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References of Consensus 7 on Testosterone Therapy of Partial Androgen Deficiency in Men

I) The level of bio-available testosterone, along with levels of other androgens, declines as men age

Senescence in men is associated with a decline in testosterone levels

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The speed of age-related decline of serum testosterone in men

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Senescence in men is associated with a decline in metabolic clearance of testosterone

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Senescence in men is associated with alterations of the circadian cycle of serum testosterone levels: reduced amplitude and desynchronisation of its circadian rhythm

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The age-related decline of serum testosterone starts at middle age in men

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Senescence in men is associated with an increased peripheral conversion of androgens into estrogens: the increased estrogen level in aging males may inhibit the androgen production

14. Drafta D, Schindler AE, Stroe E, Neacsu E. Age-related changes of plasma steroids in normal adult males. *J Steroid Biochem.* 1982 Dec;17(6):683-7 (*"The age related changes of plasma steroids in elderly men, were suggestive of decreased testicular function with increased peripheral conversion of androgens into estrogens. ... The negative correlation between estrone and 17-OH-P (precursor of testosterone) found in elderly men, suggested that increased estrogen level in aging males may be considered able to inhibit the testicular androgen production"*)

II) The decline of androgens such as testosterone is associated with physical signs and psychic symptoms generally attributed to aging

1) Low testosterone levels may be associated with lower psychic well-being in men

Low equality of life and fatigue in men: the association with lower testosterone

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Depression in men: the association with lower testosterone levels

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Memory loss and Alzheimer's disease levels in men: the association with lower testosterone

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Loss of sexual drive, sensitivity and/or potency in men: the association with lower testosterone levels

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Sarcopenia in men: the association with low testosterone levels

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Lower lean body mass and higher fat mass in men: the association with lower testosterone levels

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Hypercholesterolemia in men: the association with lower testosterone levels

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Atherosclerosis in men: the association with lower testosterone levels

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Coronary heart disease in men: the association with lower testosterone levels

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Osteoporosis in men: the association with lower sex hormone levels

Lower estrogens and androgen levels

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Lower testosterone levels

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III) Diagnosis of Partial Testosterone Deficiency in men

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The importance of the laboratory tests

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Use of youthful (young adult) male reference values in the interpretation of laboratory tests

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3) Testosterone treatment may help to prevent or slow down age-related diseases in men

Hypercholesterolemia in men: the improvement with testosterone treatment

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Peripheral vascular disease (including intermittent claudication) in men: the improvement with testosterone treatment

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Diabetes in men: the improvement with testosterone treatment

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Rheumatism in men: the improvement with testosterone treatment

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Osteoporosis in men: the improvement with testosterone treatment

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Cancer in men: the protection with testosterone or dihydrotestosterone treatment?

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V) Caution with testosterone treatment

Testosterone/androgen treatment in men: safety, adverse effects, complications

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249. Westaby D, Ogle S, Paradinas F, Randell J, Murray-Lyon I. Liver damage from long-term methyltestosterone. *Lancet.* 1977;2:262-3

Importance of reducing excessive levels of estradiol in men

250. Leder BZ, Rohrer JL, Rubin SD, Gallo J, Longcope C. Effects of aromatase inhibition in elderly men with low or borderline-low serum testosterone levels. *J Clin Endocrinol Metab.* 2004 Mar;89(3):1174-80

251. Zumoff B, Miller LK, Strain GW. Reversal of the hypogonadotropic hypogonadism of obese men by administration of the aromatase inhibitor testolactone. *Metabolism*. 2003 Sep;52(9):1126-8.
252. Raman JD, Schlegel PN. Aromatase inhibitors for male infertility. *J Urol*. 2002 Feb;167(2 Pt 1):624-9
253. Chearskul S, Charoenlarp K, Thongtang V, Nitiyanant W. Study of plasma hormones and lipids in healthy elderly Thais compared to patients with chronic diseases: diabetes mellitus, essential hypertension and coronary heart disease. *J Med Assoc Thai*. 2000 Mar;83(3):266-77 (*"Hypertensive men had the highest plasma estradiol levels"*)
254. Cengiz K, Alvur M, Dindar U. Serum creatine phosphokinase, lactic dehydrogenase, estradiol, progesterone and testosterone levels in male patients with acute myocardial infarction and unstable angina pectoris. *Mater Med Pol*. 1991 Jul-Sep;23(3):195-8 (*"Serum estradiol levels in the patient groups were significantly higher than the control group (p < 0.001). There was a positively good correlation between the serum CPK and LDH levels in acute myocardial infarction and the serum estradiol levels. ... These results suggest that hyper estrogenemia may be a risk factor for myocardial infarct in middle-aged men."*)

..... and the Importance of avoiding too low levels of estradiol in men: risk of osteoporosis

255. Carlsen CG, Soerensen TH, Eriksen EF. Prevalence of low serum estradiol levels in male osteoporosis. *Osteoporos Int*. 2000;11(8):697-701

VI) Is prostate cancer an evidence-based contra-indication for testosterone treatment? It cannot be totally excluded that prostate cancer might constitute a contra-indication. However, there appears to be very little solid supporting evidence, despite the body of research on this issue.

Prostate cancer epidemiology

On the important annual incidence of (detected) prostate cancer in men who are alive in the United States

1. Data from the Surveillance, Epidemiology, and End Results (SEER) Program Staff. Section III: Incidence. In: *Cancer statistics review 1973-1986*. Bethesda, MD: NIH;1989;III.45

On the very high incidence of prostate cancer when biopsies are made in men aged 62 or over, even with low serum PSA

2. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. *J Clin Endocrinol Metab*. 1982 Jun;54(6):1104-8 (*Among the 2950 men (age range, 62 to 91 years), prostate cancer was diagnosed in 15.2 %; 14.9 % of the prostate cancers had a Gleason score of 7 or higher. The prevalence of prostate cancer was 6.6 % among men with a PSA level of up to 0.5 ng/ml, 10.1 % among those with values of 0.6 to 1.0 ng/ml, 17.0 % among those with values of 1.1 to 2.0 ng/ml, 23.9 % among those with values of 2.1 to 3.0 ng/ml, and 26.9 % among those with values of 3.1 to 4.0 ng/ml. The prevalence of high-grade cancers increased from 12.5 % of cancers associated with a PSA level of 0.5 ng/ml, or less to 25.0 % of cancers associated with a PSA level of 3.1 to 4.0 ng/ml. Conclusions: biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with PSA levels of 4.0 ng per milliliter or less — levels generally thought to be in the normal range.*)

