

Endogenous and exogenous testosterone and prostate cancer: decreased-, increased- or null-risk?

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Abstract: For more than 70 years, the contention that high levels of testosterone or that the use of testosterone therapy (TTh) increases the development and progression of prostate cancer (PCa) has been widely accepted and practiced. Yet, the increasing and emerging evidence on testosterone research seems to challenge that contention. To review literature on the associations of endogenous and exogenous testosterone with decreased-, increased-, or null-risk of PCa, and to further evaluate only those studies that reported magnitude of associations from multivariable modeling as it minimizes confounding effects. We conducted a literature search to identify studies that investigated the association of endogenous total testosterone [continuous (per 1 unit increment and 5 nmol/L increment) and categorical (high *vs.* low)] and use of TTh with PCa events [1990–2016]. Emphasis was given to studies/analyses that reported magnitude of associations [odds ratio (OR), relative risk (RR) and hazard ratios (HRs)] from multivariable analyses to determine risk of PCa and their statistical significance. Most identified studies/analyses included observational and randomized placebo-controlled trials. This review was organized in three parts: (I) association of endogenous total testosterone (per 1 unit increment and 5 nmol/L increment) with PCa; (II) relationship of endogenous total testosterone (categorical high *vs.* low) with PCa; and (III) association of use of TTh with PCa in meta-analyses of randomized placebo-controlled trials. The first part included 31 observational studies [20 prospective (per 5 nmol/L increment) and 11 prospective and retrospective cohort studies (per 1 unit increment)]. None of the 20 prospective studies found a significant association between total testosterone (5 nmol/L increment) and increased- or decreased-risk of PCa. Two out of the 11 studies/analyses showed a significant decreased-risk of PCa for total testosterone per 1 unit increment, but also two other studies showed a significant increased-risk of PCa. Remaining studies reported null-risk values. Second part: eight out of 25 studies reported an increased-risk of PCa for men with high levels of testosterone compared to low, but only four were statistically significant. However, 17 studies showed a decreased-risk of PCa after comparing high *vs.* low levels of testosterone, but 11 studies/analyses were statistically significant. Third part: two meta-analyses of randomized placebo-controlled trials (n=8 and n=11, each) that investigated use of TTh with PCa reported not significant decreased-risks of PCa. The contention that high levels of testosterone or that the use of TTh increases the risk of PCa doesn't seem to be supported from the literature. Yet, we still need a study with the adequate power, follow-up data, epidemiological, pathological and clinical data that can support the safety and beneficial effects of high levels of endogenous testosterone or use of TTh in the natural history of PCa and in men's health.

Keywords: Testosterone; treatment; endogenous; prostate; associations

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Introduction

The relationship between high levels of endogenous testosterone or use of testosterone therapy (TTh) with risk of prostate cancer (PCa) remains one of the long-standing controversies in urological research since the past 70 years (1). Some of the contributing factors to this controversy is that PCa is still the second most commonly diagnosed cancer and the sixth most common cause of cancer-related mortality among men worldwide (2,3). Although the five-year survival rate for PCa is extremely high (99%), advanced PCa has a markedly different prognosis with only a 34% five-year survival rate (4), making advanced PCa the clinically relevant outcome.

Another contributing factor has been the increasing interest about the positive and/or negative effects of testosterone in men's health in the last decade. For instance, low levels of testosterone, or testosterone deficiency (TD), is a common medical condition affecting men, and it is characterized by having total testosterone levels <300 ng/dL (5-8). TD has been linked to a constellation of signs and symptoms that may include sexual dysfunction, decreased bone density and decreased body lean mass (5), as well as other chronic conditions such as cancer and cardiovascular diseases to name a few (9-20). Studies show that approximately 38.7% of men over 45-year-old (18) [24% among men 30–79 years old (8)] demonstrate TD. In the United States, reports show that there are approximately 2.4 million 40–69 years old men with TD (21,22). Yet, a greater concern is the projection that by 2025 approximately 6.5 million American men aged 30 to 80 will suffer from TD (8). In consequence, treatment of TD with TTh has increased dramatically as well; TTh prescriptions increased more than 3-fold, from 0.81% in 2001 to 2.9% in 2011 (23,24). Surprisingly, the controversy about testosterone and PCa is not about TD and PCa, or in conjunction with its treatment (TTh), and PCa, but mainly about the contention that high levels of testosterone and use of TTh play a role in the development or progression of PCa. Therefore, the main objectives were to review the literature on the associations of endogenous [continuous (per 1 unit increment and 5 nmol/L increment) and categorical (high *vs.* low)] and exogenous testosterone with decreased-,

increased-, or null-risk of PCa; and to further evaluate only those studies that reported magnitude of associations from multivariable modeling, that will minimized confounding effects, and their statistical significance.

