

# Il Consulente Endocrinologo in Oncologia



ITALIAN CHAPTER



Roma, 9-12 novembre



**La PROSTATE UNIT**

Mario Cappagli

La Spezia

*Riomaggiore 5 Terre*



# Agenda



## Nessun conflitto



- **Note di epidemiologia**
- **La PCU: requisiti**
- **Carcinoma prostatico: una neoplasia endocrina?**
- **La deprivazione androgenica**
- **L' Endocrinologo nella PCU: è utile?**



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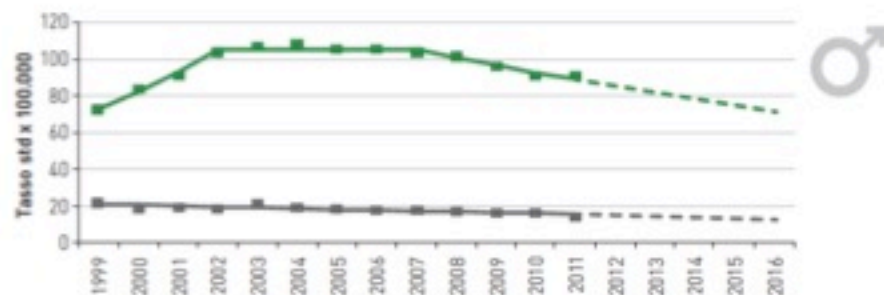
# I numeri del cancro



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## Andamento dell'incidenza e della mortalità del carcinoma della prostata



■ I-APC: 1999-2002: 13,3\* (9,3; 17,4), 2002-2007: -0,1 (-2,0; 1,9), 2007-2016: -4,1\* (-6,2; -2)  
 ■ M-APC: 1999-2016: -2,5\* (-3,5; -1,5)

- Incidenza in aumento fino al 2003 correlato alla diffusione del test per il PSA e poi progressiva riduzione
- Riduzione della mortalità (-2,5% per anno)



## I numeri del cancro in Italia 2017

Ministero della Salute – Roma  
15 Settembre 2017

## Tumori più frequentemente diagnosticati

Rango	Maschi	Femmine	Tutta la popolazione
1°	Prostata [18%]	Mammella [28%]	Colon-retto [14%]
2°	Colon-retto [16%]	Colon-retto [13%]	Mammella [14%]
3°	Polmone [15%]	Polmone [8%]	Polmone [11%]
4°	Vescica* [11%]	Tiroide [6%]	Prostata [9%]
5°	Rene, vie urinarie** [5%]	Utero corpo [5%]	Vescica* [7%]



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PERGAMON



European Journal of Cancer 36 (2000) 2288–2293

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European  
Journal of  
Cancer

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[www.ejconline.com](http://www.ejconline.com)

Position Paper

## The requirements of a specialist breast unit

EUSOMA

*EUSOMA Secretariat, Viale B. d'Este 37, 20122 Milan, Italy*

Received 24 February 2000; accepted 25 May 2000





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# Prostate Cancer Units Network



