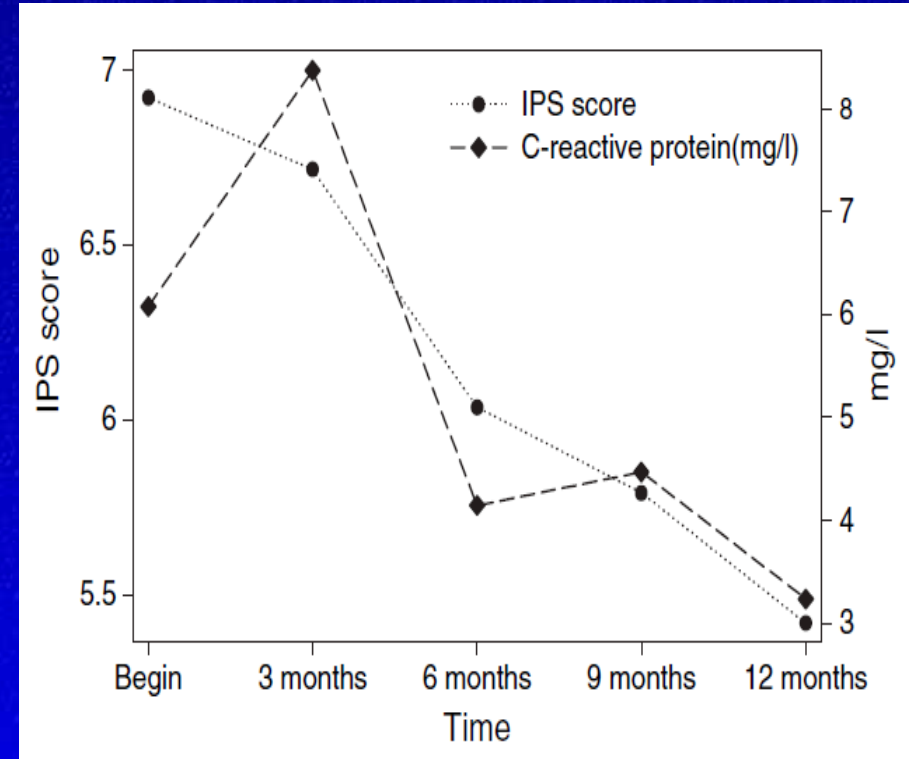
Testosterone and BPH

-----WARNINGS AND PRECAUTIONS-----

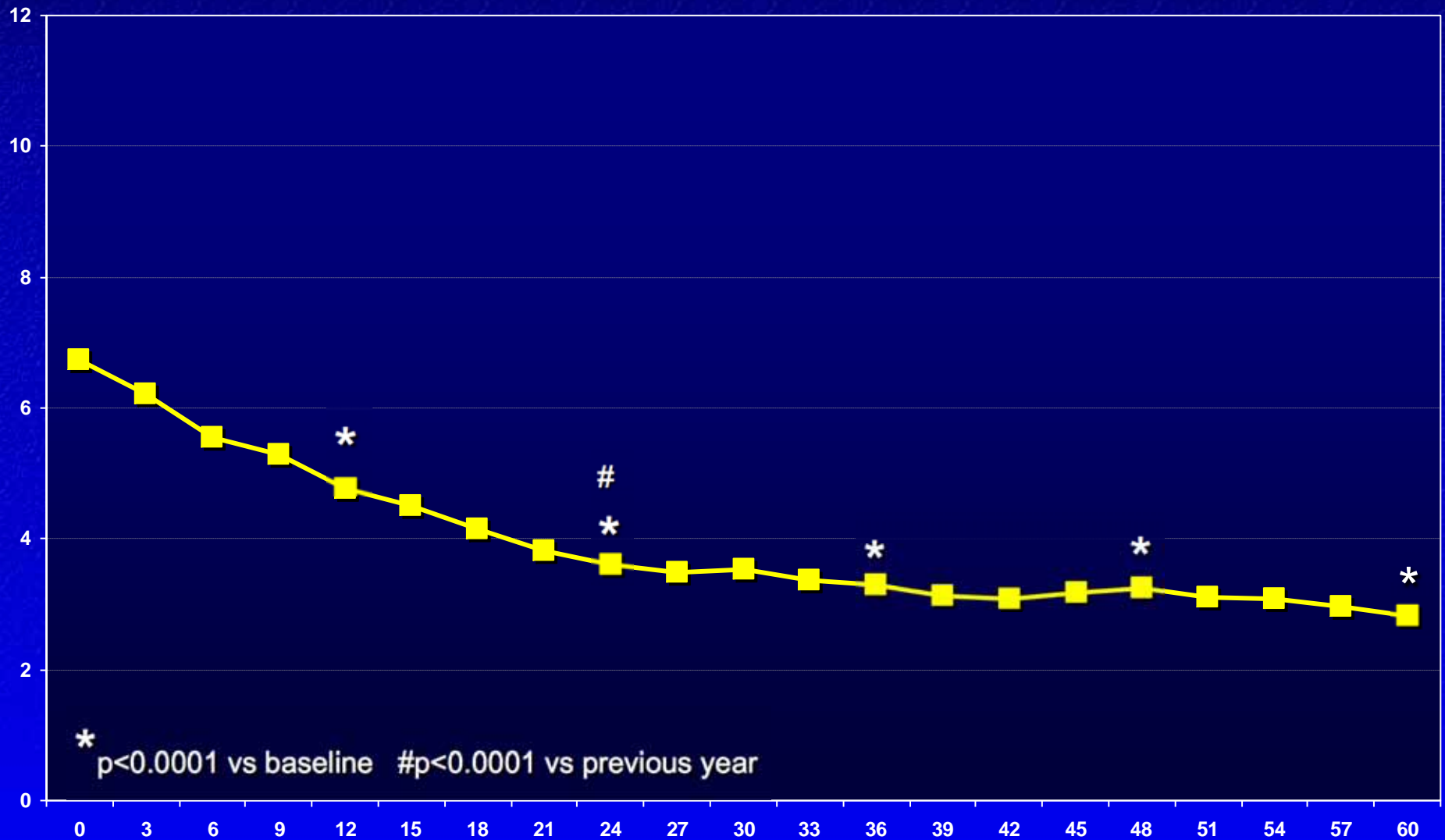
- 
- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH. (5.1)
 - Avoid unintentional exposure of women or children to Testim. Secondary exposure to testosterone can produce signs of virilization. Testim should be discontinued until the cause of virilization is identified. (5.2)
 - Exogenous administration of androgens may lead to azoospermia. (5.5)
 - Edema, with or without congestive heart failure, may be a complication in patients with preexisting cardiac, renal, or hepatic disease. (5.7, 6.2)
 - Sleep apnea may occur in those with risk factors (5.9)
 - Monitor prostate specific antigen (PSA), hematocrit, and lipid concentrations periodically. (5.1, 5.3, 5.10)