Criteria to define “decreased-risk”, “increased-risk”, and “null-risk” of PCa groups

In this review, we critically discuss previous and emerging literature on the association between continuous (per 1 unit increment and 5 nmol/L increment) and categorical (high *vs.* low) total testosterone and use of TTh with PCa from original observational research studies and meta-analyses of randomized-placebo controlled trials [1990–2016]. We mainly focused our search total testosterone due to a limited number of studies that reported free- or bioavailable-testosterone. The review is organized in three parts, where we report the association of (I) endogenous total testosterone [continuous (per 1 unit increment and 5 nmol/L increment)], (II) endogenous total testosterone (categorical high *vs.* low) and (III) use of TTh (meta-analyses) with decreased-, increased-, or null-risk of incident PCa cases. “Decreased-risk”, “increased-risk”, and “null-risk” of PCa groups were defined based on their magnitude of association, such as odd ratios (ORs), rate ratios or relative risk (RR), or hazard ratios (HRs), plus statistical significant values such as P value <0.05 or 95% confidence intervals (CIs) that does not include value of one. For instance, studies/analyses with “decreased-risk” had a magnitude of association (ORs, RRs, HRs) that is below 1; studies/analyses with “increased-risk” had ORs, RRs or HRs that are higher than 1; or “null-risk” if ORs, RRs and HRs is equal to 1 (or 0.999). These cutoff points were chosen arbitrarily, but magnitudes of association with values so close to the null (i.e., 0.999, 0.998, 1.01, 1.02) have a difficult clinical interpretation. In addition, we considered whether these magnitude of associations reached statistically significance (SS) or not (NS). For consistency, we only presented the magnitude of the association of PCa (aggressive and non-aggressive) for studies/analyses with continuous total testosterone (continuous increment of testosterone and 5 nmol/L increment) and those studies/analyses that categorized total

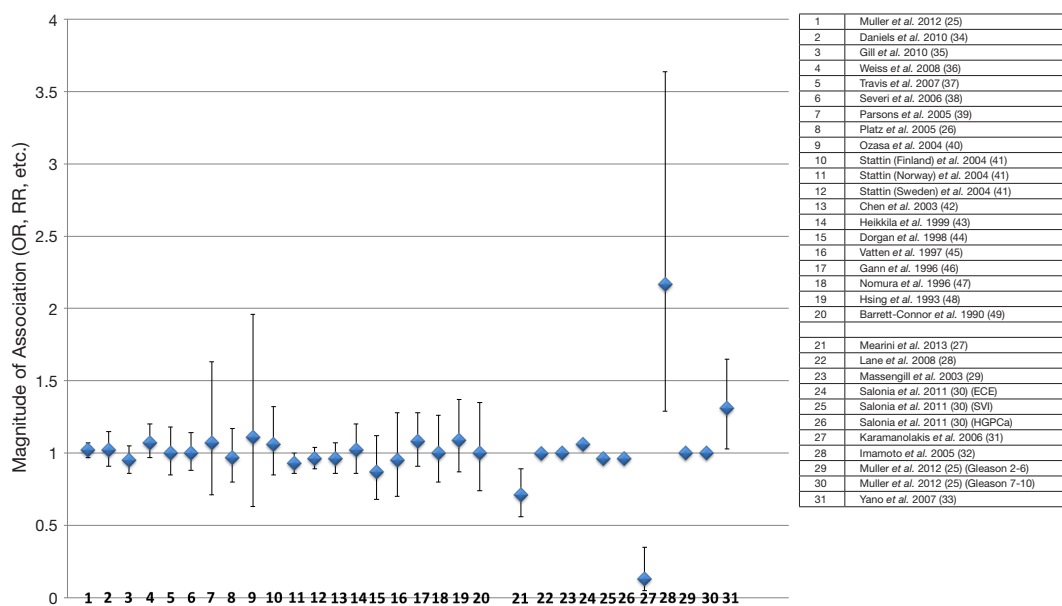


Figure 1 Serum testosterone (continuous and 5 nmol/L increments) in observational studies (prospective, retrospective) and its effects on PCa events (stage and grade). Studies/analyses only show multivariable analyses to minimize confounding effects. Magnitudes of association (ORs, RRs, etc.) and 95% CIs (25-49). PCa, prostate cancer; OR, odds ratio; RR, relative risk.

testosterone (high *vs.* low levels of testosterone). Some studies may be repeated twice because they independently investigated association of testosterone with aggressive and non-aggressive PCa; the rationale for this latter statement stems from studies (25,26) that reported opposite values for low-grade and high-grade (i.e., low-grade OR =1.91 and high-grade OR =0.26) as reporting only one value will be misleading. Therefore, we referred to these as studies/analyses, and they will be counted independently. Studies that reported their findings by comparing low to high categorical groups of total testosterone, we took the reciprocal of the magnitude of the association to present the comparison of high to low categorical groups (this is value only for studies that reported ORs). In addition, we recalculated their 95% CIs to determine their statistical significance. Furthermore, only those studies that adjusted for PCa risk factors in multivariable models were included to minimize confounding effects.