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A project of



In partnership with



with the endorsement of



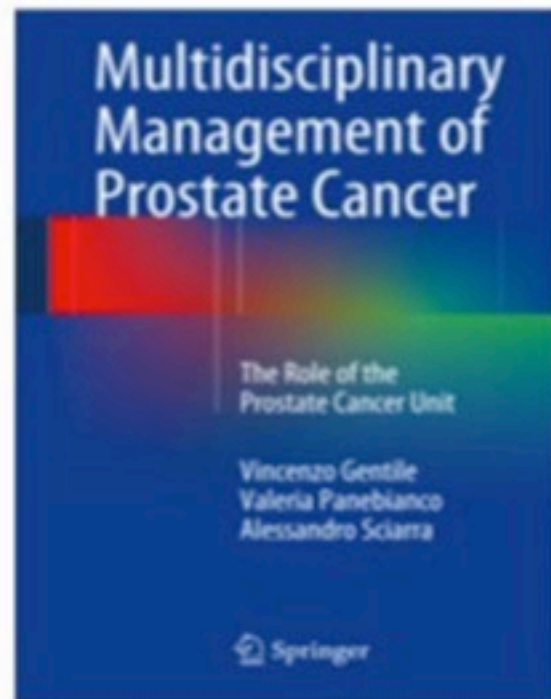
## Istruzioni per l'uso



# Prostate Cancer Units

## Come e perchè

- ✓ PCU = BU
- ✓ Patologia complessa che richiede decisioni multidisciplinari
- ✓ Semplificazione dell'iter polispecialistico
- ✓ Prevenzione-diagnosi precoce-terapia in ogni stadio-complicanze
- ✓ Alto livello di preparazione
- ✓ Facile accesso al materiale scientifico e clinico per la migliore gestione del CP
- ✓ Decisioni assunte in modo aperto e condiviso
- ✓ Paziente: disponibilità-informazione-coordinazione





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Current perspective

## The requirements of a specialist Prostate Cancer Unit: A discussion paper from the European School of Oncology

Riccardo Valdagni <sup>a,b,c</sup>, Peter Albers <sup>c</sup>, Chris Bangma <sup>d</sup>, Lawrence Drudge-Coates <sup>e</sup>,  
Tiziana Magnani <sup>b</sup>, Clare Moynihan <sup>f</sup>, Chris Parker <sup>g</sup>, Kathy Redmond <sup>h</sup>,  
Cora N. Sternberg <sup>h</sup>, Louis Denis <sup>i</sup>, Alberto Costa <sup>a</sup>

### CORE TEAM

- Urologo
- Oncologo
- Patologo
- Infermiere
- Informatico (gestione dati)
- Controllore documentazione clinica

### NON - CORE TEAM

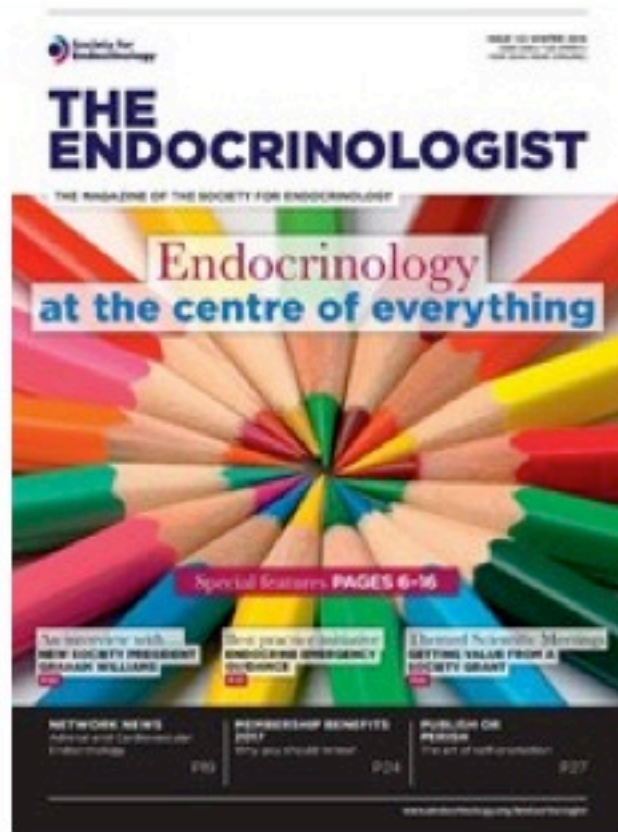
- Specialista Imaging
- Fisico
- Tecnico Radiologia
- Specialista Cure palliative
- Psicologo
- Avvocato
- Coordinatore trials clinici
- ~~Fisioterapista~~
- Sessuologo (S) o Urologo-andrologo U-A) o Infermiere specializzato coordinato da S o U-A
- Geriatra



## A ROLE FOR ENDOCRINOLOGISTS

*So what has this got to do with endocrinology? Quite a lot, in fact. ... If we consider the multiple types of cancer treatment used, we can easily see that there is a large impact on the endocrine system.*

*Two of the 'big' cancers, breast and prostate cancer, include hormone therapies rendering patients hypogonadal. This often leads to symptoms that are difficult to manage and an increased risk of osteoporosis...*