Testosterone and LUTS

- 95 hypogonadal men treated with long-acting IM testosterone undecanoate every 3 months for 12 months
- Results
 - No significant change in prostate volume
 - Significant improvement in PVR
 - Significant improvement in IPSS
 - Significant improvement in CRP



International Prostate Symptom Score (IPSS) in 255 Middle-Aged to Elderly Men Treated with TU up to 60 mo

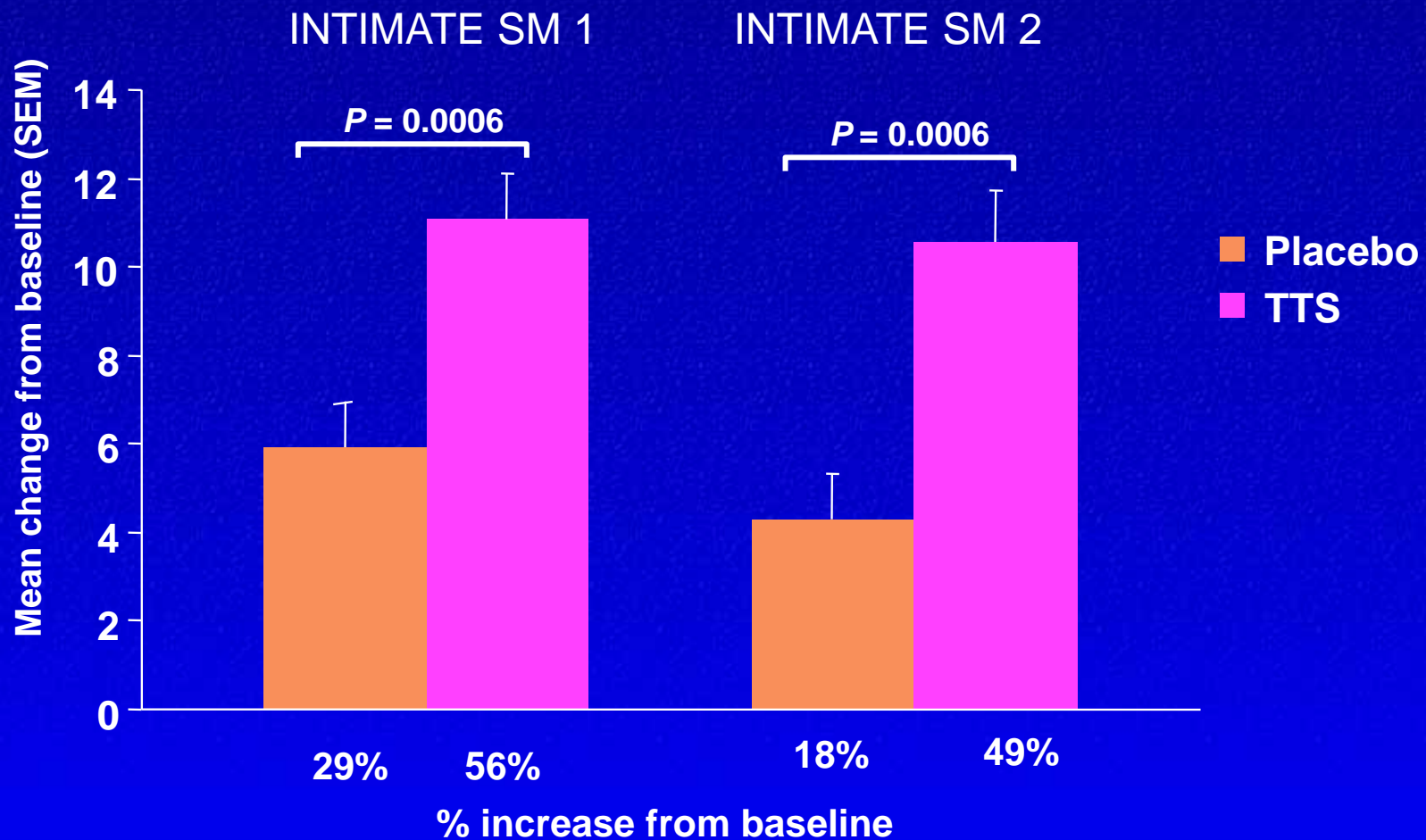


Testosterone and FSD

- 1939: Butenandt and Ruzicka win the Nobel Prize for discovery and synthesis of testosterone
- 1939: Researchers report that testosterone improved female sexual dysfunction
- Currently TTh for FSD is not FDA approved