On the real incidence of prostate cancer: much higher prevalence rate of prostate cancer is found at post-mortem

3. Stemmermann GN, Nomura AM, Chyou PH, Yatani R. A prospective comparison of prostate cancer at autopsy and as a clinical event: the Hawaii Japanese experience. *Cancer Epidemiol Biomarkers Prev*. 1992 Mar-Apr;1(3):189-93 (*"3.6% of men in life were diagnosed with prostate cancer, whereas 27% of autopsied Hawaii Japanese men who died after 50 years of age had prostate cancer, reaching a frequency of 63% among men over 80 years of age. The volume of 48(60%) of these cancers was less than 150 mm³. These small tumors would probably not have been discovered in a screening program. Tumors larger than 1000 mm³ would probably be discovered using modern diagnostic procedures but were found in only 13 (4.4%) of the autopsied men"*)
4. Oishi K, Yoshida O, Schroeder FH. The geography of prostate cancer and its treatment in Japan. *Cancer Surv*. 1995;23:267-80 (*"The vast majority of cases of prostate cancer remain undetected during life, the prevalence of prostate cancer detected at autopsy being 2800 times that of lethal cancer in Japanese in Japan, 570 times in whites in the USA and 470 times in blacks in the USA. A case-control study of prostate cancer carried out in Japan and the Netherlands revealed a number of*

- statistically significant risk factors, including ... no morning erections, , episodes of sexually transmitted disease, lower plasma testosterone and dihydrotestosterone concentrations.”)*
5. Sanchez-Chapado M, Olmedilla G, Cabeza M, Donat E, Ruiz A. Prevalence of prostate cancer and prostatic intraepithelial neoplasia in Caucasian Mediterranean males: an autopsy study. *Prostate*. 2003 Feb 15;54(3):238-47 (“*The prevalence of prostate cancer (CaP) is 3.58, 8.82, 14.28, 23.80, 31.7, and 33.33% in the 3rd, 4th, 5th, 6th, 7th, and 8th decades, respectively. The rates of high-grade prostatic intraepithelial neoplasia (HGPIN) were 7.14, 11.75, 35.71, 38.06, 45.40, and 48.15% at the 3rd, 4th, 5th, and 8th decades of life....in 21/27 cases (77.7%), an association between CaP and HGPIN was found. The prevalence of both lesions in Caucasian Mediterranean males is significantly lower than in Caucasian American and Afro-American males in all the age groups evaluated.*”)
 6. Rich AR. *J Urol*. 1935; 33: 215-33
 7. Baron E et al. *Arch Path*. 1941;32:787-93
 8. Dixon RJ et al. *Atlas of Tumor Pathology*. 1952, p.197

Prostate cancer patients have a low risk of dying from cancer

9. Stemmermann GN, Nomura AM, Chyou PH, Yatani R. A prospective comparison of prostate cancer at autopsy and as a clinical event: the Hawaii Japanese experience. *Cancer Epidemiol Biomarkers Prev*. 1992 Mar-Apr;1(3):189-93. (“*Prostate cancer was diagnosed in life among 274 of 8006 (3.6%) members of a cohort of Japanese men in Hawaii between 1965 and 1990. Only 55 (20%) of the 274 diagnosed cases died with prostate cancer, and they accounted for only 2% of the 2893 deaths that occurred among the men during this period.*”)
10. Quinn M. *Cancer Trends in the USA - A View From Europe*. *J Nat Cancer Inst*. 2003;95(17):1258-61

Prostate cancer, esp. non-metastized, is rarely a cause of death in men

11. Oishi K, Yoshida O, Schroeder FH. The geography of prostate cancer and its treatment in Japan. *Cancer Surv*. 1995;23:267-80
12. Oefelein MG, Ricchiuti VS, Conrad PW, Goldman H, Bodner D, Resnick MI, Seftel A. Clinical predictors of androgen-independent prostate cancer and survival in the prostate-specific antigen era. *Urology*. 2002 Jul;60(1):120-4

Side effects of testosterone/androgen deprivation therapy of prostate cancer

Androgen deprivation therapy may severely impair the quality of life

13. Dacal K, Sereika SM, Greenspan SL. Quality of life in prostate cancer patients taking androgen deprivation therapy. *J Am Geriatr Soc*. 2006 Jan;54(1):85-90 (“*Participants receiving androgen deprivation therapy (ADT) reported significantly poorer quality of life in the areas of physical function (P<.001), general health (P<.001), and physical health component summary (P<.001) than men not receiving ADT; After controlling for comorbidity, total testosterone level rather than ADT accounted for a small yet statistically significant percentage of the total variance of the physical health ..*”)
14. Chen AC, Petrylak DP. Complications of androgen-deprivation therapy in men with prostate cancer. *Curr Urol Rep*. 2005 May;6(3):210-6 (“*Androgen-deprivation therapy (ADT) is indicated for the treatment of metastatic prostate cancer and locally advanced disease. In addition to sexual side effects, long-term ADT results in several other changes, including hot flashes; gynecomastia; changes in body composition, metabolism, and the cardiovascular system; osteoporosis; anemia; psychiatric and cognitive problems; and fatigue and diminished quality of life*”)

Androgen deprivation causes anaemia

15. Choo R, Chander S, Danjoux C, Morton G, Pearce A, Deboer G, Szumacher E, Loblaw A, Cheung P, Woo T. How are hemoglobin levels affected by androgen deprivation in non-metastatic prostate cancer patients? *Can J Urol*. 2005 Feb;12(1):2547-52 (“*The decline and recovery of hemoglobine was closely related to that of testosterone.*”)

Androgen deprivation causes impotence

16. Basaria S, Lieb J 2nd, Tang AM, DeWeese T, Carducci M, Eisenberger M, Dobs AS. Long-term effects of androgen deprivation therapy in prostate cancer patients. *Clin Endocrinol (Oxf)*. 2002 Jun;56(6):779-86

17. Potosky AL, Knopf K, Clegg LX, Albertsen PC, Stanford JL, Hamilton AS, Gilliland FD, Eley JW, Stephenson RA, Hoffman RM. Quality-of-life outcomes after primary androgen deprivation therapy: results from the prostate cancer outcomes study. *J Clin Oncol*. 2001 Sep 1;19(17):3750-7
18. Fowler FJ, McNaughton Collins M, Walker Corkery E, Elliott DB, Barry MJ. The impact of androgen deprivation on quality of life after radical prostatectomy for prostate carcinoma. *Cancer*. 2002 Jul 15;95(2):287-95

