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Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate specific antigen (PSA): a meta-analysis

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Abstract

Objective: To review and quantify the association between endogenous and exogenous testosterone and prostate specific antigen (PSA) and prostate cancer.

Methods: Literature searches were performed following the PRISMA guidelines. Prospective cohort studies that reported data on the associations between endogenous testosterone and prostate cancer, and placebo controlled randomised trials of testosterone replacement therapy (TRT) that reported data on PSA and/or prostate cancer cases were retained. Meta-analyses were performed using random-effects models with tests for publication bias and heterogeneity.

Results: Twenty estimates were included in a meta-analysis which produced a summary relative risk of prostate cancer for an increase of 5 nmol/L of testosterone of 0.99 (95% CI (0.96, 1.02)) without heterogeneity ($I^2 = 0\%$). Based on 26 trials, the overall difference in PSA levels following onset of use of TRT was 0.10 ng/mL (-0.28, 0.48). Results were similar when conducting heterogeneity analyses by mode of administration, region, age at baseline, baseline testosterone, trial duration, type of patients and type of testosterone replacement therapy. The summary relative risk of prostate cancer as an adverse effect from 11 TRT trials was 0.87 (0.30; 2.50). Results were consistent across studies.

Conclusions: Prostate cancer appears to be unrelated to endogenous testosterone levels. Testosterone replacement therapy for symptomatic hypogonadism does not appear to increase PSA levels nor the risk of prostate cancer development. The current data are reassuring although some care is essential until multiple studies with longer follow-up are available.

Keywords: prostate cancer, testosterone, PSA, meta-analysis

Introduction

Testosterone is important for normal growth, development and maintenance of the prostate gland. Testosterone deficiency in aging men has become a topic of increasing interest and debate worldwide. Cross-sectional and longitudinal data indicate that testosterone levels are reduced progressively with age and that a significant percentage of men aged over 60 years have serum testosterone levels that are below the lower limits of young adult men aged 20–30 years [1-3]. Late onset hypogonadism (LOH) is a clinical and biochemical syndrome associated with advancing age and characterized by a deficiency in serum testosterone levels, among other signs and symptoms [4, 5]. Late onset hypogonadism may result in significant detriment to quality of life and adversely affect the function of multiple organ systems. Therefore, there has been a growing awareness of the potential health benefits of testosterone therapy for men with testosterone deficiency, including improved sexual desire and performance, improved mood, increased muscle mass and strength, decreased fat mass and improved bone mineral density [6].

More than 60 years ago, Huggins demonstrated that suppression of testosterone levels caused regression of prostate cancer, and it is now commonplace for men with metastatic prostate cancer to undergo treatment designed to lower testosterone levels [7]. Many urologists are concerned that testosterone replacement therapy may accelerate prostate growth not only in benign disease but also in cancer. If lowering testosterone causes prostate cancer to regress in men, does elevating testosterone cause prostate cancer to appear?

Prostate cancer is the second most common cancer in men and a high proportion of men harbour microscopic foci of prostate cancer [8]. It has been hypothesized that sex hormones and androgens in particular might be involved in prostate cancer carcinogenesis. Zaridze and co-workers concluded from qualitative analysis that there was little, if any, association between serum levels of testosterone and the risk of prostate cancer [9]. A collaborative analysis of 18 prospective studies on endogenous sex hormones and prostate cancer conducted in 2008 found no associations between the risk of prostate cancer and serum concentrations of testosterone, or other sex hormones [10]. Additionally, an increase in exogenous testosterone replacement therapies has been encouraged by media attention and marketing of new transdermal formulations (patches or gels) for the treatment of LOH. Several systematic reviews discussed about the benefits and risks of testosterone treatment [11-13], and several meta-analyses tried to quantify these risks [14-16].