# Shifting the Paradigm of Testosterone and Prostate Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth

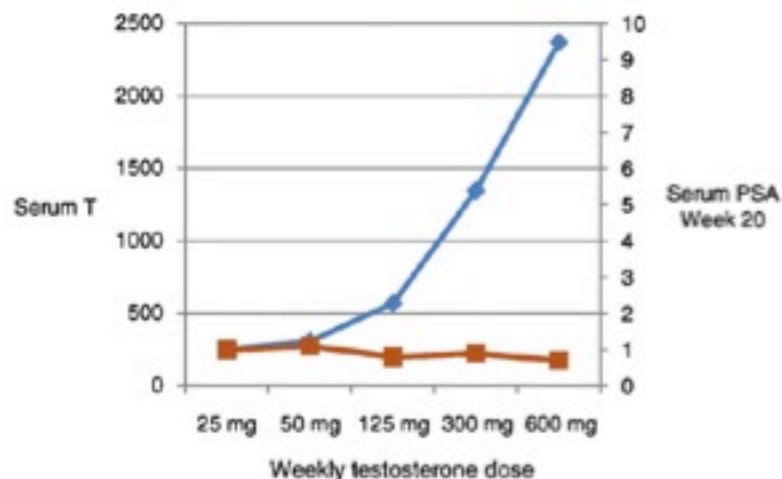
Abraham Morgentaler<sup>a,\*</sup>, Abdulmaged M. Traish<sup>b</sup>

<sup>a</sup>Division of Urology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, United States

<sup>b</sup>Department of Biochemistry and Division of Urology, Boston University School of Medicine, Boston, Massachusetts, United States



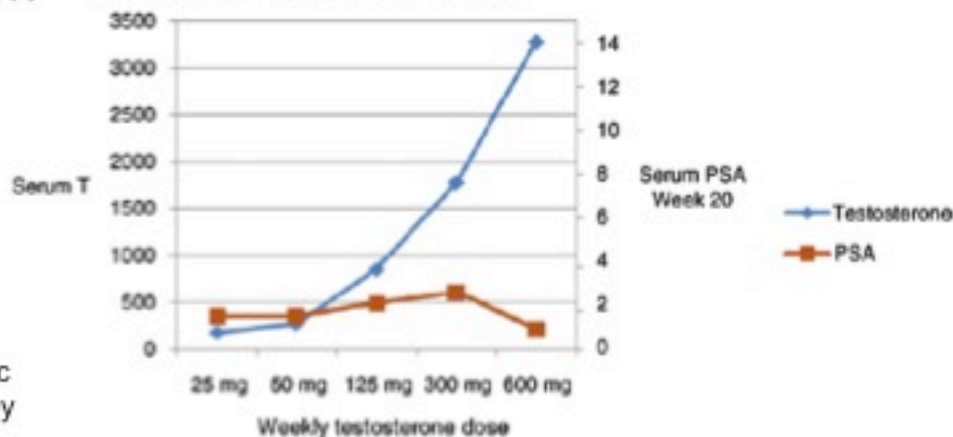
(a) Serum testosterone and PSA in young men



These results convincingly demonstrate that variation of serum T concentrations changes in the near-physiologic to supraphysiologic range appears **to have no effect on the prostate**, as measured by prostate volume or the androgen-dependent protein marker, PSA.

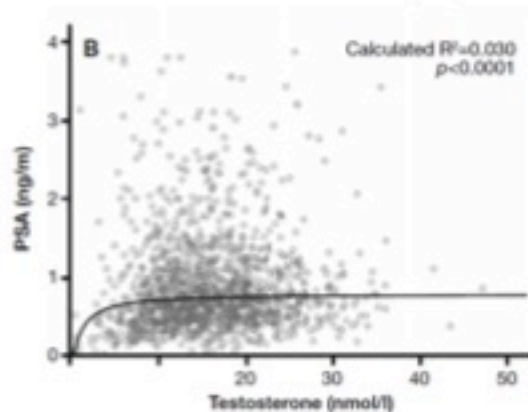
## “Inversione” del Paradigma Testosterone & Carcinoma Prostatico