Androgen deprivation therapy may cause urinary incontinence

19. Miller NL, Bissonette EA, Bahnson R, Wilson J, Theodorescu D. Impact of a novel neoadjuvant and adjuvant hormone-deprivation approach on quality of life, voiding function, and sexual function after prostate brachytherapy. *Cancer*. 2003 Mar 1;97(5):1203-10

Androgen deprivation therapy generates a greater rate of bone loss in men with prostate cancer

20. Preston DM, Torrens JI, Harding P, Howard RS, Duncan WE, McLeod DG. Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. *Prostate Cancer Prostatic Dis*. 2002;5(4):304-10

Testosterone deprivation therapy increases arterial stiffness in men with prostate cancer

21. Dockery F, Bulpitt CJ, Agarwal S, Rajkumar C. Testosterone suppression in men with prostate cancer is associated with increased arterial stiffness. *Aging Male*. 2002 Dec;5(4):216-22

Dihydrotestosterone deprivation therapy increases the risk of aggressive prostate cancer

22. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA Jr. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003 Jul 17;349(3):215-24

Arguments against population-based PSA screening for prostate cancer and against treatment of prostate cancer:

1. High prevalence rates of prostate cancer at postmortem
 2. Increasing biopsy rates leads to overdiagnosis and overtreatment
 3. Despite widespread use of such tests in the USA, and apparent incidence rates of detected prostate cancer almost 3 times higher than in the U.K., the mortality in the USA has for many years been almost the same as in the U.K. and other European countries
 4. 1/3 of screen-detected cases are incurable
 5. No clear benefit of treatment
 6. Side effects of prostatectomy include impotence in a large proportion of cases and incontinence in a smaller proportion
 7. Screening and follow-up of treatment (much of which may be unnecessary) is expensive (high costs)
 8. Few years of life to gain in many elderly patients
 9. No consequent reduction in mortality has yet been demonstrated in a randomized controlled trial
23. Quinn M. Cancer Trends in the USA-A View From Europe. *J Nat Cancer Inst*. 2003; 95 (17): 1258-61

ARGUMENTS FOR TESTOSTERONE THERAPIES in prevention of prostate cancer

HUMAN STUDIES:

Studies where low testosterone apparently increases the risk of prostate cancer

The urinary free testosterone decreases with aging, while the incidence of prostate cancer increases

24. Morer-Fargas F, Nowakowski H. Die Testosteronausscheidung im Harn bei Männlichen Individuen. *Acta Endocrinol*. 1965; 49: 443-52
25. Data from the Surveillance, Epidemiology, and End Results (SEER) Program Staff. Section III: Incidence. In: *Cancer statistics review 1973-1986*. Bethesda, MD: NIH;1989;III.45

Low serum testosterone is associated with an increased prostate cancer risk

26. Chen C, Weiss NS, Stanczyk FZ, Lewis SK, DiTommaso D, Etzioni R, Barnett MJ, Goodman GE. Endogenous sex hormones & prostate cancer risk: a case-control study nested within the Carotene and Retinol Efficacy Trial. *Cancer Epidemiol Biomarkers Prev.* 2003;12(12):1410-6
27. Stattin P, Lumme S, Tenkanen L, Alfthan H, Jellum E, Hallmans G, Thoresen S, Hakulinen T, Luostarinen T, Lehtinen M, Dillner J, Stenman UH, Hakama M. High levels of circulating testosterone are not associated with increased prostate cancer risk: a pooled prospective study. *Int J Cancer.* 2004 Jan 20;108(3):418-24

Low serum testosterone levels have been found in prostate cancer patients

28. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. *J Clin Endocrinol Metab* 1982 Jun;54(6):1104-8
29. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a "two-disease" theory. *Prostate.* 1982;3(6):579-88 (*Low testosterone in prostate cancer patients less than 65 years*)
30. Kumar VL, Wadhwa SN, Kumar V, Farooq A. Androgen, estrogen, and progesterone receptor contents and serum hormone profiles in patients with benign hypertrophy and carcinoma of the prostate. *J Surg Oncol.* 1990 Jun;44(2):122-8
31. Turkes AO, Turkes A, Read GF, Fahmy DR. A sensitive fluorometric enzyme immunoassay for testosterone in plasma and saliva [proceedings] *J Endocrinol.* 1979 Oct;83(1):31P
32. Vestsi Akademii Medicina Navuk USSR 1980; 3: 72-7 (*mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1)*)°
33. Revista Experimental Fisiology 1990; 46:63-8 (*mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1)*)
34. Revista Experimental Fisiology 1991; 47: 161-6 (*mentioned in The natural prostate cure (Proger Mason 2000 ISBN 1-884820-61-1)*)
35. Progress in Clinical Biological Research 1975; 6: 143-58 (*mentioned in The natural prostate cure - Proger Mason 2000 ISBN 1-884820-61-1)*)
36. Zhonghua Yi Xue Za Zhi 1993; 73: 489-90 (*mentioned in The natural prostate cure - Proger Mason 2000 ISBN 1-884820-61-1)*)

Close to statistical significance lower testosterone levels in prostate cancer patients

37. Hulka BS, Hammond JE, DiFerdinando G, Mickey DD, Fried FA, Checkoway H, Stumpf WE, Beckman WC Jr, Clark TD. Serum hormone levels among patients with prostatic carcinoma or benign prostatic hyperplasia and clinic controls. *Prostate.* 1987;11(2):171-82
38. Gustafsson O, Norming U, Gustafsson S, Eneroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer: a study of a randomized population. *Br J Urol.* 1996 Mar;77(3):433-40
39. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. *Cancer Res.* 1988 Jun 15;48(12):3515-7

Low testosterone levels are found in prostate cancer patients and in their (not yet affected) relatives with familial predisposition to prostate cancer

40. Meikle AW, Stanish WM. Familial prostatic cancer risk and low testosterone. *J Clin Endocrinol Metab.* 1982 Jun;54(6):1104-8

A high serum SHBG (and thus less bioavailable testosterone) is found in men with family history of prostate cancer

41. Wu AH, Whittemore AS, Kolonel LN, John EM, Gallagher RP, West DW, Hankin J, Teh CZ, Dreon DM, Paffenbarger RS Jr. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. *Cancer Epidemiol Biomarkers Prev.* 1995 Oct-Nov;4(7):735-41

A high incidence of prostate cancer is found in patients with low testosterone and normal digital rectal examination and normal PSA (≤ 4 ng/ml)

42. Morgentaler A, Bruning CO 3rd, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. *JAMA.* 1996 Dec 18;276(23):1904-6.