- Dosage: 1/10

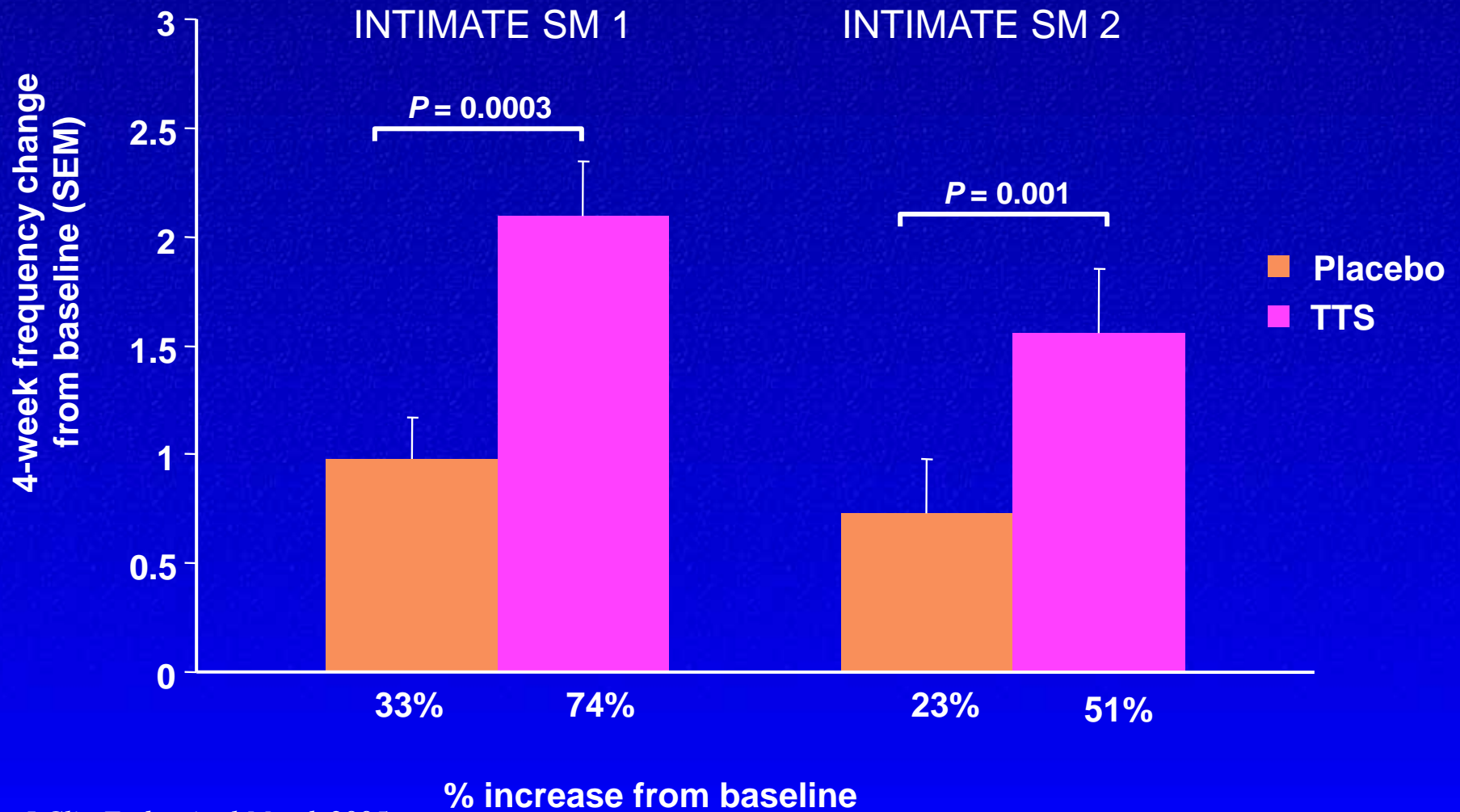


Increase in Desire at 24 Weeks from Profile of Female Sexual Function



Simon *J Clin Endocrinol Metab* 2005
Buster *Obstet Gynecol* 2005

Increases in Total Satisfying Sexual Activity at 24 Weeks



Testosterone and Bone Mineral Density in Women

- Thirty-four postmenopausal women were randomized to treatment with either:
 - estradiol implants 50 mg or
 - estradiol 50 mg plus testosterone 50 mg
- Treated for 2 years
- Results:
 - BMD increased more rapidly in the estradiol plus **testosterone** treated group
 - total body ($P < 0.008$),
 - vertebral spine L1-L4 ($P < 0.001$)
 - hip ($P < 0.005$)