(b) Serum T and PSA in older men

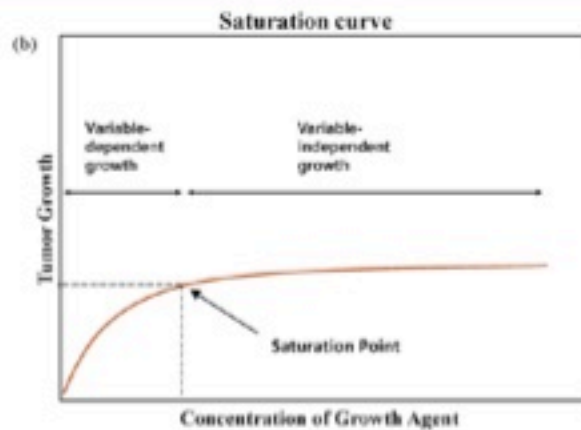




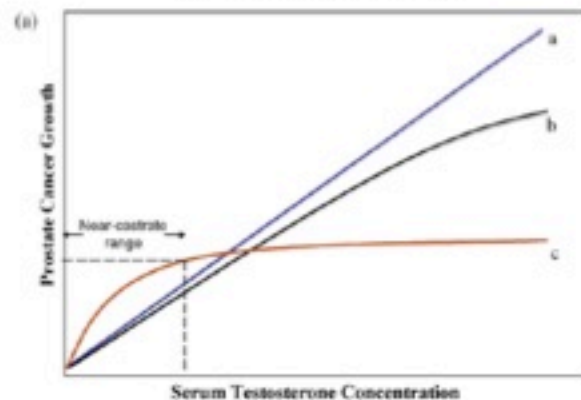
# The Saturation Hypothesis



Maggi et al



Morgentaler et al



{ **modello «classico»**

{ **modello «saturazione»**



## Testosterone Therapy on Active Surveillance and Following Definitive Treatment for Prostate Cancer

Vishnukamal Golla<sup>1</sup> · Alan L. Kaplan<sup>1</sup>

With the absence of large randomized placebo-controlled trials, the uncertainty surrounding the safety of testosterone therapy and prostate cancer will remain. However, as Morgentaler has elegantly stated, we have the results of the largest prospective experiment available and that is the natural history of prostate cancer. Prostate cancer is non-existent in men in their 20s when the prostate is bathed in a high testosterone concentration. Rather, the disease becomes more prevalent as men age and testosterone levels decline which more accurately aligns with what we see in the literature.

This review demonstrates that, to date, there is overwhelming evidence that testosterone therapy does not increase prostate cancer risk in the untreated and treated population. This challenges a urological belief that has been cemented in our teaching for over three quarters of a century. We hope that, as we continue to scrutinize the literature in the years to come, we will continue to push forth this paradigm shift.



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UROLOGY 68: 1263-1267, 2006. © 2006 Elsevier Inc.

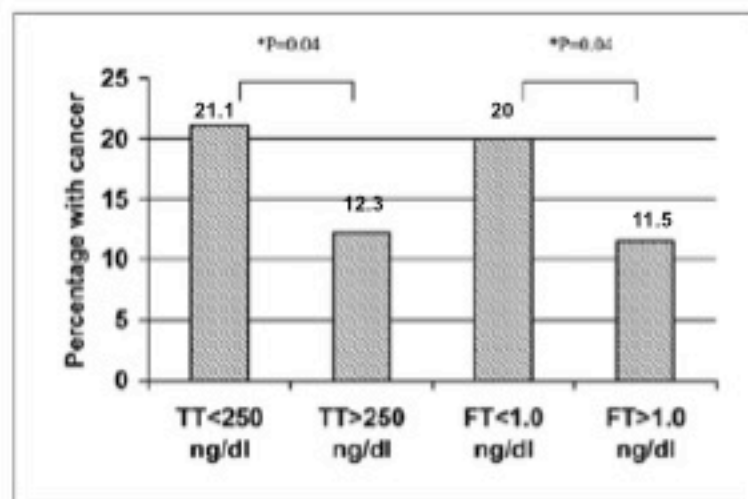
ADULT UROLOGY



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### PREVALENCE OF PROSTATE CANCER AMONG HYPOGONADAL MEN WITH PROSTATE-SPECIFIC ANTIGEN LEVELS OF 4.0 ng/mL OR LESS