This review aims at evaluating the potential relationship between testosterone and prostate cancer, and to synthesise all available data regarding the impact of testosterone replacement therapy (TRT) on changes in Prostate Specific Antigen (PSA) levels and on the risk of development of prostate cancer. Two approaches have been employed, separately for endogenous and exogenous testosterone. A meta-analysis of long-term observational data has been retained for quantifying the relationship between endogenous levels of testosterone and prostate cancer. A meta-analysis of short-term placebo-controlled randomised trials of testosterone supplementation and their adverse effects was done in order to test the hypothesis of a rapid acceleration of prostatic cancer development with the use of exogenous testosterone.

Methods

A systematic literature search and quantitative analysis was planned, conducted and reported following PRISMA guidelines [17]. Published reports were obtained from the Cochrane library and PUBMED. Other sources were found in the reference lists of the retrieved articles and preceding reviews on the topic. There was no restriction on geographical location of studies, but only articles published in English were considered. Articles were first screened by title and abstract. Then, full copies of the potentially relevant articles were retrieved and read by at least two co-authors. Data were then extracted in a predefined database by one author, and double-checked by the statistician who performed the analyses.

Endogenous testosterone

The Endogenous Hormones and Prostate Cancer Collaborative Group (EHPCCG) published a pooled analysis of 18 prospective studies [10]. Original articles from each study identified by the EHPCCG, including those not included in the pooled analysis, were retrieved. Then, a literature search was performed in May 2015 for the period 2007-2015 in order to collect articles published after the EHPCCG pooled analysis.

Only prospective studies including cohort studies, nested case-control studies, case-cohort studies and control arms of randomized controlled trials were eligible. Articles had to report risk estimates for prostate cancer according to baseline serum testosterone levels. The list of keywords for literature search is reported in supplementary figure (Figure S1). A dose-response meta-analysis was conducted for the calculation of the summary relative risk (SRR) corresponding to an increase of 5 nmol/L of baseline testosterone [18]. A change of 5nmol/L corresponds broadly to the average difference between tertiles of population in the studies included in the present meta-analysis. Heterogeneity analyses were performed in order to investigate potential sources of variation between studies: by region (USA, Europe), age at baseline (cut-off 65 years) and follow-up duration (cut-off 10 years).

The following variables were extracted: first author name and year of publication, country, baseline age, baseline testosterone (nmol/L), follow-up duration and for each quantile of testosterone, mean or median testosterone (nmol/L), number of subjects, person-years, relative risk estimate and 95% confidence interval (CI).

Exogenous testosterone

The meta-analyses focused on the potential associations between use of TRT and 1) changes in PSA level and 2) incidence of prostate cancer. Placebo-controlled, randomized trials reporting statistics on these two outcomes were eligible for the meta-analysis. The included outcome for change in PSA level could have been PSA level at baseline and end of study or change in PSA level during the study. For incidence of prostate cancer, it could have been number of prostate cancer occurring in each treatment arm, incidence rate, or odds-ratio comparing treatment arm to control group.

The following variables were extracted: first author name and year of publication, country, baseline age, baseline testosterone (nmol/L), follow-up duration, type of subjects (healthy or other), drug name and dose, mode of administration, number of participants by group, PSA level related data and number of prostate cancer cases by group.

Increase in PSA level

Data were abstracted on change in PSA level and its corresponding standard deviation. For studies that reported only baseline and end of study PSA with corresponding standard deviation, the variance of the average difference was estimated with the variance of PSA baseline and PSA end of study using a correlation factor to account for auto-correlation. This correction factor was calculated using data from the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial [19]. Detailed information about this correction factor are available in the Supplementary methods.

Heterogeneity analyses were undertaken by region (USA, Europe), mode of administration (transdermal, intramuscular, oral), type of patients (healthy subjects, subjects with pre-existing comorbidities), age at baseline (cut-off 65 years), trial duration (cut-off one year) and baseline testosterone (cut-off 11 nmol/L). This cut-off was chosen because it was the 5th percentile of the serum testosterone distribution of healthy men aged 35-44 [20]. An analysis by dose of testosterone could not be undertaken because of differences in modes and frequencies of administrations.

Prostate cancer

Following Cochrane review guidelines [21], studies reporting zero cases in both intervention and control arms were excluded. Since these studies deal with rare events, odds ratios and corresponding 95% CI were calculated applying a correction of 0.5 to all entries. The same heterogeneity analyses as for the TRT and PSA were conducted.