Testosterone Therapy for Female Sexual Dysfunction

Mohit Khera, MD, MBA, MPH

Baylor College of Medicine, Houston, TX, USA

DOI: 10.1002/smrj.53

- **No data to support that testosterone causes an increased risk of cardiovascular events in women**
- **No evidence to indicate that testosterone results in increased risk of endometrial cancer or ovarian cancer**
- **Strong evidence to suggest that testosterone supplementation does not increase the risk for breast cancer**
 - **The addition of testosterone to estrogen therapy in postmenopausal women may reduce the risk of estrogen related breast cancer**

Testosterone and Cardiovascular Disease



Millions of Men at Potential Risk for Fatal Harm Due to Unnecessary 'Low T' Therapy

If you, or a loved one, have been prescribed any of the following low testosterone drugs, you may be entitled to compensation, and should speak to an attorney about your legal rights.

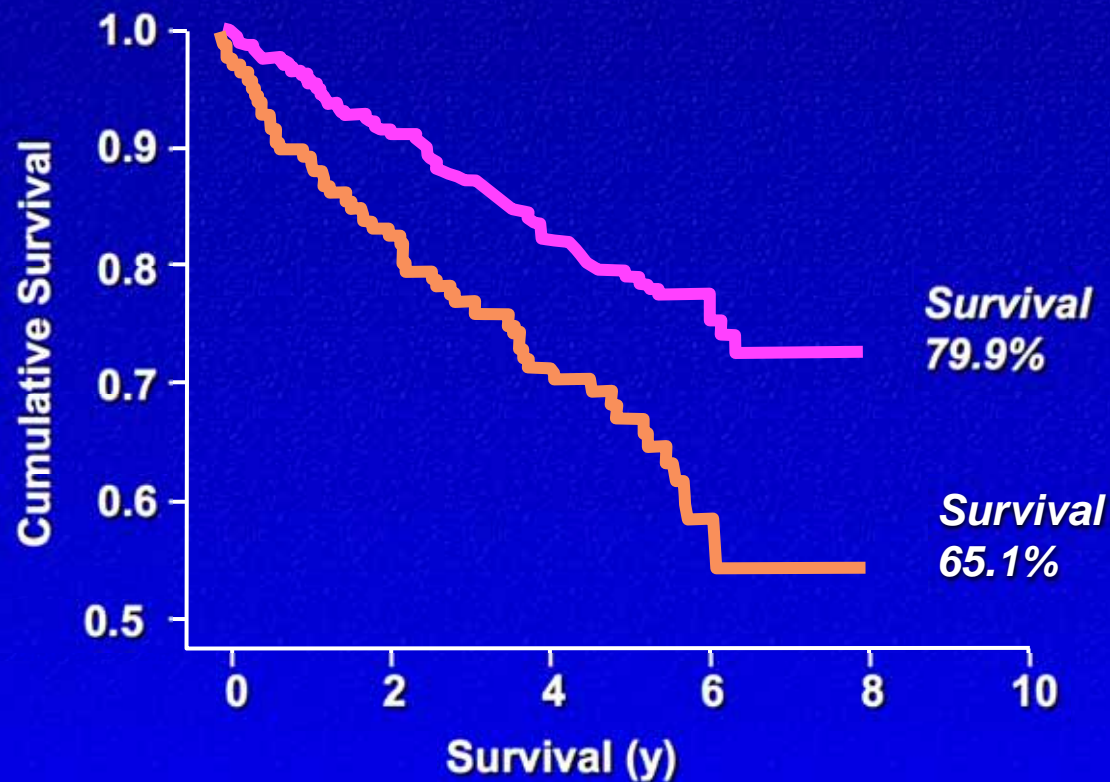
**McLaughlin & Lauricella P.C.
Low-T Testosterone Lawsuit Lawyers**

Aging Males and Mortality

Low Serum T and Mortality in Male Veterans

— Men With a Normal T-Level (n = 452)

— Men With a Low T-Level (n = 166)



Low Testosterone and Increased Mortality (N >500)

Recent Studies	HR (95% CI)	Nature	Men, n	Follow-Up, y	Mortality
Shores, 2006	1.88 (1.34–2.63)	Retrospective	858	8	All-cause
Laughlin, 2008	1.38 (1.02–1.85)	Prospective	794	20	CVD
Khaw, 2007	2.29 (1.60–3.26)	Prospective	2314 of 11,606	10	All-cause and CVD
Haring, 2010	2.32 (1.38–3.89)	Prospective	1954	7.2	All-cause
	2.56 (1.15-6.52)				CVD
Malkin, 2010	2.27 (1.45–3.60)	Prospective	930	6.9	All-cause in men with coronary disease
Tivesten, 2009	1.65 (1.29–2.12)	Prospective	3014	4.5	All-cause
Menke, 2010	1.43 (1.09–1.87)	Prospective	1114	9	All-cause
Vikan, 2009	1.24 (1.01–1.54)	Prospective	1568	11.2	All-cause
Corona, 2010	7.1 (1.8–28.6)	Prospective	1687	4.3	CVD

HR=hazard ratio; CI=confidence interval.