ABRAHAM MORGENTALER AND ERNANI LUIS RHODEN



No. prostate cancer	23	29	29	23
No. men evaluated	109	236	145	200



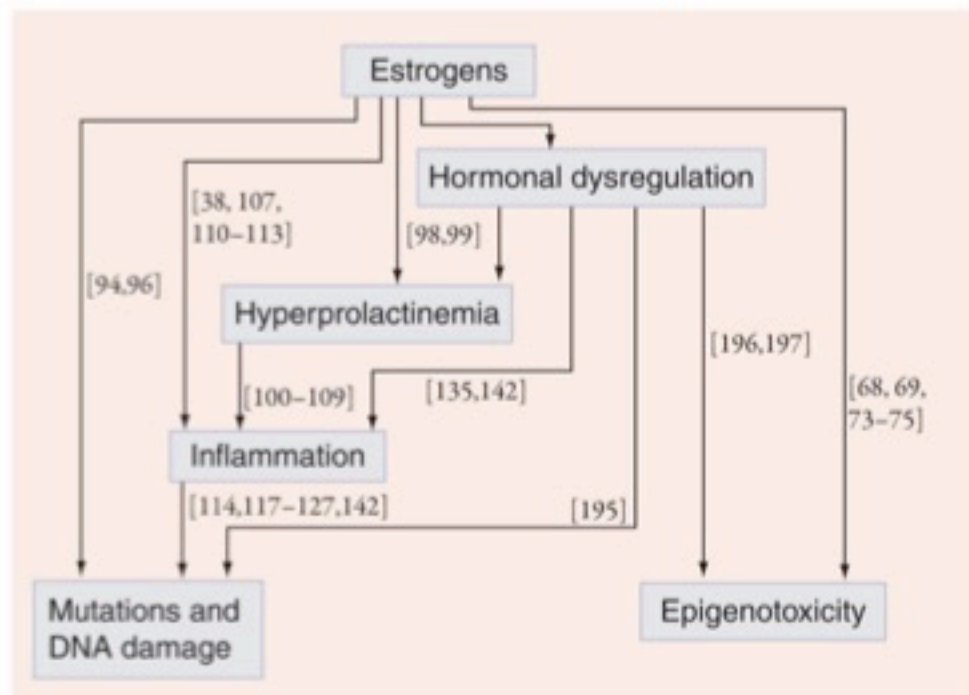


## Estrogen action and prostate cancer

Jason L Nelles<sup>1</sup>, Wen-Yang Hu<sup>1</sup>, and Gail S Prins<sup>1,†</sup>

<sup>1</sup> Department of Urology, University of Illinois at Chicago, 820 South Wood Street, MC 955, Chicago, IL 60612, USA