First part: association of endogenous total testosterone (continuous increment and 5 nmol/L increment) with decreased-, increased-, or null-risk of PCa

Thirty-one observational studies were identified that investigated the association of endogenous total testosterone

with risk of PCa (aggressive and non-aggressive) (25-49). Twenty studies (25,26,34-49), out of the 31, were prospective and previously analyzed in a meta-analysis to determine association of continuous (5 nmol/L increment) endogenous total testosterone with risk of PCa (Figure 1 and Table 1) (50). The remaining 11 studies/analyses (25,27-33), which some may be repeated because they reported findings for both aggressive and non-aggressive PCa in opposite directions (25,26), were a combination of prospective and retrospective studies that focused on the association of continuous total testosterone (per 1 unit increment) with PCa.

None of the twenty prospective studies reported a statistical significant association between continuous [5 nmol/L increment] total testosterone and increased- or decreased-risk of PCa [Figure 1 (numbers 1-20) and Table 1]. In fact, these 20 studies were used for analyses in a meta-analysis (50) that reported a summary RR of 0.99, which also did not reach statistical significance (95% CI =0.96-1.02).

Interestingly, two (27,31) of the 11 remaining studies/analyses, which were a combination of prospective and retrospective studies, showed a significant decreased-risks of PCa for continuous increment of total testosterone [OR =0.706; 95% CI =0.556-0.897 (27) and OR =0.13; 95% CI =0.05-0.35 (31)] [Figure 1 (numbers 21 and 27) and Table 1]. However, there were also two other studies (32,33) that

Table 1 Serum testosterone (continuous 5 nmol/L increments) in observational studies (prospective, retrospective) and its effects on PCa events (stage and grade). Only included studies that conducted multivariable analyses and reported magnitude of association (odds ratio, relative risk, etc.)

Study author and year	Study design	Number of participants for independent studies	Follow-up (years or months)	Total or free testosterone (continuous increment 5 nmol/L, low levels vs. high levels)	Prostate cancer: total, grade and/or stage (n)	Results: only adjusted multivariable models	Statistically significant (SS: P<0.05) or not significant (NS)
Mearini <i>et al.</i> 2013 (27)	Prospective	206 (103 PCa cases and 103 BPH)	Not applicable	Total testosterone, ng/mL	Total prostate cancer, n=103	Continuous: OR =0.706; 95% CI =0.556–0.897	SS (P=0.004)
Lane <i>et al.</i> 2008 (28)	Prospective study, radical prostatectomy	455	Median 14 (range 2–29 months)	Total testosterone, ng/dL	Gleason score pattern 4–5 at prostatectomy	Continuous: OR =0.998; 95% CI =0.997–1.000	SS (P=0.048)
Massengill <i>et al.</i> 2003 (29)	Retrospective, radical prostatectomy	879	Mean 37.7 (months)	Total testosterone, ng/dL	Extraprostatic disease (pT3–T4)-cancer on any inked margin, any capsular penetration, or pelvic lymph node or seminal vesicle involvement, n=343	Continuous: OR =0.999; 95% CI =0.998–1.000	SS (P=0.0464)
Salonia <i>et al.</i> 2011 (30)	Prospective, radical prostatectomy	673	Not applicable	Total testosterone, ng/mL	Extracapsular extension (ECE), n=96	Continuous: OR =1.06; 95% CI (not provided)	NS (P=0.26)
					Seminal vesicle invasion (SVI), n=88	Continuous: OR =0.96; 95% CI (not provided)	NS (P=0.47)
					High-grade prostate cancer (HGPCa) [defined with ECE, SVI, or Gleason grades (≥4+3)], n=153	Continuous: OR =0.96; 95% CI (not provided)	NS (P=0.48)
Karamanolakis <i>et al.</i> 2006 (31)	Prospective	85	Not applicable	Total testosterone, ng/mL	Incident prostate cancer, n=22	Continuous: OR =0.13; 95% CI =0.05–0.35	SS (P=0.0001)
Imamoto <i>et al.</i> 2005 (32)	Prospective, radical prostatectomy	82	Mean 20 (months)	Total testosterone, ng/mL	Extraprostatic disease (PT3-T4, N1), n= 24	Continuous: HR =2.167; 95% CI =1.291–3.637)	SS (P=0.0034)
Muller <i>et al.</i> 2012 (25)	Prospective	3,255	Prostate biopsy at 24 and 48 (months)	Total testosterone, nmol/L	Gleason 2–6, n=819	Continuous (untransformed): OR =1.0; 95% CI =0.99–1.03)	NS (P=0.59)
					Gleason 7–10, n=228	Continuous (untransformed): OR =1.00; 95% CI =0.98–1.03)	NS (P=0.72)
Yano <i>et al.</i> 2007 (33)	Retrospective	420	Not applicable	Total testosterone, ng/mL	Positive prostate biopsy	Continuous: HR =1.31; 95% CI =1.03–1.65	SS (0.02)

Table 1 (continued)

Table 1 (continued)