Low serum levels of total and bio-available testosterone are found in populations with a higher risk of prostate cancer (such as African-Americans and whites)

43. Wu AH, Whittemore AS, Kolonel LN, John EM, Gallagher RP, West DW, Hankin J, Teh CZ, Dreon DM, Paffenbarger RS Jr. Serum androgens and sex hormone-binding globulins in relation to lifestyle factors in older African-American, white, and Asian men in the United States and Canada. *Cancer Epidemiol Biomarkers Prev.* 1995 Oct-Nov;4(7):735-41 (*Asian-Americans had higher total and bioavailable testosterone compared to African-Americans and whites*)

Studies where a low serum dihydrotestosterone (DHT) was found in prostate cancer patients

44. Zumoff B, Levin J, Strain GW, Rosenfeld RS, O'Connor J, Freed SZ, Kream J, Whitmore WS, Fukushima DK, Hellman L. Abnormal levels of plasma hormones in men with prostate cancer: evidence toward a "two-disease" theory. *Prostate.* 1982;3(6):579-88 (*Low in prostate cancer patients less than 65 years*)
45. Signorello LB, Tzonou A, Mantzoros CS, Lipworth L, Lagiou P, Hsieh C, Stampfer M, Trichopoulos D. Serum steroids in relation to prostate cancer risk in a case-control study (Greece). *Cancer Causes Control.* 1997 Jul;8(4):632-6

A study where DHT is inversely, significantly, and strongly associated with the risk of prostate cancer

46. Signorello LB, Tzonou A, Mantzoros CS, Lipworth L, Lagiou P, Hsieh C, Stampfer M, Trichopoulos D. Serum steroids in relation to prostate cancer risk in a case-control study (Greece). *Cancer Causes Control.* 1997 Jul;8(4):632-6

Studies where close to statistical significance lower DHT levels were found in prostate cancer patients

47. Gustafsson O, Norming U, Gustafsson S, Eneroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer: a study of a randomized population. *Br J Urol.* 1996 Mar;77(3):433-40
48. Nomura A, Heilbrun LK, Stemmermann GN, Judd HL. Prediagnostic serum hormones and the risk of prostate cancer. *Cancer Res.* 1988 Jun 15;48(12):3515-7

High grade prostate cancers are associated with low testosterone levels

49. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM. (editorial note *A Bohle*). Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. *Int Braz J Urol.* 2005 Nov-Dec;31(6):609
50. Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, Graziottin TM. Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. *J Urol.* 2005 Dec;174(6):2178-80.
51. Schatzl G, Madersbacher S, Haitel A, Gsur A, Preyer M, Haidinger G, Gassner C, Ochsner M, Marberger M. Associations of serum testosterone with microvessel density, androgen receptor density and androgen receptor gene polymorphism in prostate cancer. *J Urol.* 2003 Apr;169(4):1312-5
52. Schatzl G, Madersbacher S, Thurnher T, Waldmuller J, Kramer G, Haitel A, Marberger M. High-grade prostate cancer is associated with low serum testosterone levels. *Prostate.* 2001 Apr;47(1):52-8
53. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? *J Urol.* 2000 Mar;163(3):824-7

Gene polymorphisms with increased risk of high grade prostate cancer are associated with low testosterone levels

54. Schatzl G, Marberger M, Remzi M, Grosser P, Unterlechner J, Haidinger G, Zidek T, Preyer M, Micksche M, Gsur A. Polymorphism in ARE-I region of prostate-specific antigen gene associated with low serum testosterone level and high-grade prostate cancer. *Urology.* 2005 Jun;65(6):1141-5

Metastatic prostate cancer (PC) is associated with a low serum testosterone compared to localized PC

55. Imamoto T, Suzuki H, Fukasawa S, Shimbo M, Inahara M, Komiya A, Ueda T, Shiraishi T, Ichikawa T. Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with radical prostatectomy. *Eur Urol.* 2005 Mar;47(3):308-12

A low serum testosterone level in patients with metastatic prostate cancer predicts a worse response to androgen withdrawal therapy (progression to androgen-independent prostate cancer)

56. Furuya Y, Nozaki T, Nagakawa O, Fuse H. Low serum testosterone level predicts worse response to endocrine therapy in Japanese patients with metastatic prostate cancer. *Endocr J*. 2002 Feb;49(1):85-90
57. Imamoto T, Suzuki H, Akakura K, Komiya A, Nakamachi H, Ichikawa T, Igarashi T, Ito H. Pretreatment serum level of testosterone as a prognostic factor in Japanese men with hormonally treated stage D2 prostate cancer. *Endocr J*. 2001 Oct;48(5):573-8

Lower prostate tissue levels of DHT (but similar levels of testosterone) are found in men with recurrent prostate cancer compared to men with benign prostate hypertrophy

58. Mohler JL, Gregory CW, Ford OH 3rd, Kim D, Weaver CM, Petrusz P, Wilson EM, French FS. The androgen axis in recurrent prostate cancer. *Clin Cancer Res*. 2004 Jan 15;10(2):440-8

Low testosterone levels are associated with an increased prostate cancer mortality in prostate cancer patients

59. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predict for a poor outcome in metastatic prostate cancer. *Am J Clin Oncol* 1997 Dec;20(6):605-8
60. Iversen P, Rasmussen F, Christensen IJ. Serum testosterone as a prognostic factor in patients with advanced prostatic carcinoma. *Scand J Urol Nephrol Suppl*. 1994; 157: 41-7
61. Haapiainen R, Rannikko S, Alfthan O, Adlercreutz H. Pretreatment plasma levels of testosterone and sex hormone binding globulin binding capacity in relation to clinical staging and survival in prostatic cancer patients. *Prostate*. 1988;12(4):325-32
62. Ribeiro M, Ruff P, Falkson G. Low serum testosterone and a younger age predict for a poor outcome in metastatic prostate cancer. *Am J Clin Oncol*. 1997 Dec;20(6):605-8.