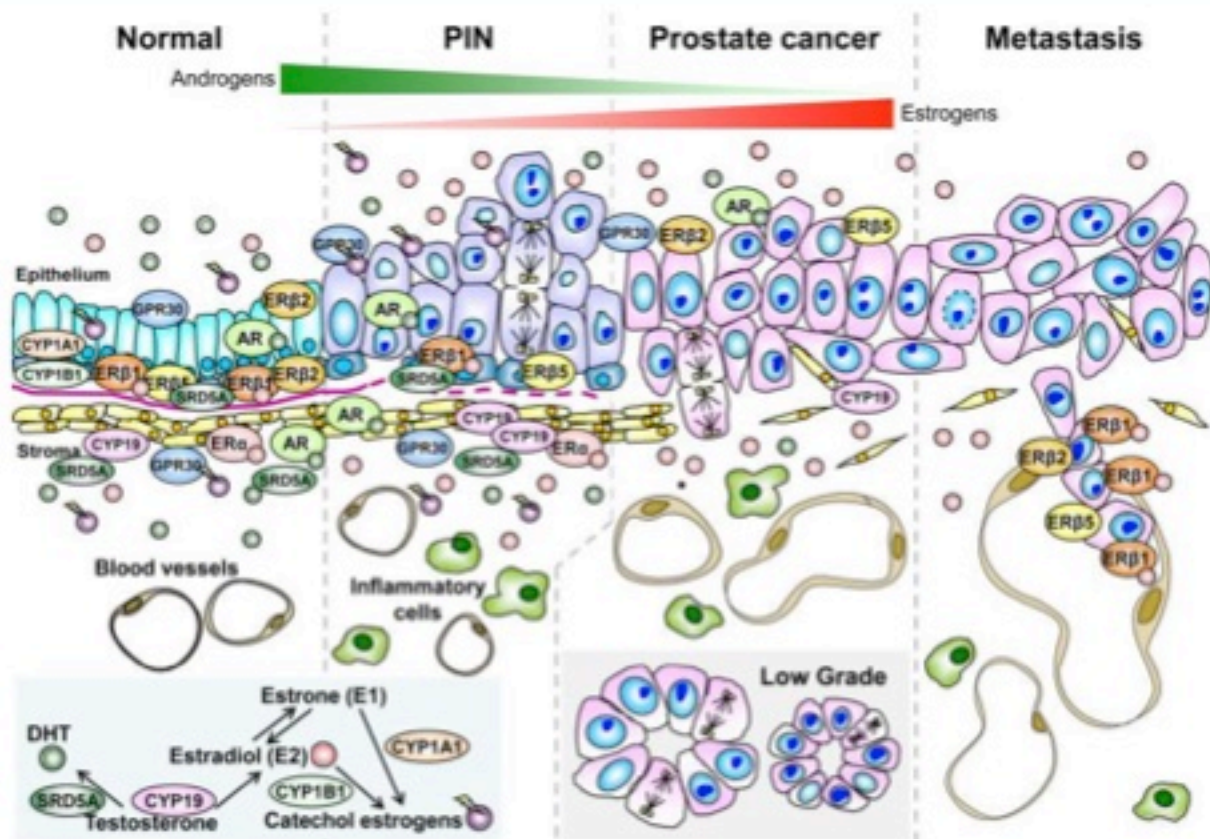
... that aromatase (CYP19), the enzyme that catalyzes estradiol production from testosterone, is altered in prostate cancer tissues [23] and **CYP19A1 expression is elevated 30-fold in prostate cancer metastatic tissue, as compared with primary tumors.** Montgomery RB *Cancer Res.* 2008; 68:4447-4454.





Estrogens and Prostate Cancer: Etiology, Mediators, Prevention, and Management  
 Shuk-Mei Ho, Ph.D.,  
 Ming-tsung Lee, M.Phil., [...], and  
 Yuet-Kin Leung, Ph.D.

[Endocrinol Metab Clin North Am. 2011 Sep; 40\(3\): 591-614.](#)





## Metabolic imbalance and prostate cancer progression



Int J Mol Epidemiol Genet  
2010;1(4):248-271



## BMI AND PROSTATE CANCER PROGRESSION

[Int J Cancer](#). 2017 Sep 1;141(5):933-944. doi: 10.1002/ijc.30803. Epub 2017 Jun 8.

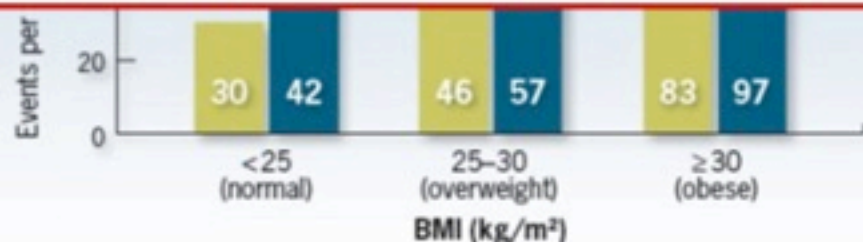
**Weight change, obesity and risk of prostate cancer progression among men with clinically localized prostate cancer.**

[Dickerman BA](#)<sup>1</sup>, [Ahearn TU](#)<sup>1</sup>, [Giovannucci E](#)<sup>1,2,3</sup>, [Stampfer MJ](#)<sup>1,2,3</sup>, [Nguyen PL](#)<sup>4</sup>, [Mucci LA](#)<sup>1,3</sup>, [Wilson KM](#)<sup>1,3</sup>.

### Abstract

Obesity is associated with an increased risk of fatal prostate cancer. .... Our findings ...diagnosed with localized prostate cancer suggest a positive association between long-term weight gain and risk of lethal prostate cancer.

Metabolic changes associated with weight gain may promote prostate cancer progression.