Study author and year	Study design	Number of participants for independent studies	Follow-up (years or months)	Total or free testosterone (continuous increment 5 nmol/L, low levels vs. high levels)	Prostate cancer: total, grade and/or stage (n)	Results: only adjusted multivariable models	Statistically significant (SS: P<0.05) or not significant (NS)
Muller <i>et al.</i> 2012 [†] (25)	Prospective	3,255	4 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=679)	Continuous (for 5 nmol/L): RR =1.02; 95% CI =0.97–1.07	NS
Daniels <i>et al.</i> 2010 [†] (34)	Prospective	2,025	4.7 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=275)	Continuous (for 5 nmol/L): RR =1.02; 95% CI =0.91–1.15	NS
Gill <i>et al.</i> 2010 [†] (35)	Prospective	1,388	1.9 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=452)	Continuous (for 5 nmol/L): RR =0.95; 95% CI =0.86–1.05	NS
Weiss <i>et al.</i> 2008 [†] (36)	Prospective	1,614	13 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=727)	Continuous (for 5 nmol/L): RR =1.07; 95% CI =0.97–1.20	NS
Travis <i>et al.</i> 2007 [†] (37)	Prospective	1,066	3.4 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=533)	Continuous (for 5 nmol/L): RR =1.00; 95% CI =0.85–1.18	NS
Severi <i>et al.</i> 2006 [†] (38)	Prospective	2,377	8.7 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=518)	Continuous (for 5 nmol/L): RR =1.00; 95% CI =0.88–1.14	NS
Parsons <i>et al.</i> 2005 [†] (39)	Prospective	794	18.5 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=88)	Continuous (for 5 nmol/L): RR =1.07; 95% CI =0.71–1.63	NS
Platz <i>et al.</i> 2005 [†] (26)	Prospective	896	5 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=448)	Continuous (for 5 nmol/L): RR = 0.97; 95% CI =0.80–1.17	NS
Ozasa <i>et al.</i> 2004 [†] (40)	Prospective	141	10 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=40)	Continuous (for 5 nmol/L): RR =1.11; 95% CI =0.63–1.96	NS
Stattin (Finland) <i>et al.</i> 2004 [†] (41)	Prospective	375	10.8 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=84)	Continuous (for 5 nmol/L): RR =1.06; 95% CI =0.85–1.32	NS
Stattin (Norway) <i>et al.</i> 2004 [†] (41)	Prospective	2,133	16.4 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=534)	Continuous (for 5 nmol/L): RR =0.93; 95% CI =0.86–1.00	NS

Table 1 (continued)

Table 1 (continued)

Study author and year	Study design	Number of participants for independent studies	Follow-up (years or months)	Total or free testosterone (continuous increment 5 nmol/L, low levels vs. high levels)	Prostate cancer: total, grade and/or stage (n)	Results: only adjusted multivariable models	Statistically significant (SS: P<0.05) or not significant (NS)
Stattin (Sweden) <i>et al.</i> 2004 [†] (41)	Prospective	423	3.5 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=86)	Continuous (for 5 nmol/L): RR =0.96; 95% CI =0.89–1.04	NS
Chen <i>et al.</i> 2003 [†] (42)	Prospective	600	3 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=300)	Continuous (for 5 nmol/L): RR =0.96; 95% CI =0.86–1.07	NS
Heikkilä <i>et al.</i> 1999 [†] (43)	Prospective	466	24 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=166)	Continuous (for 5 nmol/L): RR =1.02; 95% CI =0.86–1.20	NS
Dorgan <i>et al.</i> 1998 [†] (44)	Prospective	344	4.1 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=166)	Continuous (for 5 nmol/L): RR =0.87; 95% CI =0.68–1.12	NS
Vatten <i>et al.</i> 1997 [†] (45)	Prospective	239	10 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=59)	Continuous (for 5 nmol/L): RR =0.95; 95% CI =0.70–1.28	NS
Gann <i>et al.</i> 1996 [†] (46)	Prospective	612	6.3 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=222)	Continuous (for 5 nmol/L): RR =1.08; 95% CI =0.91–1.28	NS
Nomura <i>et al.</i> 1996 [†] (47)	Prospective	282	22 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=141)	Continuous (for 5 nmol/L): RR =1.00; 95% CI =0.80–1.26	NS
Hsing <i>et al.</i> 1993 [†] (48)	Prospective	196	13 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=98)	Continuous (for 5 nmol/L): RR =1.09; 95% CI =0.87–1.37	NS
Barrett-Connor <i>et al.</i> 1990 [†] (49)	Prospective	1,001	14 (years)	Total testosterone, nmol/L (increase of 5 nmol/L)	Incident prostate cancer (n=57)	Continuous (for 5 nmol/L): RR =1.00; 95% CI =0.74–1.35	NS

[†], previously meta-analyzed in Boyle *et al.* 2016 (50).