A study where low testosterone levels are found in men with benign prostate hypertrophy

63. Ortega E, Ruiz E, Mendoza MC, Martin-Andres A, Osorio C. Plasma steroid and protein hormone concentrations in patients with benign prostatic hypertrophy and in normal men. *Experientia*. 1979 Jun 15;35(6):844-5

A study where a low androstenediol glucuronide level was found in patients with benign prostate hypertrophy

64. Wright F, Poizat, Bongini M, Bozzolan F, Doukani A, Mauvais-Jarvis P. Decreased urinary 5-alpha-androstenediol glucuronide excretion in patients with benign prostatic hyperplasia. *J Clin Endocrinol Metab*. 1985; 60 (2) 294-8

Men with chronic prostatitis have often low testosterone

65. Yunda IF, Imshinetskaya LP. Testosterone excretion in chronic prostatitis. *Andrologia*. 1977 Jan-Mar;9(1):89-94 (*In 73.1% of patients considerable reduction of testosterone excretion was revealed. Reduction of testicular endocrine function is in direct correlative dependence on severity of clinical symptoms, duration of disease and form of chronic prostatitis.*)

A history of prostatitis is positively associated with a history of benign prostatic hyperplasia and cancer

66. Daniels NA, Ewing SK, Zmuda JM, Wilt TJ, Bauer DC; Osteoporotic Fractures in Men (MrOS) Research Group. Correlates and prevalence of prostatitis in a large community-based cohort of older men. *Urology*. 2005 Nov;66(5):964-70 (*"We found positive associations for a history of prostatitis with a history of benign prostatic hyperplasia (odds ratio 8.0, 95% confidence interval 6.8 to 9.5) and a history of prostate cancer (odds ratio 5.4, 95% CI: 4.4 to 6.6)"*)

A study where testosterone treatment at high doses prevented the prostate stromal proliferation that estradiol may induce in the presence of physiological concentrations of testosterone

67. Feyel-Cabanes T, Secchi J, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on rat ventral prostate in organ culture. *Cancer Res*. 1978 Nov;38(11 Pt 2):4126-34.
68. Feyel-Cabanes T, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on the ventral lobe of the rat prostate in organ culture. *C R Acad Sci Hebd Seances Acad Sci D*. 1977 Oct 31;285(11):1119-22

Studies where testosterone treatment appears to protect against prostate cancer

Studies where testosterone/androgen treatment of patients with advanced prostate cancer increased their survival time and quality of life

69. Morales A, Connolly JG, Bruce AW. Androgen therapy in advanced carcinoma of the prostate. *Can Med Assoc J.* 1971;105(1):71-2
70. Prout GR Jr, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. *Cancer.* 1967 Nov;20(11):1871-8

Studies where testosterone /androgen treatment inhibits the proliferation of human prostate cancer cells or induces their apoptosis in vitro

71. Joly-Pharaboz MO, Soave MC, Nicolas B, Mebarki F, Renaud M, Foury O, Morel Y, Andre JG. Androgens inhibit the proliferation of a variant of the human prostate cancer cell line LNCaP. *J Steroid Biochem Mol Biol* 1995 Oct;55(1):67-76
72. Wolf DA, Schulz P, Fittler F. Synthetic androgens suppress the transformed phenotype in human prostate carcinoma cell line LNCaP. *Br J Cancer.* 1991 Jul; 64 (1): 47-53
73. Andrews P, Krygier S, Djakiew D. Dihydrotestosterone (DHT) modulates the ability of NSAIDs to induce apoptosis of prostate cancer cells. *Cancer Chemother Pharmacol.* 2002 Mar;49(3):179-86

Studies where testosterone treatment reduces prostate dysfunction complaints (dysuria, nocturia)

74. Flamm J, Kiesswetter H, Englisch M. An urodynamic study of patients with benign prostatic hypertrophy treated conservatively with phytotherapy or testosterone. *Wien Klin Wochenschr* 1979 Sep 28;91(18):622-7
75. Kearns WM. Testosterone in the treatment of testicular deficiency and prostatic enlargement. *Wisconsin Med J.* 1941; 40:927 (*testosterone propionate therapy did not reduce the size of the prostate, but reduced the dysuria*)
76. Meltzer M. Male hormone therapy of prostatic hypertrophy. *Lancet.* 1939; 59: 279
77. Trasoff A. The treatment of benign prostatic hypertrophy with testosterone propionate. *J Lab Clin Med.* 1940; 25: 377
78. Markham MJ. The clinical use of peroral methyltestosterone in benign prostatic hypertrophy. *Urol Cutan Rev.* 1942; 46: 225
79. Markham MJ. The clinical use of testosterone propionate in benign prostatic hypertrophy. *Urol Cutan Rev.* 1941; 45: 35
80. Laqueur E. Behandlung der Prostathypertropie mit männlichen Hormone (Hombreol) une experimentell Begründung dieser Therapie. *Schweiz Med Wochenschr.* 1934; 64: 1116
81. *South Med J,* 1939, 32: 154

Study where testosterone treatment reduces prostate stromal hyperplasia and prostatic complaints (prostatism)

82. *South Med J,* 1939, 32: 154

Studies where dihydrotestosterone treatment reduced the prostate volume (-15 to -20% after 1 year treatment)

83. de Lignieres B. Transdermal dihydrotestosterone treatment of 'andropause. *Ann Med* 1993 Jun;25(3):235-41
84. Swerdloff RS, Wang C. Dihydrotestosterone: a rationale for its use as a non-aromatizable androgen replacement therapeutic agent. *Baillieres Clin Endocrinol Metab.* 1998 Oct;12(3):501-6
85. Sitruk-Ware R. *Contraception,* 1989, 39: 1-191

ANIMAL STUDIES:

Studies where androgen deprivation stimulates the progression of hormone-sensitive mouse prostate cancer cells to hormone insensitive in vitro

86. Sato N, Watabe Y, Suzuki H, Shimazaki J. Progression of androgen-sensitive mouse tumor (Shionogi carcinoma 115) to androgen-insensitive tumor after long-term removal of testosterone. *Jpn J Cancer Res.* 1993 Dec;84(12):1300-8

Studies where antiandrogens (which cause androgen deficiency) may promote DMAB-induced prostate cancer incidence or increase its malignancy

87. Akaza H, Tsukamoto S, Morita T, Yamauchi A, Onozawa M, Shimazui T, Ideyama Y, Shirai T. Promoting effects of antiandrogenic agents on rat ventral prostate carcinogenesis induced by 3,2'-dimethyl-4-aminobiphenyl (DMAB). *Prostate Cancer Prostatic Dis.* 2000 Aug;3(2):115-9

88. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA Jr. The influence of finasteride on the development of prostate cancer. *N Engl J Med.* 2003;349(3):215-24

A study where significantly lower testosterone (and androstenedione) levels are found in mice with prostate inflammation. This means that testosterone (and androstenedione) may be necessary to counter prostate inflammation.