Meta-analysis

Meta-analyses were undertaken with restricted maximum likelihood (REML) random effects models [22]. The 95% confidence intervals of summary estimates were calculated using a t-distribution.

To summarize incidence of prostate cancer from TRT trials, because of very low event rates, the Mantel-Haenszel method was used [23, 24].

Heterogeneity across studies was evaluated by the Cochran's Q statistic and with Higgins' I^2 [25]. Publication bias was investigated using the funnel plot and Macaskill test [26], Begg test [27], and Egger test [28]. The meta-analyses were carried out in programming language R (version 3.0.0, GNU General Public License, 2013) and package *metafor* [29]. In addition to the heterogeneity analyses described above, sensitivity analyses, excluding one study at a time, were performed in order to evaluate the influence of individual studies on the overall result (leave-one-out). In sensitivity analysis, the association between endogenous testosterone and prostate cancer was also computed as a high versus low meta-analysis comparing the risk in the highest quantile of PSA to the lowest quantile of PSA.

Results

Endogenous testosterone levels and prostate cancer

The literature search yielded 151 articles. After title review, 27 articles were selected for abstract reading. Twenty studies reporting risk of prostate cancer for different levels of PSA were identified (Supplementary figure 1). Two studies provided data on testosterone levels to EHPCCG, but did not publish these data independently and could not be included in the present work [30, 31]. Data from the Janus databank were used twice in the pooled analysis, but the two datasets were independent and were considered as two separate studies [32, 33]. Stattin and colleagues published data from three cohorts and risk estimates were included separately [32]. Studies included in the meta-analysis included 5,623 prostate cancer cases and 14,604 controls. Average follow-up was 10 years (Table 1).

The summary relative risk (SRR) for an increase of 5 nmol/L of serum testosterone was 0.99 (95% CI (0.96; 1.02)). There was no evidence of heterogeneity (I^2 = 0%) nor of publication bias (p_{Begg} = 0.87; p_{Egger} = 0.17; $p_{Macaskill}$ = 0.69) (Figure 1). In addition, visual inspection of the funnel plot did not suggest publication bias. The leave-one-out analysis showed that no study taken individually had a big influence on the SRR. The heterogeneity analyses showed that results were consistent by region, age at baseline and duration of follow-up. A sensitivity analysis based on high versus low serum testosterone approach yielded similar results: SRR=0.98 (95% CI (0.88; 1.09)) (Table 3).

Testosterone supplementation and increase in PSA levels

Twenty-seven placebo-controlled trials were included in the quantitative analysis of testosterone supplementation and its adverse effects. Twenty-seven studies reported data on PSA levels, and 11 reported data on incidence of prostate cancer (Supplementary Figure 2). This involved a total of 2213 subjects in the intervention groups, and 1456 subjects in the placebo control groups. The median trial duration was 196 days. In 13 trials, TRT was administered transdermally (patch or gel), in nine trials intramuscularly, and in four trials orally. Thirteen studies were conducted in the United States, 10 in Europe, two in Asia and one in Australia. Fifteen trials were carried out in healthy subjects and 11 in patients with pre-existing comorbidities such as diabetes mellitus or metabolic syndrome (Table 2).

A total of 27 studies produced unique estimates of the change in PSA levels after onset of use of testosterone replacement therapy. One of them did not provide variability data and was excluded from the main analysis [34]. The summary difference (SES) in PSA levels was found to be SES=0.10 ng/mL (95% CI (-0.28; 0.48); (figure 2). There was no evidence of heterogeneity (I^2=0%). Tests of publication bias produced conflicting results: while visual inspection of the funnel plot did not suggest publication bias and while there was no evidence of publication bias from the Begg test (p_{Begg}=0.88) and the Macaskill test ($p_{Macaskill}$=0.52), the Egger test was statistically significant (p_{Egger}=0.01). In a sensitivity analysis, the study with no measure of dispersion was added, assuming a standard deviation of 1 in intervention and control arms; it did not modify the SES: 0.10 ng/mL (95% CI (-0.27; 0.48)).