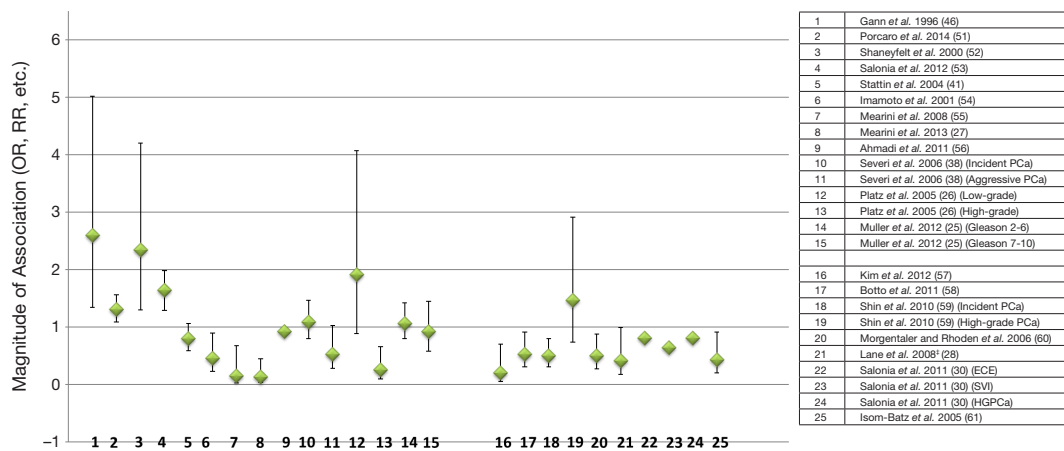


Figure 2 Serum testosterone (categorical: high *vs.* low levels) in observational studies (prospective, retrospective, case-control) and its effects on PCa events. Studies/analyses only show multivariable analyses to minimize confounding effects. Previous studies comparing low *vs.* high levels of testosterone were inverted to compare high *vs.* low levels of testosterone and 95% CIs were recalculated (25-28,30,38,41,46,51-61). PCa, prostate cancer.

showed significant increased-risks of PCa for continuous increment of total testosterone [HR =2.167; 95% CI =1.291–3.637 (32) and HR =1.31; 95% CI =1.03–1.65 (33)] [Figure 1 (numbers 28 and 31) and Table 1]. The remaining studies reported not significant and “null-risks” values for PCa [Figure 1 (numbers 22, 23, 24, 25, 26,29, 30)] (25,28-30).

Second part: relationship of endogenous total testosterone (categorical high *vs.* low) with decreased-, increased-, or null-risk of PCa

In this section, we identified 25 studies/analyses that investigated endogenous total testosterone in categorical format high *vs.* low levels (Figure 2 and Table 2) (25-28,30,38,41,46,51-61). This was a combination of prospective, retrospective, nested-control studies and one meta-analysis of two nested-control studies (52). There were some studies that originally reported low to high levels of testosterone [Figure 2 (numbers 16 to 25) and Table 2 (28,30,57-61)], but we converted these comparisons to high to low and recalculated the 95% CIs for statistical significance purposes. This conversion was conducted to maintain consistency among all studies about their comparison groups (high *vs.* low) and because the contention is that high levels of testosterone increase risk of PCa. For the meta-analyses [Figure 2 (number 3) and Table 2] of the two nested-control studies, we only provided the summary OR as the direction of the measure of association of both independent studies is similar to the meta-analyses (52).

Eight out of 25 studies/analyses reported an increased-risk of PCa for men with high levels of testosterone compared to low [Figure 2 (numbers 1–4, 10, 12, 14, 19)] (25,26,38,46,51-53,59), but only four were statistically significant (numbers 1–4) (46,51-53). The remaining 17 studies/analyses showed a decreased-risk of PCa after comparing high *vs.* low levels of testosterone [Figure 2 (numbers 5–9,11, 13, 15, 16, 17, 18, 19 and 20–25) and Table 2] (25-28,30,38,41,54-61), but only 11 were statistically significant [Figure 2 (numbers 6–9,13, 16, 17, 18, 20, 21, 25) and Table 2] (26,27,54-61).

Third part: association of use of TTh with decreased-, increased-, or null-risk of PCa in meta-analyses of randomized placebo-controlled trials

As of to date, two meta-analyses of randomized placebo-controlled trials that investigated use of TTh with risk of PCa have been conducted (Figure 3 and Table 3) (50,62). The first meta-analyses (62) consisted of 8 trials, and they were separated in two groups: first group (n=5 trials) consisted of men who used TTh for less than 12 months and the second group (n=3 trials) consisted of men who used TTh between 12 and 36 months. Findings from the first group reported a non-significant reduced-risk of PCa (summary OR_{<12 months} =0.74; 95% CI =0.25–4.65). However, results from the second group were considered null-risk of PCa (summary OR_{12-36 months} =0.99; 95% CI =0.24–4.02), possibly due to the few number of trials (3 trials) and small