Prior to 2010 Articles Demonstrating Beneficial Effects of T Against CVD

Type of Article	Number of Articles
Low levels of endogenous testosterone and increased mortality	8
Low testosterone levels and increased incidence of coronary artery disease	6
Low testosterone level correlates with increased severity of coronary artery disease	4
Low endogenous testosterone level and increased carotid intima-media thickness	8
TRT decreases obesity	6
TRT improved cholesterol levels (meta- analysis)	3
TRT improves glycemic control	6
TRT decreases markers of inflammation	8

Total studies= 49

Basaria et al NEJM 2010

- RPCT frail elderly men
- 15 grams of testosterone
- CVD not an endpoint
- Treatment arm greater CV risks
- 5 vs 2 major CV events (ie MI)
- No difference if exclude CHF

- No randomization or placebo
- No control group or clinical info
- Health insurance database
- 90 days after start testosterone
- Pre-prescription MI rate 3.48/1000
- Post-prescription MI rate 4.75/1000

Finkle et al PLoS One 2014

TRT Causes CVD

Vigen et al JAMA 2013

- No randomization or placebo
- 2 major corrections
 - “Absolute risk” of MI (19.9 vs 25.7%) vs (21 vs 10%)
 - Exclusion of 1132 men
- RETRACTION 29 societies

- Meta- analysis of CV events in 27 PC studies of >12 weeks
- Just 2 studies provided 1/3 of all CV events in T treat arm
- If exclude 2 studies CV events in T and placebo are identical

Xu et al BMC 2013

FDA Warning



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FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use

The [testosterone product labels](#) have been updated. The revised labels clarify the approved uses of these medications and include information about a possible increased risk of heart attacks and strokes in patients taking testosterone.

This information is an update to the FDA Drug Safety Communication: FDA Evaluating Risk of Stroke, Heart Attack, and Death with FDA-Approved Testosterone Products issued on **January 31, 2014**.

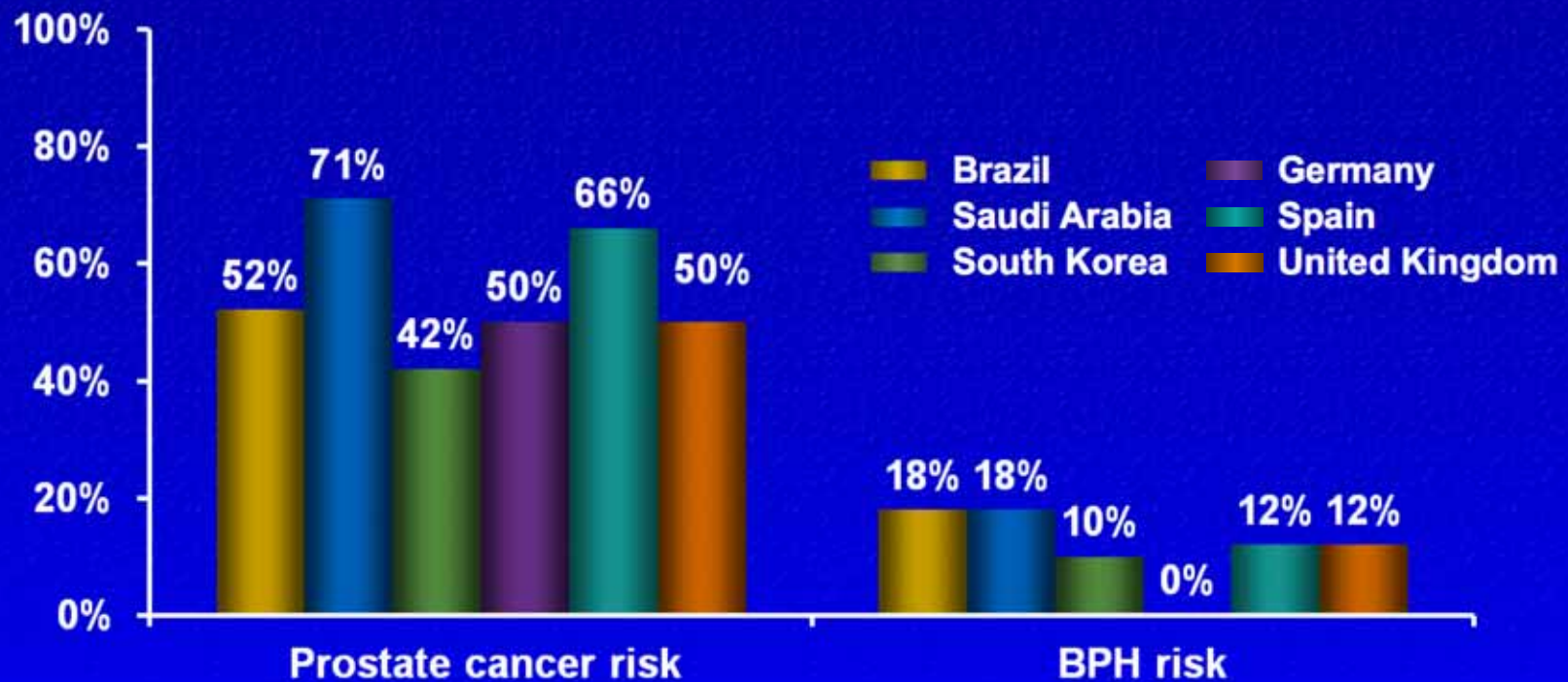
Testosterone Therapy and Cardiovascular Risk: Advances and Controversies