89. Bondarenko LA, Breslavskii AS, Vartapetov BA, Gladkova AI. Secretion of testicular androgens under conditions of chronic experimental inflammation of the prostate gland. *Probl Endokrinol (Mosk).* 1977 Jul-Aug;23(4):111-5

A study where testosterone treatment may prevent benign prostate hypertrophy by inhibiting stromal proliferation-induced by estradiol and by keeping prostate glandular cells health, preventing their atrophy in vitro

90. Feyel-Cabanes T, Secchi J, Robel P, Baulieu EE. Combined effects of testosterone and estradiol on rat ventral prostate in organ culture. *Cancer Res.* 1978 Nov;38(11 Pt 2):4126-34.

A study where testosterone treatment reduces the proliferation of mouse prostate cancer cells in vitro

91. Suzuki H, Nihei N, Sato N, Ichikawa T, Mizokami A, Shimazaki J. Inhibition of growth and increase of acid phosphatase by testosterone on androgen-independent murine prostatic cancer cells transfected with androgen receptor cDNA. *Prostate.* 1994 Dec;25(6):310-9

A study where testosterone treatment reduces the proliferation of guinea pig prostate stroma cells in vitro

92. Ricciardelli C, Horsfall DJ, Sykes PJ, Marshall VR, Tilley WD. Effects of oestradiol-17 beta and 5 alpha-dihydrotestosterone on guinea-pig prostate smooth muscle cell proliferation and steroid receptor expression in vitro. *J Endocrinol.* 1994 Mar;140(3):373-83

A study where testosterone treatment at high doses does not increase the incidence of prostate cancer cells in mice

93. Mainwaring WI. The effect of testosterone on the age-associated changes in the ventral prostate gland of the mouse. *Testosterone and ageing of the prostate. Gerontologia.* 1968;14(1):133-41

A study where testosterone, DHT and progesterone protects the prostate glandular epithelium against metaplasia and excessive stroma proliferation induced by estrogens in castrated male mice

94. Burrows H. *Nature (London).* 1936, 138: 164

A study where testosterone treatment of certain species of mice can inhibit prostate cancer growth

95. Umekita Y, Hiipakka RA, Kokontis JM, Liao S. Human prostate tumor growth in athymic mice: inhibition by androgens and stimulation by finasteride. *Proc Natl Acad Sci U S A* 1996 Oct 15;93(21):11802-7

Studies where dihydrotestosterone treatment of certain species of rats can inhibit prostate cancer growth

96. Pollard M. Dihydrotestosterone prevents spontaneous adenocarcinomas in the prostate-seminal vesicle in aging L-W rats. *Prostate* 1998 Aug 1;36(3):168-71
97. Pollard M, Luckert PH, Snyder D. Prevention and treatment of experimental prostate cancer in Lobund-Wistar rats. I. Effects of estradiol, dihydrotestosterone, and castration. *Prostate* 1989;15(2):95-103

A study where dihydrotestosterone treatment stimulates apoptosis of prostate cancer cells

98. Bruckheimer EM, Kyprianou N. Dihydrotestosterone enhances transforming growth factor-beta-induced apoptosis in hormone-sensitive prostate cancer cells. *Endocrinology.* 2001 Jun;142(6):2419-26

Breast Cancer in women: protection with testosterone or dihydrotestosterone treatment?

99. Dimitrakakis C, Jones RA, Liu A, Bondy CA. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause.* 2004 Sep-Oct;11(5):531-535

NEUTRAL EFFECTS OF TESTOSTERONE THERAPIES

REVIEW STUDIES where the authors did not find an adverse effect of testosterone levels or treatment on the prostate cancer risk

Review studies with conclusions that there is no data to support the view that testosterone treatment could increase the risk of prostate cancer, making e.g. a prostate cancer progress from a preclinical to a clinical stage

100. Rolf C, Nieschlag E. Potential adverse effects of long-term testosterone therapy. *Baillieres Clin Endocrinol Metab.* 1998 Oct;12(3):521-34.
101. Wirth MP, Hakenberg OW Testosterone and the prostate. *Urologe A* 2000 Sep;39(5):418-20
102. Morley JE. Testosterone replacement and the physiologic aspects of aging in men. *Mayo Clin Proc.* 2000 Jan;75 Suppl:S83-7 (*"There is no clinical evidence that the risk of either prostate cancer or benign prostate hypertrophy increases with testosterone treatment"*)
103. Rhoden NEJM 2004 (*"No compelling evidence at present to suggest that men with higher testosterone levels are at greater risk of prostate cancer or that treating men who have hypogonadism with exogenous androgens increases this risk. In fact, it should be recognized that prostate cancer becomes more prevalent exactly at the time of a man's life when testosterone levels decline."*)
104. Basaria S, Wahlstrom JT, Dobs AS. Anabolic-Androgenic Steroid Therapy in the Treatment of Chronic Diseases. *J Clin Endocrinol Metab.* 2001Nov;86(11):5108-17(*"...recent reviews suggest that the incidence of prostate cancer is not increased by testosterone administration"*)
105. Morales A. Androgen replacement therapy and prostate safety. *Eur Urol* 2002 Feb;41(2):113-20 (*"To date there is no evidence that exogenous androgens promote development of prostate cancer"*)
106. Prehn RT. On the prevention and therapy of prostate cancer by androgen administration. *Cancer Res.* 1999 Sep 1;59(17):4161-4 (*"... contrary to prevalent opinion, declining rather than high levels of androgens probably contribute more to human prostate carcinogenesis and ;.. androgen supplementation would probably lower the incidence of the disease. ... consider the possibility that the growth of androgen-independent prostate cancers might be reduced by the administration of androgens"*)

STUDIES with no association between serum androgen levels and prostate disease, including cancer

Studies with no significant difference in plasma testosterone and/or DHT and/or androstanediol glucuronide between prostate cancer patients and controls

107. Heikkila R, Aho K, Heliovaara M, Hakama M, Marniemi J, Reunanen A, Knekt P. Serum testosterone and sex hormone-binding globulin concentrations and the risk of prostate carcinoma: a longitudinal study. *Cancer.* 1999 Jul 15;86(2):312-5
108. Carter HB, Pearson JD, Metter EJ, Chan DW, Andres R, Fozard JL, Rosner W, Walsh PC. Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. *Prostate.* 1995 Jul;27(1):25-31
109. Nomura AM, Stemmermann GN, Chyou PH, Henderson BE, Stanczyk FZ. Serum androgens and prostate cancer. *Cancer Epidemiol Biomarkers Prev* 1996 Aug;5(8):621-5
110. Habib FK, Lee IR, Stitch SR, Smith PH. Androgen levels in the plasma and prostatic tissues of patients with benign hypertrophy and carcinoma of the prostate. *J Endocrinol* 1976 OCT;71(1):99-107
111. Vatten LJ, Ursin G, Ross RK, Stanczyk FZ, Lobo RA, Harvei S, Jellum E. Androgens in serum and the risk of prostate cancer: a nested case-control study from the Janus serum bank in Norway. *Cancer Epidemiol Biomarkers Prev* 1997 Nov;6(11):967-9
112. Wright F, Poizat R, Bongini M, Bozzolan F, Doukani A, Mauvais-Jarvis P. Decreased urinary 5-alpha-androstanediol glucuronide excretion in patients with benign prostatic hyperplasia. *J Clin Endocrinol Metab.* 1985; 60 (2) 294-8