Heterogeneity analyses revealed that the increase in PSA levels following testosterone supplementation were slightly higher among Americans (SES = 0.34 ng/ml) than in Europeans (SES = 0.09 ng/ml); in older subjects (SES for ≥ 65 years = 0.30 ng/ml vs. 0.11 ng/ml for under 65 years at baseline) and among subjects with high levels of testosterone

(SES = 0.25 ng/ml for baseline testosterone > 11 ng/mL vs. 0.07 ng/ml for others). However, these differences were small and did not reach statistical significance. TRT had a similar effect of PSA levels in healthy subjects and others. Duration of the trial had no influence on the results. There were not enough studies in the analysis by subtype of testosterone to draw conclusions (Table 3).

Testosterone supplementation and risk of prostate cancer

A total of 11 studies produced unique estimates of the risk of prostate cancer diagnosis associated following the use of testosterone replacement therapy (Table 2). The Summary Odds Ratio (SOR) was 0.87 (95% CI (0.30; 2.50)) based on 20 prostate cancer cases. There was no evidence of heterogeneity (I^2=0%) nor publication bias (p_{Begg}=0.82, p_{Egger}=0.26, $p_{Macaskill}$=0.70 (Figure 3). From the leave-one-out analysis, no study had a big impact on the SOR. In a sensitivity analysis, prostate cancer cases diagnosed during open-label extensions of studies were included. Three new cases of prostate cancer and two additional studies were included in this analysis [34, 35]; these did not modify the results: SOR = 0.84 (95% CI (0.31; 2.25)).

Results of heterogeneity analyses should be interpreted with caution because of the low number of studies included in each analysis, resulting in poor statistical power. None of the subgroup analysis showed a statistically significant increased risk of prostate cancer (Table 3).

Discussion

Endogenous Testosterone

Serum androgens in general and testosterone in particular have been widely studied in relationship with prostate cancer development as they are potential risk factors for this disease. Results of individual studies often lacked of statistical power and were sometimes inconsistent with each other. In 2008, the EHPCCG conducted a large pooled analysis in order to summarize the existing evidence on this topic [10]. No association was found between levels of sex hormones, including testosterone, and incidence of prostate cancer.

The present work included four new studies compared to the earlier pooled analysis. In addition, this meta-analysis used a dose-response modelling instead of using a high vs. low approach. Our results confirmed those of the EHPCCG pooled analysis, i.e. high serum testosterone levels were not associated with increased risk of prostate cancer in prospective observational studies. Heterogeneity analyses showed that results were similar by region, age at baseline and duration of follow-up.

Exogenous testosterone

Testosterone supplementation for the treatment of hypogonadism is controversial. With the direct-to-consumer advertising and very rapid increase in testosterone prescription, some authors suggested that hypogonadism was largely disease mongering [36]. There is some evidence to suggest improved libido, muscle mass or mood [6], but also several concerns about the possible stimulation of prostate growth.

There was no evidence of increased PSA levels after testosterone supplementation from an analysis of data from 27 placebo controlled, randomized trials. No major source of heterogeneity was identified. From the 11 trials reporting prostate cancer cases, the meta-analysis found no evidence of an increased risk of prostate cancer associated with testosterone replacement therapy.

A limitation to this analysis is the relative short duration of the trials with most of the trials lasting less than one year. This was an issue mainly for the prostate cancer analysis. With such a short follow-up, few prostate cancers cases were reported, resulting in low statistical power. The analysis restricted to studies with a follow-up greater than one year did not show an increase risk of prostate cancer nor a change in PSA level. A possible publication bias might be taken into consideration, as more than half of the articles that were found otherwise eligible, were excluded because they did not report enough data.