Abraham Morgentaler, MD; Martin M. Miner, MD; Monica Caliber, MSc;
Andre T. Guay, MD[†]; Mohit Khera, MD; and Abdulmageed M. Traish, PhD

- **Low levels of Total T, bioavailable T and free T are associated with increased risk of mortality from all causes and CVD (LOE IIa)**
- **Severity of CAD is inversely correlated with serum concentrations of total T, bioavailable T or free T (LOE IIa)**
- **Testosterone therapy is associated with a significant reduction in obesity and fat mass (LOE Ib)**
- **Testosterone therapy improves time to onset of symptomatic angina (LOE 1b)**
- **Exercise capacity and peak oxygen consumption in men with symptomatic CHF as defined by New York Heart Association functional class II (LOE Ia)**

Physician Concerns About the Prostate in 2006

- Multinational physician survey on testosterone therapy
 - Most common physician concern is prostate cancer risk



Concerns Rated "Very Important"

BPH, benign prostatic hyperplasia.

Reproduced from Gooren LJ et al. *Aging Male*. 2007;10(4):173-181.

Historical Basis for Concern



In 1941 – Huggins & Hodges reported:

1.Reducing T to castrate levels caused prostate cancer to regress

2.Administration of exogenous T caused prostate cancer to grow

Historical Basis for Concern



In 1941 – Huggins & Hodges reported:

1.Reducing T to castrate levels caused prostate cancer to regress

2.Administration of exogenous T caused prostate cancer to grow

(based on a single patient)

**Number of articles showing
testosterone therapy causes prostate
cancer in PSA era**



A New Era of Testosterone and Prostate Cancer: From Physiology to Clinical Implications

Mohit Khera^{a,*}, David Crawford^b, Alvaro Morales^c, Andrea Salonia^d, Abraham Morgentaler^e

Study	No. of Patients	Intervention	Follow-up (months)	Pre TRT PSA	Post TRT PSA	Pre TRT T (ng/dl)	Post TRT T (ng/dl)	Cancer Recurrence
Agarwal et al	10	RP	19	<0.1	<0.1	197	591	No
Kaufman et al	7	RP	24	<0.1	<0.1	97	434	No
Khera et al	57	RP	13	0.005	0.005	255	459	No
Pastuszak et al	103	RP	27.5	0.004	0.007	261	460	Yes (4)
Pastuszak et al	98	Brachy and XRT	41	0.08	0.09	209	420	Yes (6)
Sarosdy	31	Brachy	60	n/a	< 1	188	489	No
Morales et al	5	XRT	14.5	0.1-0.97	< 0.1 – 1.08	150	507	No
Pastuszak et al	13	Brachy and XRT	29.7	0.30	0.66	178	368	No
Balbontin et al	20	Brachy	31	0.7	0.1	343	592	No

Testosterone Replacement Therapy in Patients with Prostate Cancer After Radical Prostatectomy

Alexander W. Pastuszak,* Amy M. Pearlman,* Win Shun Lai,* Guilherme Godoy,*
Kumaran Sathyamoorthy,* Joceline S. Liu,* Brian J. Miles,* Larry I. Lipshultz†
and Mohit Khera‡,§

- **Retrospective review of 103 hypogonadal men treated with TRT after RP between 2003-2011 and 49 eugonadal controls having undergone RP treated during this time**
 - **High Risk CaP** - post-surgical pathology with one or more of the following: 1) Gleason score ≥ 8 , 2) positive surgical margins, or 3) positive lymph nodes
 - **TRT Group** - 77 men with low/intermediate risk CaP (non-high risk) and 26 with high-risk CaP
 - **Control Group** – 34 men non-high risk and 15 men high-risk CaP
- **Results:**
 - **12 biochemical recurrences ONLY in high risk patients after 36 months**
 - **4 biochemical recurrence in TRT group (15.3%)**
 - **8 biochemical recurrences in control (non-TRT group) (53.3%)**

TRT after Prostate Cancer

- A total of 8 studies (abstracts + manuscripts) thus far have provided information on TRT after treatment for prostate cancer (RP, brachytherapy, EBRT)
 - Total of 484 patients treated with testosterone after prostate cancer
- Only 10 men, or roughly 2% of men, were noted to have a biochemical recurrence
- Recurrence rate is less than published series in favorable groups²
- TRT protective?