Studies with no correlation between serum testosterone and serum PSA

113. Monath JR, McCullough DL, Hart LJ, Jarow JP. Physiologic variations of serum testosterone within the normal range do not affect serum prostate-specific antigen. *Urology* 1995 Jul;46(1):58-61
114. Monda JM, Myers RP, Bostwick DG, Oesterling JE. The correlation between serum prostate-specific antigen and prostate cancer is not influenced by the serum testosterone concentration. *Urology* 1995 Jul;46(1):62-4
115. Schatzl G, Reiter WJ, Thurridl T, Waldmuller J, Roden M, Soregi S, Madersbacher S. Endocrine patterns in patients with benign and malignant prostatic diseases. *Prostate* 2000;44(3):219-24
116. Vijayakumar S, Quadri SF, Dong L, Ignacio L, Kathuria IN, Sutton H, Halpern H. Results of a study to correlate serum prostate specific antigen and reproductive hormone levels in patients with localized prostate cancer. *J Natl Med Assoc* 1995 Nov;87(11):813-9

A study with no correlation between serum testosterone and prostate tumour volume, weight or Gleason score

117. Monda JM, Myers RP, Bostwick DG, Oesterling JE. The correlation between serum prostate-specific antigen and prostate cancer is not influenced by the serum testosterone concentration. *Urology*. 1995 Jul;46(1):62-4

A study where therapeutic androgen deprivation (blockade) has no beneficial effect on the evolution of the prostate cancer

118. Young HH 2nd, Kent JR. Plasma testosterone levels in patients with prostatic carcinoma before and after treatment. *J Urol*. 1968 Jun;99(6):788-92

A study with no significant association of serum testosterone with benign prostate hyperplasia

119. Lagiou P, Mantzoros CS, Tzonou A, Signorello LB, Lipworth L, Trichopoulos D. Serum steroids in relation to benign prostatic hyperplasia. *Oncology*. 1997 Nov-Dec;54(6):497-501

STUDIES where testosterone/androgen treatments had no adverse effect on the risk of prostate disease, including the risk of prostate cancer

Small clinical studies, performed before the days of PSA, where androgen treatment, usually with small dosages of androgen, did not stimulate the growth of many prostatic tumors and in some cases the tumours were even inhibited by the treatment; the responses were extremely variable

120. Prout GRJ, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. *Cancer (Phila.)*. 1967;20:1871-8
121. Trunnell JD, Duffy BJ Jr. The influence of certain steroids on the behavior of human prostate cancer. *Trans. NY Acad Sci*. 1950;11:238-41
122. Brendler H, Lowry O, Brock M. Further investigation of hormonal relationships. *Arch Surg*. 1950;61:433-40
123. Pearson OH. Discussion of Dr. Huggins' paper: "Control of cancers of man by endocrinological methods." *Cancer Res*. 1957;17:473-9
124. Morales A, Connolly J, Burr R, Bruce A. The use of radioactive phosphorus to treat bone pain in metastatic carcinoma of the prostate. *Can Med Assoc J*. 1970;103: 372-3

Studies where testosterone treatment had no significant effect on PSA and/or prostate volume

125. Cooper CS, Perry PJ, Sparks AE, MacIndoe JH, Yates WR, Williams RD. Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. *J Urol*. 1998 Feb;159(2):441-3
126. Cooper CS, MacIndoe JH, Perry PJ, Yates WR, Williams RD. The effect of exogenous testosterone on total and free prostate specific antigen levels in healthy young men. *J Urol*. 1996 Aug;156(2 Pt 1):438-41
127. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin Endocrinol (Oxf)*. 1994 Mar;40(3):341-9
128. Douglas TH, Connelly RR, McLeod DG, Erickson SJ, Barren R 3rd, Murphy GP. Effect of exogenous testosterone replacement on prostate-specific antigen and prostate-specific membrane antigen levels in hypogonadal men. *J Surg Oncol*. 1995 Aug;59(4):246-50
129. Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab*. 1997 Jun;82(6):1661-7
130. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. *J Clin Endocrinol Metab*. 1997 Nov;82(11):3793-6
131. Rhoden EL, Morgentaler A. Influence of demographic factors and biochemical characteristics on the prostate-specific antigen (PSA) response to testosterone replacement therapy. *Int J Impot Res*. 2005 Sep 22 (No statistical increase: average = 0.31 ng/ml after 1 year of treatment of hypogonadal men)
132. Shibasaki T, Sasagawa I, Suzuki Y, Yazawa H, Ichiyonagi O, Matsuki S, Miura M, Nakada T. Effect of testosterone replacement therapy on serum PSA in patients with Klinefelter syndrome. *Arch Androl*. 2001 Nov-Dec;47(3):173-6

A study where dihydrotestosterone treatment had no significant effect on serum PSA

133. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. *J Clin Endocrinol Metab.* 2002 Apr;87(4):1467-72

Studies where testosterone treatment increases the serum PSA but normalizes it in patients with initial atrophic prostate bringing it up to normal levels without any excessive increase

134. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin Endocrinol (Oxf).* 1994 Mar;40(3):341-9.
135. Behre HM, Nieschlag E. Testosterone buciclate (20 Aet-1) in hypogonadal men: pharmacokinetics and pharmacodynamics of the new long-acting androgen ester. *J Clin Endocrinol Metab.* 1992 Nov;75(5):1204-10
136. Guay AT, Perez JB, Fitaihi WA, Vereb M. Testosterone treatment in hypogonadal men: prostate-specific antigen level and risk of prostate cancer. *Endocr Pract.* 2000 Mar-Apr;6(2):132-8
137. McClellan KJ, Goa KL. Transdermal testosterone. *Drugs* 1998 Feb;55(2):253-8; discussion 259
138. Arver S, Dobs AS, Meikle AW, Caramelli KE, Rajaram L, Sanders SW, Mazer NA. Long-term efficacy and safety of a permeation-enhanced testosterone transdermal system in hypogonadal men. *Clin Endocrinol (Oxf).* 1997 Dec;47(6):727-37
139. Tenover JS. Effects of testosterone supplementation in the aging male. *J Clin Endocrinol Metab.* 1992 Oct;75(4):1092-8