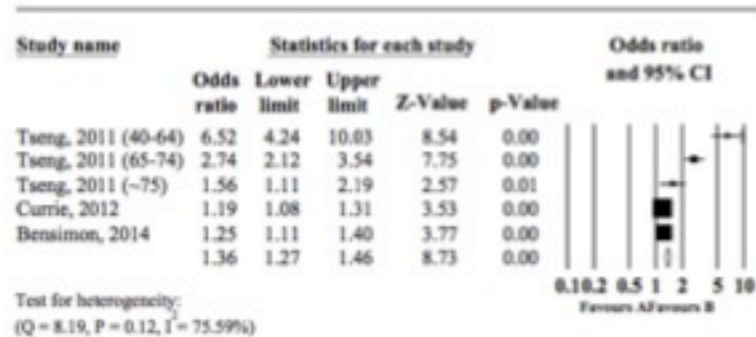


Source: Bhindi B et al. Obesity is associated with risk of progression for low risk prostate cancers being management expectantly. Data presented in poster format at the Canadian Urological Association annual meeting in St. John's, Newfoundland.

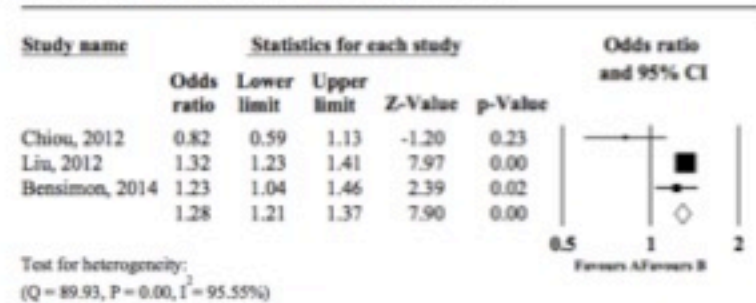




## Prostate cancer-specific mortality: type 2 diabetes vs. non-type 2 diabetes



## All-cause mortality: type 2 diabetes vs. non-type 2 diabetes



Diabetes and mortality in patients with prostate cancer: a meta-analysis

Junga Lee, Edward Giovannucci and Justin Y. Jeon *SpringerPlus* (2016) 5:1548

Fig. 3 Relative risk for the association between pre-existing type 2 diabetes, prostate cancer-specific mortality, and all-cause mortality



# Le (complesse) decisioni terapeutiche



## CP localizzato

Sorveglianza attiva

Chirurgia

Radioterapia

Terapia focale

## CP avanzato

Radioterapia

Terapia focale

Deprivazione androgenica

Chemioterapia

Altro



# Effetti collaterali ...



## The Castration Syndrome

- Loss of libido and sexual interest, erectile dysfunction, impotence
- Fatigue
- Hot flushes
- Decline in intellectual capacity, emotional lability, depression
- Decrease in muscular strength
- Increase in (abdominal) fat apposition
- Osteoporosis
- Cardiovascular



# Deprivazione androgenica



Effetti collaterali	Trattamento/Profilassi
Perdita della libido	-
Disfunzione erettile	Inibitori fosfo-diesterasi 5 Iniezioni intra-cavernose
Vampate	Dietilstilbestrolo Ciproterone acetato - Clonidina
Ginecomastia	Radioterapia profilattica, Mastectomia - Tamoxifene - Inibitori aromatasi
Accumulo tessuto adiposo	Attività fisica
Perdita massa muscolare	Attività fisica
Osteoporosi	Calcio - Vitamina D – Bisfosfonati
Anemia	Eritropoietina
Declino cognitivo	-





### Disfunzione erettile

- ✓ It has been postulated that only 10 to 23% of men aged below 60 years regain their baseline potency after bilateral nerve-sparing radical prostatectomy (NSRP).
- ✓ The use of robot-assisted radical prostatectomy (RARP) has not significantly reduced these postoperative ED rates.
- ✓ A recent prospective trial comparing RARP to open retropubic radical prostatectomy (RRP) showed that only 29.6% of patients did not suffer from ED at 1 year following open RRP compared with 25.3% after RARP, despite RARP patients having a better performance status and more likely to undergo a nerve-sparing procedure