¹Morgentaler J Urol 2009; 181:972

²van Oort et al. Urol Oncol 2008 Epub

TRT and Prostate Cancer Cell Suppression

- **Hatzoglou et al- membrane androgen receptor activation induced apoptotic regression of human prostate cancer cells in vitro and in vivo¹**
- **Sonnenschein et al. - androgens were able to trigger an inhibition of prostate cancer cell proliferation at higher concentration²**
- **Chuu et al. - androgens caused growth suppression and then reversion of androgen independent tumors to an androgen dependent tumors³**

¹ Hatzoglou et al J Clin Endocrinol Metab 2005, 90:893-903

² Sonnenschein et al. Cancer Res 1989, 49:3474-81

³ Chuu et al Cancer Res 2005, 65:2082-4



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PROSTATE CANCER

DISCOVERY

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VOLUME 9 • WINTER 2013

A PUBLICATION OF THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

The Patrick C. Walsh Prostate Cancer Research Fund

A New Way to Treat Recurrent Prostate Cancer: More Testosterone?

[Volume 9, Winter 2013](#)

Effect of bipolar androgen therapy for asymptomatic men with castration-resistant prostate cancer: Results from a pilot clinical study

Michael T. Schweizer,^{*†} Emmanuel S. Antonarakis, Hao Wang, A. Seun Ajiboye, Avery Spitz, Haiyi Cao, Jun Luo, Michael C. Haffner, Srinivasan Yegnasubramanian, Michael A. Carducci, Mario A. Eisenberger, John T. Isaacs, Samuel R. Denmeade[†]

- **14 patients with CRPC**
- **TE 400mg IM for 3 months**
- **Castrating therapy continued to suppress endogenous testosterone production, allowing for rapid cycling from supraphysiologic to near-castrate serum testosterone levels = bipolar androgen therapy (BAT)**
- **BAT was well tolerated and resulted in high rates of PSA (7 of 14 evaluable patients) and radiographic responses (5 of 10 evaluable patients)**

Testosterone Therapy in Men With Untreated Prostate Cancer

Abraham Morgentaler,^{*} † Larry I. Lipshultz,[‡] Richard Bennett,[§] Michael Sweeney,[§] Desiderio Avila, Jr.[§] and Mohit Khera^{||}

From Men's Health Boston, Division of Urology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts (AM, MS), and the Department of Urology, Baylor Medical College, Houston, Texas (LIL, RB, DA, MK)

- **Retrospective study of 13 men who elected surveillance of prostate cancer and received testosterone therapy for minimum of 6 months and followed for 24 months**
- **No cancer progression seen in any individual**
- **No cancer identified in 54% of follow-up biopsies**

Conclusion

- TTh has been shown to improve BPH and LUTS
- TTh can safely be administered to women suffering from FSD
- Low serum testosterone has been associated with an increased risk of MI and CV risk factors
- There is no convincing data to support that TTh causes prostate cancer

Thank you for your attention

B.Z. Toons

by Brian Zaikowski





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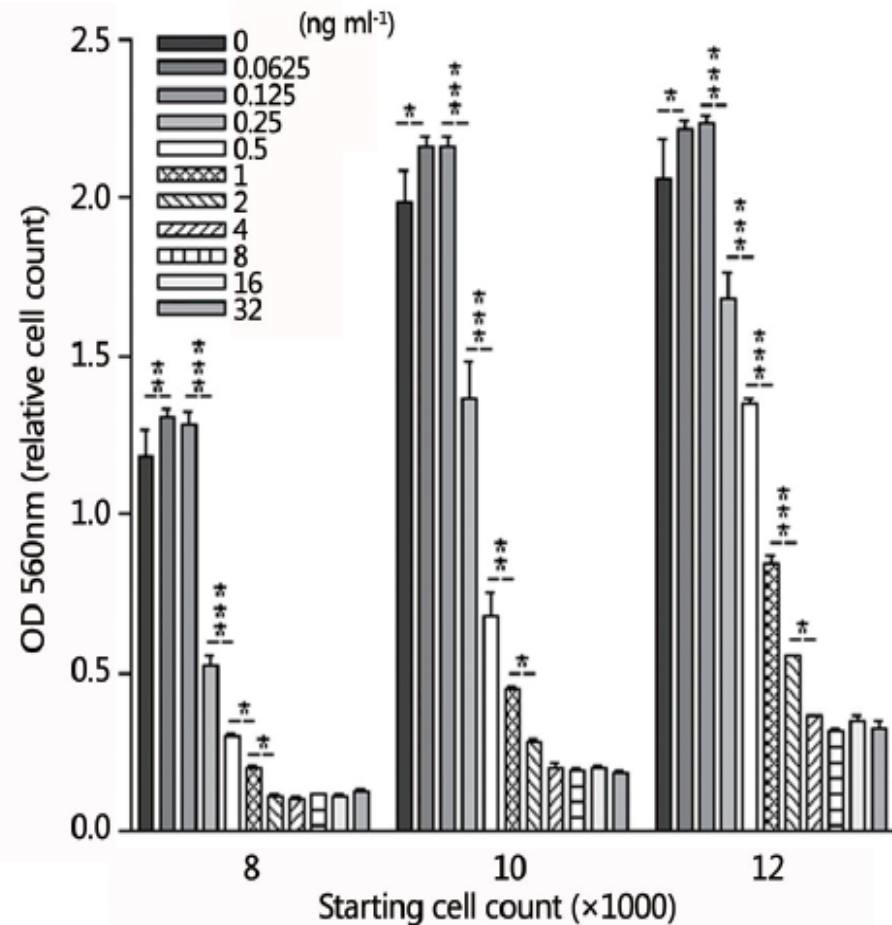
ORIGINAL ARTICLE