Table 2 Serum testosterone (categorical: high vs. low levels) in observational studies (prospective, retrospective, case-control) and its effects on PCa events (stage and grade). Only included studies that conducted multivariable analyses and reported magnitude of association (odds ratio, relative risk, etc.). Previous studies comparing low vs. high levels of testosterone were inverted to compare high vs. low levels of testosterone and 95% CIs recalculated

Study author and year	Study design	Number of participants for independent studies	Follow-up (years)	Total or free testosterone [continuous increment (high levels vs. low levels)]	Prostate cancer: total, grade and/or stage (n)	Results: only adjusted multivariable models	Statistically significant (SS: P<0.05) or not significant (NS)
Gann <i>et al.</i> 1996 (46)	Prospective, nested case-control study	612	Mean 18 (range 12–48)	Total testosterone, ng/mL	Incident prostate cancer, n=222	High quartile (7.02 median) vs. low quartile (2.99); median: OR =2.60; 95% CI =1.34–5.02	SS (P for trend =0.004)
Porcaro <i>et al.</i> 2014 (51)	Retrospective, radical prostatectomy	220	Not applicable	Total testosterone, ng/mL (15.5 nmol/L converted to ng/mL)	Gleason score (high-grade tumor-pathology Gleason ≥8.0)	≥4.47 vs. <4.47: OR =1.31; 95% CI =1.09–1.56	SS
Shaneyfelt <i>et al.</i> 2000 (52)	Meta-analysis (2 nested case-control studies)	808 (320 cases/488 control)	12 years and 6.3	Total testosterone	Incident prostate cancer, n=320	High quartile vs. low quartile: OR =2.34; 95% CI =1.30–4.20	SS
Salonia <i>et al.</i> 2012 (53)	Retrospective, radical prostatectomy	724	Not applicable	Total Testosterone, ng/mL	High- or very high-risk (tumors stage, ≥T3a; Gleason score, 8–10; and serum PSA level, >20 ng/mL) of recurrence	>10 th –<90 th percentile: OR =0.64; 95% CI =0.54–0.80 90 th vs. 10 th of percentile: OR =1.64; 95% CI =1.29–1.98	SS (<0.01) SS (<0.01)
Stattin <i>et al.</i> 2004 (41)	Nested case-control study	2,242	Not applicable	Total testosterone, nmol/L Free testosterone, nmol/L	Total prostate cancer, n=708	High quintile vs. low quintile: OR =0.80; 95% CI =0.59–1.06 High quintile vs. low quintile: OR =0.82; 95% CI =0.60–1.14	NS (P for trend =0.05) NS (P for trend =0.44)
Imamoto <i>et al.</i> 2001 (54)	Retrospective	130	Mean 6.3 years	Total testosterone, ng/mL	Progression-free survival-metastatic prostate cancer (stage D2)	High vs. low (≥ 4.9 vs. <4.9 ng/mL): HR =0.46; 95% CI =0.23–0.90	SS (P=0.03)
Mearini <i>et al.</i> 2008 (55)	Prospective	65	Median 13 months	Total testosterone, ng/mL	Incident total prostate cancer	>2.4 vs. ≤2.4: OR =0.147; 95% CI =0.03–0.68	SS (P=0.014)

Table 2 (continued)

Table 2 (continued)

Study author and year	Study design	Number of participants for independent studies	Follow-up (years)	Total or free testosterone [continuous increment (high levels vs. low levels)]	Prostate cancer: total, grade and/or stage (n)	Results: only adjusted multivariable models	Statistically significant (SS: P<0.05) or not significant (NS)
Mearini <i>et al.</i> 2013 (27)	Prospective	206 (103 PCa cases and 103 BPH)	Not applicable	Total testosterone, ng/mL	Total prostate cancer, n=103	≥2.4 vs. <2.4 ng/mL: OR =0.134; 95% CI =0.039–0.453	SS (P=0.001)
Ahmadi <i>et al.</i> 2011 (56)	Hospital-based case-control study	511	Not applicable	Total testosterone, nmol/L	Incident total prostate cancer, n=194	>13.5 vs. ≤13.5: OR =0.92; 95% CI =0.89–0.96	SS (P for trend <0.001)
				Calculated free testosterone, nmol/L		>160.8 vs. ≤ 160.8: OR =0.99; 95% CI =0.98–0.99	SS (P for trend =0.04)
Severi <i>et al.</i> 2006 (38)	Case-Cohort design	2,383	Mean 8.7 years	Total testosterone, nmol/L	Incident total prostate cancer, n=614	4 th quartile vs. 1 st quartile: HR =1.09; 95% CI =0.80–1.47	NS (P for trend =0.9)
				Total testosterone, nmol/L	Aggressive prostate cancer (Gleason score >7 or poorly differentiated, stage T ₄ or N ₊ (positive lymph node) or M ₁ (distant metastases), n=88	4 th quartile vs. 1 st quartile: HR =0.53; 95% CI =0.28–1.03	SS (P for trend =0.03)
Platz <i>et al.</i> 2005 (26)	Nested case-control design	920	Not applicable	Total testosterone, ng/mL	Low-grade prostate cancer (Gleason sum <7)	4 th quartile vs. 1 st quartile: OR =1.91; 95% CI =0.89–4.07	SS (P for trend =0.02)
					High-grade prostate cancer (Gleason sum ≥7)	4 th quartile vs. 1 st quartile: OR =0.26; 95% CI =0.10–0.66	SS (P for trend =0.01)
Muller <i>et al.</i> 2012 (25)	Prospective	3,255	Prostate biopsy at 24 and 48	Total testosterone, nmol/L	Gleason 2–6, n= 819	Fifth quintile (20.6–45.7 nmol/L) vs. first quintile (2.7–10.3 nmol/L): OR =1.06; 95% CI =0.80–1.43)	NS (P=0.64)
					Gleason 7–10, n= 228	Fifth quintile (20.6–45.7 nmol/L) vs. first quintile (2.7–10.3 nmol/L): OR =0.92; 95% CI =0.58–1.45)	NS (P=0.70)