Testosterone treatment does not increase the incidence of prostate disease

140. Hartnell J, 72nd Endocrine Soc. Meeting, 1990, A 428

A study where previous testosterone propionate treatment (terminated 1 to 7 years before the study) did not increase the risk of prostate hypertrophy or palpable prostate irregularities in men over 45 years, whatever the treatment length or dose

141. Lesser MA, Vose SN, Dixey GM. Effect of testosterone propionate on the prostate gland of patients over 45. *J Clin Endocrinol Metab.* 1955 Mar;15(3):297-300

Studies where DHT treatment had no effect on the prostate volume

142. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. *J Clin Endocrinol Metab.* 2002 Apr;87(4):1467-72.
143. Ly LP, Jimenez M, Zhuang TN, Celermajer DS, Conway AJ, Handelsman DJ. A double-blind, placebo-controlled, randomized clinical trial of transdermal dihydrotestosterone gel on muscular strength, mobility, and quality of life in older men with partial androgen deficiency. *J Clin Endocrinol Metab.* 2001 Sep;86(9):4078-88

ARGUMENTS AGAINST TESTOSTERONE THERAPIES in prevention of prostate cancer

Studies that suggest that testosterone may increase the prostate cancer risk

Prostate cancer: the association with high free testosterone levels

144. Parsons JK, Carter HB, Platz EA, Wright EJ, Landis P, Metter EJ. Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. *Cancer Epidemiol Biomarkers Prev.* 2005 Sep;14(9):2257-60(*critics: a potential bias may come from nutritional factors: individuals who eat a lot of food related to a higher cancer risk such as meat, particularly if cooked well-done, and/or milk, have also higher levels of testosterone as well as of other hormones associated with a higher cancer risk. Moreover, there is no information in this study on estradiol levels. This is important as the simultaneous presence of high levels of testosterone and estradiol may, following certain reports, increase the prostate cancer (PC) risk, not testosterone levels alone; heavy alcohol drinking, another risk factor for PC, that is in some countries of the world frequent can considerably increase both the estradiol levels and the PC risk in consumers. Other possible bias: data were not adjusted for other PC risk factors such as smoking, nutritional deficiencies, etc.*)
145. Mydlo JH, Tieng NL, Volpe MA, Chaiken R, Kral JG. A pilot study analyzing PSA, serum testosterone, lipid profile, body mass index and race in a small sample of patients with and without carcinoma of the

- prostate. Prostate Cancer Prostatic Dis. 2001;4(2):101-105 (*critics: no dietary factors were taken into account, only high BMI as a risk factor, none was serum SHBG analysed: dehydrated persons have usually high SHBG, and thus higher total testosterone, which is bound to it, but generally low active, bioavailable and free testosterone levels*)
146. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst. 1996 Aug 21;88(16):1118-26 (*critics: study did not consider dietary or BMI PC risk factors*)
147. Stahl F, Schnorr D, Pilz C, Dorner G. Dehydroepiandrosterone (DHEA) levels in patients with prostatic cancer, heart diseases and under surgery stress. Exp Clin Endocrinol. 1992;99(2):68-70 (*critic: no estrogen levels, nor dietary factors checked*)

Note: on the importance to check dietary factors:

Studies where the consumption of high amounts of protein and saturated fat such as milk products and meat increased testosterone levels

148. Sharpe RM, Martin B, Morris K, Greig I, McKinnell C, McNeilly AS, Walker M. Infant feeding with soy formula milk: effects on the testis and on blood testosterone levels in marmoset monkeys during the period of neonatal testicular activity. Hum Reprod. 2002 Jul;17(7):1692-703
149. Dorgan JF, Judd JT, Longcope C, Brown C, Schatzkin A, Clevidence BA, Campbell WS, Nair PP, Franz C, Kahle L, Taylor PR. Effects of dietary fat and fiber on plasma and urine androgens and estrogens in men: a controlled feeding study. Am J Clin Nutr. 1996 Dec;64(6):850-5
150. Hamalainen E, Adlercreutz H, Puska P, Pietinen P. Diet and serum sex hormones in healthy men. J Steroid Biochem. 1984 Jan;20(1):459-64
151. Volek JS, Kraemer WJ, Bush JA, Incledon T, Boetes M. Testosterone and cortisol in relationship to dietary nutrients and resistance exercise. J Appl Physiol. 1997 Jan;82(1):49-54

Milk or meat intake may increase the risk of prostate (in fact the increased risk may disappear if the vegetable intake which is lower in meat eaters is taken into account)

Link between meat, milk and/or protein intake, and prostate cancer

152. Norrish AE, Lynnette R. Ferguson, Mark G. Knize, James S. Felton, Susan J. Sharpe, Jackson RT. Heterocyclic Amine Content of Cooked Meat and Risk of Prostate Cancer. J Nat Cancer Inst. 1999; 91(23):2038-44
153. Wolk A. Diet, lifestyle and risk of prostate cancer. Acta Oncol. 2005;44(3):277-81
154. Grant WB. An ecologic study of dietary links to prostate cancer. Altern Med Review 1999; 4(3):162-9 (study in 14 European countries)

A study where higher levels of testosterone were found in patients who are in the advanced D-stage of PC, compared to the levels found in patients in the more moderate B and C-stages of prostate cancer

155. Imamoto T, Suzuki H, Akakura K, Komiya A, Nakamachi H, Ichikawa T, Igarashi T, Ito H. Pretreatment serum level of testosterone as a prognostic factor in Japanese men with hormonally treated stage D2 prostate cancer. Endocr J. 2001 Oct;48(5):573-8 (*note: but those in D-stage that had the highest testosterone had the best prognosis, including longer cancer-free survival time*)

A study where a higher rate of metastasis (-relapse) is found in prostate cancer patients with testosterone > 500 ng/dl that have been locally irradiated (*critic: the irradiation may change the risk*)

156. Zagars GK, Pollack A, von Eschenbach AC. Serum testosterone - a significant determinant of metastatic relapse for irradiated localized prostate cancer. Urology. 1997 Mar;49(3):327-34

A study where testosterone treatment increases the growth of prostate cancer: in vitro

157. Tymchuk CN, Barnard RJ, Ngo TH, Aronson WJ. Role of testosterone, estradiol, and insulin in diet- and exercise-induced reductions in serum-stimulated prostate cancer cell growth in vitro. Nutr Cancer. 2002;42(1):112-6