Prostate Cancer

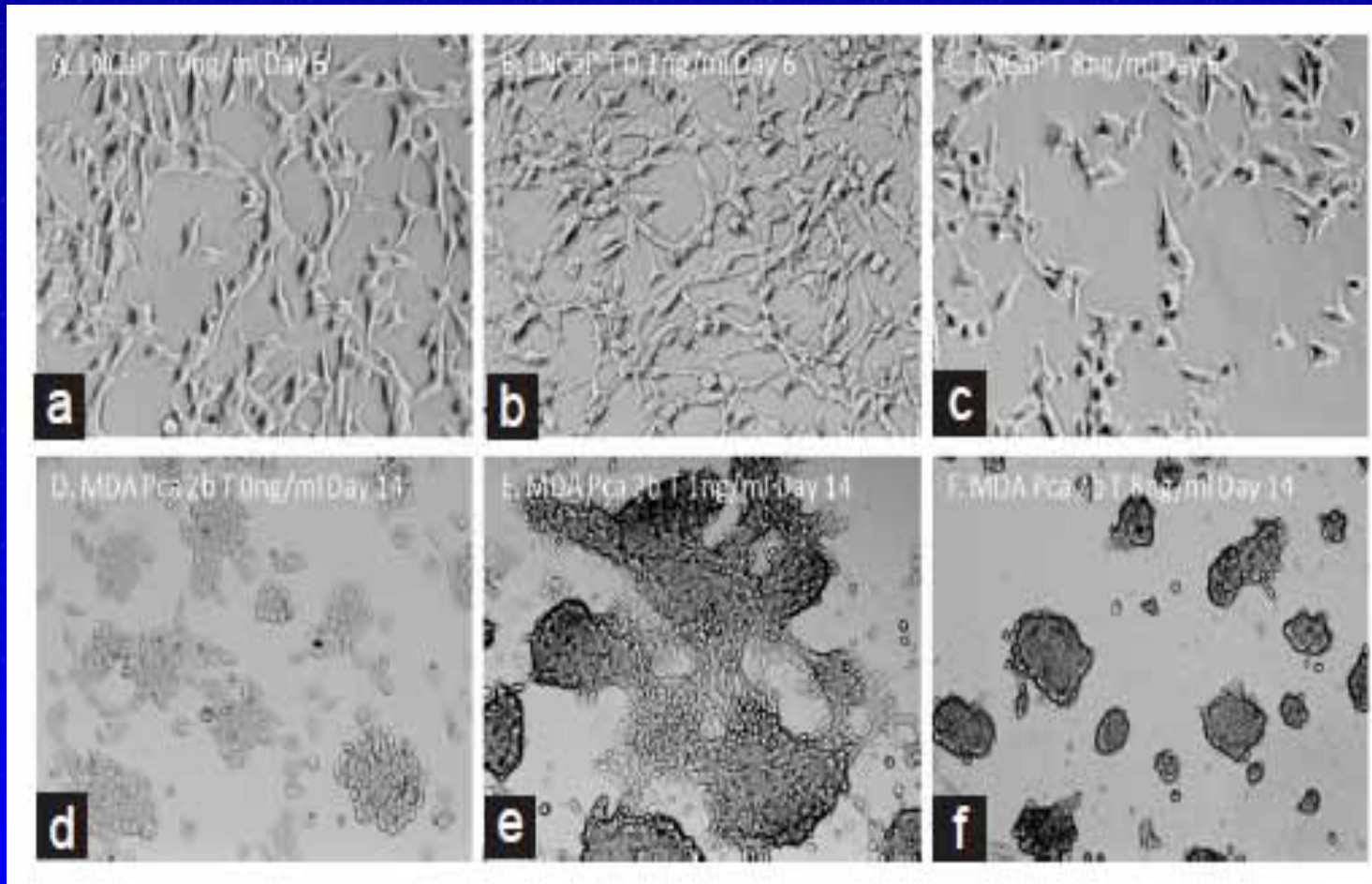
Physiological normal levels of androgen inhibit proliferation of prostate cancer cells *in vitro*

Weitao Song, Mohit Khhera

- Prostate cancer LNCaP cells were treated with various levels of testosterone (T) (0 to 16ng/ml)
- 8-12K cells were seeded in triplets, T treatment for 10 days
- The growth rate of prostate cancer cells was assessed



LNCaP and MDA Pca 2b Cells Treated with Testosterone



Testosterone and Prostate Cancer: In-vivo Experiments

- **Male nude mice divided into 4 categories**
 - **Normal control (n=45)**
 - **Orchiectomy (n=44)**
 - **2mg testosterone pellet (n=44)**
 - **5mg testosterone pellet (n=44)**
- **5 million LNCaP cells injected s.c. one week post surgery**
- **Mice followed for 84 days**
- **Serum testosterone and tumor size assessed**







Tumor Development Rate