Table 2 (continued)

Table 2 (continued)

Study author and year	Study design	Number of participants for independent studies	Follow-up (years)	Total or free testosterone [continuous increment (high levels vs. low levels)]	Prostate cancer: total, grade and/or stage (n)	Results: only adjusted multivariable models	Statistically significant (SS: P<0.05) or not significant (NS)
Kim <i>et al.</i> 2012 [‡] (57)	Retrospective, radical prostatectomy	60	Mean 18 (range 12–48)	Total testosterone, ng/mL	Extraprostatic invasion	≥3 vs. <3 ng/mL: OR =0.20; 95% CI =0.057–0.706	SS
Botto <i>et al.</i> 2011 [‡] (58)	Prospective, radical prostatectomy	431	Not applicable	Total testosterone, ng/mL	Predominant Gleason Pattern 4 (Gleason score 7=4+3, 8=4+4, and 9=4+5), n=132	≥3 vs. <3 ng/mL: OR =0.53; 95% CI =0.31–0.91	SS
Shin <i>et al.</i> 2010 [‡] (59)	Prospective, prostate biopsy	568	Not applicable	Total testosterone, ng/mL	Total prostate cancer (incidence), n=194	≥3.85 vs. <3.85 ng/mL: OR =0.50; 95% CI =0.31–0.80	SS
					High grade prostate cancer (Gleason score ≥7), n=18	≥3.85 vs. <3.85 ng/mL: OR =1.47; 95% CI =0.74–2.91	NS
Morgentaler and Rhoden <i>et al.</i> 2006 [‡] (60)	Retrospective, hypogonadism	345	Not applicable	Total testosterone, ng/dL	Total prostate cancer, n=52	Total testosterone >250 vs. ≤250 ng/dL: OR =0.50; 95% CI =0.27–0.88	SS
Lane <i>et al.</i> 2008 [‡] (28)	Prospective study, radical prostatectomy	455	Median 14 (range 2–29)	Total testosterone, ng/dL	Gleason score pattern 4–5 at prostatectomy	≥220 vs. <220 ng/dL: OR =0.41; 95% CI = 0.18–0.99	SS
Salonia <i>et al.</i> 2011 [‡] (30)	Prospective, radical prostatectomy	673	Not applicable	Total testosterone, ng/mL	Extracapsular extension (ECE)	≥3 vs. <3 ng/mL: OR =0.81; 95% CI (not provided)	NS
					Seminal vesicle invasion (SVI)	OR =0.64; 95% CI (not provided)	NS
					HGPCa	OR =0.81; 95% CI (not provided)	NS
Isom-Batz <i>et al.</i> 2005 [‡] (61)	Retrospective, radical prostatectomy	326	Median 36 (range 4–133)	Total testosterone, ng/mL	Pathological stage (organ confined, focal or extracapsular extension, invasion into the seminal vesicles or nodal metastasis), n=245	≥ 300 vs. <300 ng/mL: OR =0.43; 95% CI =0.20–0.91	SS

[‡], low to high levels of testosterone comparison groups were inverted to compare “high to low” testosterone levels, and 95% CIs recalculated. ECE, extracapsular extension; SVI, seminal vesicle invasion; HGPCa, high-grade prostate cancer.