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# Hormone therapy

## Side effects



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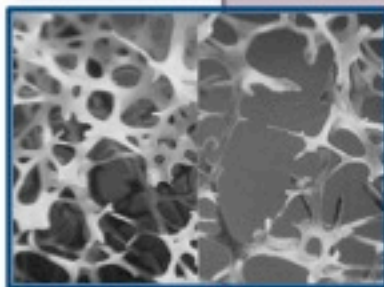
Conditions

Side-effects

Complications



Sarcopenic  
obesity



Bone  
loss

CV events

Osteoporosis

CV death

Fracture (SREs)



Roma, 9-12 novembre 2017

# La terapia con testosterone nel CP



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## Effect of Testosterone Replacement Therapy on Prostate Tissue in Men With Late-Onset Hypogonadism: A Randomized Controlled Trial

[Leonard S. Marks, MD](#) et al

*JAMA*. 2006;296(19):2351-2361. doi:10.1001/jama.296.19.2351

November 15, 2006

**Conclusions** These preliminary data suggest that in aging men with late-onset hypogonadism, 6 months of TRT normalizes serum androgen levels but appears to have little effect on prostate tissue androgen levels and cellular functions.

Establishment of prostate safety for large populations of older men undergoing longer duration of TRT requires further study.



## Testosterone Therapy in Men With Prostate Cancer

Alan L. Kaplan [a,\\*](#), Jim C. Hu [b](#),  
Abraham Morgentaler [c](#), John P.  
Mulhall [d](#), Claude C. Schulman [e](#),  
Francesco Montorsi  
**European Urology 2016**

**Table 1 – Summary of known evidence regarding testosterone deficiency**

Known evidence in testosterone deficiency	Levels of evidence
TD confers negative impact on health and quality of life [17–22]	1a
Testosterone therapy can mitigate untoward effects of TD [17–22]	1a
Higher endogenous serum androgen concentrations are not associated with increased risk of developing prostate cancer, or severity of prostate cancer [32,33]	1a
Testosterone therapy is not associated with increased risk or severity of prostate cancer [34–40]	2a
Impact of androgen on prostate cells is subject to a saturation effect [7,9,10,26–28]	2b
TD = testosterone deficiency.	

**Conclusions:** An improved understanding of the negative effects of testosterone deficiency on health and health-related quality of life—and the ability of testosterone therapy to mitigate these effects has triggered a re-evaluation of the role testosterone plays in prostate cancer. **An important paradigm shift has occurred** within the field, in which testosterone therapy may now be regarded as a viable option for selected men with prostate cancer suffering from testosterone deficiency.





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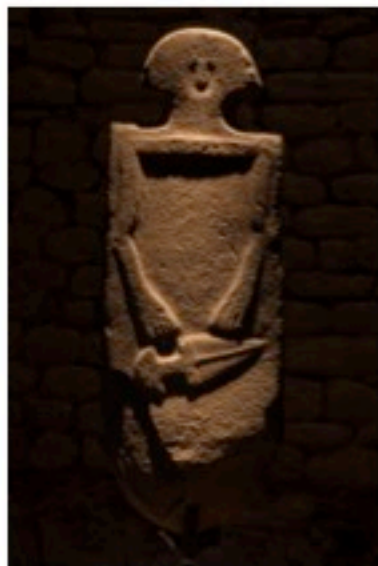
**... pertanto l'Endocrinologo può avere un ruolo importante all'interno della PU ...**



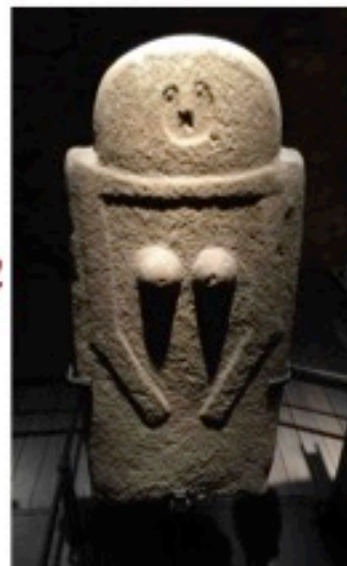
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*grazie per l'attenzione*



Statue stele Lunigiana (SP)