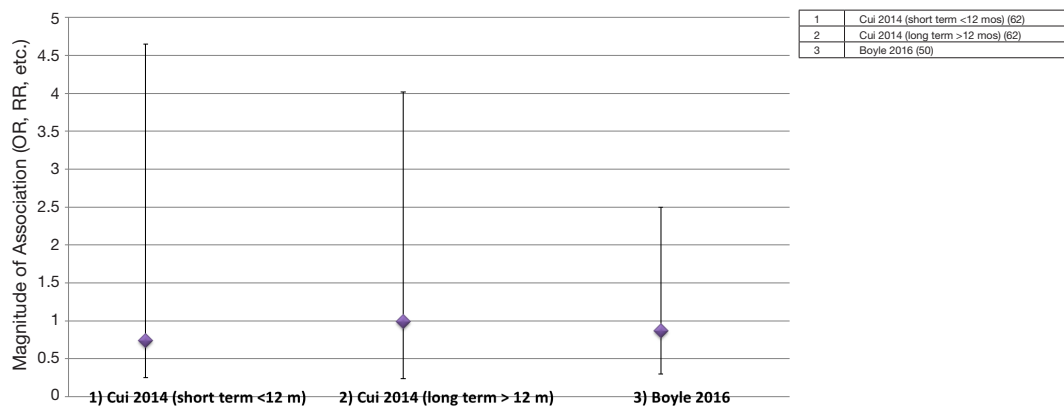


Figure 3 Meta-analyses of randomized controlled trials (RCTs) that investigated the effect of TTh on PCa events (stage and grade). Studies/analyses only show multivariable analyses to minimize confounding effects. Magnitudes of association (ORs, RRs, etc.) and 95% CIs (50,62). TTh, testosterone therapy; PCa, prostate cancer; OR, odds ratio; RR, relative risk.

Table 3 Meta-analyses of randomized controlled trials (RCTs) that investigated the effect of TTh on PCa events (stage and grade). Only included studies that conducted multivariable analyses and reported magnitude of association (odds ratio, relative risk, etc.)

Study author and year	Study design	Number of studies/trials	Number of participants (n)	TTh/ placebo (n)	Prostate cancer: total, grade and/or stage (n)	Results: only multivariable models	Statistically significant (SS: P<0.05) or not significant (NS)
Cui <i>et al.</i> 2014 (62)	Randomized controlled trials: short term (<12 months)	5	1,168	778/390	Incident prostate cancer, n=12	Summary: OR =0.74; 95% CI =0.25–4.65	NS
	Randomized controlled trials: long term (12–36 months)	3	379	191/188	Incident prostate cancer, n=6	Summary: OR =0.99; 95% CI =0.24–4.02	NS
Boyle <i>et al.</i> 2016 (50)	Randomized controlled trials (most of the trials <12 months)	11	2,013	1,114/899	Incident prostate cancer, n=20	Summary: OR =0.87; 95% CI =0.30–2.5	NS

sample size of PCa cases (n=6). The most recent meta-analyses (50), which included 11 trials, reported a reduced-risk of PCa for men who used TTh for less than 12 months, but it was not statistically significant (summary OR_{<12 months} =0.87; 95% CI =0.30–2.5).

Discussion

The contention that high levels of testosterone or that the use of TTh increases the risk of PCa doesn't seem to be supported with the present body of literature, which were adjusted for potential PCa risk factors. A significant number of observational studies (prospective and retrospective) that investigated the association of endogenous (continuous per 1 unit increment or 5 ng/mL increment) total testosterone with PCa were not statistically significant. Most of these

studies reported magnitudes of association that were null. On the other hand, those observational studies that categorized endogenous total testosterone (high *vs.* low) and investigated its relationship with PCa seemed to show a different picture; there were more studies/analyses reporting a reduced-risk of PCa (17 out of 25) than increased-risk of PCa (8 out of 25) among men with high levels of total testosterone compared to those with low levels. Most of these reduced-risks findings were statistically significant (11 out of 17) than the increased-risk of PCa ones (4 out of 8). Meta-analyses of randomized placebo-controlled trials that investigated use of TTh and its association with PCa were more consistent on reporting magnitude of associations of reduced-risks of PCa, but they did not reach statistical significance.

Although the contention of high levels of testosterone

is challenged by the body of literature presented, we can't conclude or promote that there is "zero" risk by using TTh or increasing levels of testosterone among PCa patients. It is important to note that any kind of epidemiologic study design experience different limitations such as sample size/power (mainly in randomized trials), no randomization (i.e., observational studies), no or limited follow-up data, different methodology on data collection and different definitions of exposures and outcomes to conduct pooled-analysis. In addition, comparison among studies is challenging as some studies define high *vs.* low levels of testosterone with different cutoff points or develop different criteria to define aggressive and non-aggressive PCa. Therefore, there is a need further studies with the adequate power, follow-up data, epidemiological and clinicopathological data that can provide a better explanation about the safety and protective effects of high levels of endogenous testosterone or use of TTh in the natural history of PCa and in men's health.

Furthermore, it seems that the long-standing controversy between endogenous/exogenous testosterone and PCa will remain for some time. First, the evolution of PCa research shows that advanced PCa is the most clinical relevant outcome (4). However, there are few studies, observational and randomized controlled trials, focusing on advanced PCa and endogenous/exogenous testosterone. In addition, there are significant racial disparities of PCa showing African-American men with the highest incident and mortality rates (63,64); yet, there are limited number of studies investigating the relationship between endogenous/exogenous testosterone and PCa among African-American men (65-67). These can be relevant research topics that should be addressed in future studies.

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Footnote

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