These results were consistent with data reported in previous meta-analyses. Cui and colleagues [14], using data from eight trials, concluded that TRT did not promote prostate cancer development; furthermore, using data from 12 trials, they found no difference in abnormal PSA levels between treated and un-treated patients. Fernandez-Balsells and colleagues reported the SRR for prostate cancer to be 0.79 (95% CI (0.28; 2.28)), based on five studies [16]. Calof and colleagues concluded that the number of “prostate events” (biopsies, cancers, increase in IPSS > 4, PSA > 4 ng/mL or PSA increment > 1.5 ng/mL during treatment, and acute urinary retention) was higher in the intervention group than in the placebo group (pooled OR 1.78 (95% CI 1.07; 2.95)). However, the risk of “prostate events” was essentially limited to prostate biopsies (pooled OR 1.87), and prostate cancer alone was not significantly higher (pooled OR 1.09 (95% CI 0.48; 2.49)) [15].

It could also be hypothesised that the potential impact of testosterone therapy on prostate growth be limited to older men, or individuals with initially low level of testosterone, or vary according to route of administration. However, none of the heterogeneity analysis confirmed these hypotheses.

Conclusions

The earlier work of the EHPCCG showed no association between serum testosterone levels and risk of prostate cancer [10]. More recent studies confirmed this lack of association; no individual study found any increased or decreased risk of prostate cancer among men with high levels of testosterone compared to lower levels. Meta-analysis showed no association between testosterone levels and prostate cancer risk. Prostate cancer development appears unrelated to endogenous serum testosterone levels.

The available data do not support an increase in the risk of prostate cancer associated with testosterone replacement therapy nor do they support a change in PSA levels when testosterone replacement therapy is used. Testosterone replacement therapy for symptomatic hypogonadism does not appear to increase PSA levels nor the risk of prostate cancer development. The current data are reassuring although some care is still essential until multiple studies with longer follow-up are available.

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Legends to Figures

Figure 1: Serum testosterone and risk of prostate cancer (Dose-response meta-analysis)

Figure 2: Testosterone Replacement Therapy (all forms) and absolute difference in PSA levels.

Figure 3: Testosterone Replacement Therapy risk of prostate cancer

Table 1. Description of studies included in the endogenous testosterone levels and prostate cancer analysis

Author, year (acronym) [reference]	Country	Design	Cases	Non-cases	Age	Baseline Testosterone (nmol/L)	Follow-up (years)
Barrett-Connor, 1990 (RBS) [37]	USA	Cohort	57	944	63	18.0	14
Chen, 2003 (CARET) [38]	USA	NCC	300	300	61	14.8	3
Daniels, 2010 (OFM) [39]	USA	Cohort	275	1750	73	14.3	4.7
Dorgan, 1998 (ATBC) [40]	Finland	NCC	116	228	61	20.3	4.1
Gann, 1996 (PHS) [41]	USA	NCC	222	390	62	16.4	6.3
Gill, 2010 (MEC) [42]	USA	NCC	452	936	69	18.9	1.9
Heikkila, 1999 (FMC) [43]	Finland	NCC	166	300	58	25.1	24
Hsing, 1993 (CLUE I) [44]	USA	NCC	98	98	65	15.5	13
Muller, 2012 (REDUCE) [45]	USA	Placebo arm of RCT	679	2576	63	15.8	4
Nomura, 1996 (JHCS) [46]	USA	NCC	141	141	62	18.7	22
Ozasa, 2004 (JACC) [47]	Japan	NCC	40	101	69	15.8	10
Parsons, 2005 (BLSA) [48]	USA	Cohort	88	706	52	16.0	18.5
Platz, 2005 (HPFS) [49]	USA	NCC	448	448	65	16.8	5
Severi, 2006 (MCCS) [50]	Australia	Case-cohort	518	1859	55	15.7	8.7
Stattin, 2004 (NBSBWG/HHS) [32]	Finland	NCC	84	291	51	20.7	10.8
Stattin, 2004 (NBSBWG/NSHDC) [32]	Sweden	NCC	86	337	59	30.7	3.5
Stattin, 2004 (NBSBWG/Janus) [32]	Norway	NCC	534	1599	47	23.6	16.7
Travis, 2007 (EPIC) [51]	Europe	NCC	533	533	61	15.7	3.4
Vatten, 1997 (Janus)[33]	Norway	NCC	59	180	59	19.9	10
Weiss, 2008 (PLCO) [52]	USA	NCC	727	887	66	17.2	13

ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BLSA: Baltimore Longitudinal Study of Aging; CARET: Carotene and Retinol Efficacy Trial; CLUE I: CLUE Study; EPIC: European Prospective Investigation into Cancer and Nutrition; FMC: Finnish Mobile Clinic Health Examination Survey; HHS: Helsinki Heart Study; NBSBWG: Nordic Biological Specimen Biobank Working Group; HPFS: Health Professionals Follow-up Study; JACC: Japan Collaborative Cohort Study; Janus: Janus Serum Bank; JHCS: Japan – Hawaii Cancer Study; MCCS: Melbourne Collaborative Cohort Study; MEC: Multiethnic cohort; NSHDC: Northern Sweden Health and Disease Cohort; OFM: Osteoporotic fractures in men; PHS: Physicians' Health Study; PLCO: Prostate, Lung, Colorectal and Ovarian cancer screening trial; RBS: Rancho Bernardo Study; REDUCE: Reduction by Dutastenide of Prostate cancer events trial

Table 2. PSA and prostate cancer outcomes in trials of testosterone replacement therapy included in meta-analysis

Study	Mode	Duration (days)	Subjects (Intervention)	Subjects (Control)	Country	Study population	Age	Baseline testosterone (nmol/L)
Amory, 2004 [53]	IM	1095	24	24	USA	Healthy	71	10.2
Aversa, 2010 [54]	IM	365	40	10	Italy	MS/T2DM	58	8.5
Basaria, 2010 [55]	TD	180	106	103	USA	Limitations in mobility	74	8.4
Behre, 2012 [56]	TD	180	183	179	Europe	Healthy	62	10.5
Bhasin, 1998 [57]	TD	84	20	21	USA	HIV infected	39	8.1
Caminiti, 2009 [58]	IM	84	35	35	Italy	CHF	71	7.6
Chiang, 2009 [59]	TD	90	20	20	Taiwan	Healthy	47.5*	0.6
Emmelot-Vonk, 2008 [60]	oral	180	113	110	The Netherlands	Healthy	67	10.7
Ferrando, 2002 [61]	IM	180	7	5	USA	Healthy	68	12.6
Hackett, 2013 [62]	IM	210	92	98	UK	T2DM	61	9.1
Hildreth, 2013 [63]	TD	365	111	56	USA	Healthy	67	10.3
Holmäng, 1993 [64]	Oral	240	11	12	Sweden	Healthy	52	16.4
Jones, 2011 [65]	TD	365	108	112	Europe	MS/T2DM	60	9.4
Kalinchenko, 2010 [66]	IM	210	113	71	Russia	MS	52	7.0
Kaufman, 2011 [35]	TD	182	234	40	USA	Healthy	54	10.0
Kenny, 2001 [67]	TD	365	34	33	USA	Healthy	76	13.5
Kenny, 2004 [68]	IM	84	6	5	USA	Early cognitive decline	80	14.1
Kenny, 2010 [69]	TD	365	53	46	USA	Osteoporosis/frailty	77	13.8
Malkin, 2006 [70]	TD	365	37	39	UK	CHF	64	13.0
Marks, 2006 [71]	IM	180	22	22	USA	Healthy	69	8.2
Morgentaler, 2014 [34]	TD	182	234	40	USA	Healthy	54	8.5
Nair, 2006 [72]	TD	730	30	32	USA	Healthy	67	13.2
Park, 2003 [73]	Oral	90	33	6	South Korea	Healthy	NR	9.2
Sih, 1997 [74]	IM	365	17	15	USA	Healthy	68	9.2

Snyder, 1999 [75]	TD	1095	54	54	USA	Bone mineral density < 1.26 g/cm²	73	12.8
Srinivas-Shankar, 2010 [76]	TD	180	130	132	UK	Frailty	74	10.9
Steidle, 2003 [77]	TD	90	307	99	USA	Healthy	58	8.1
Wittert, 2003 [78]	Oral	365	39	37	Australia	Healthy	69	16.3

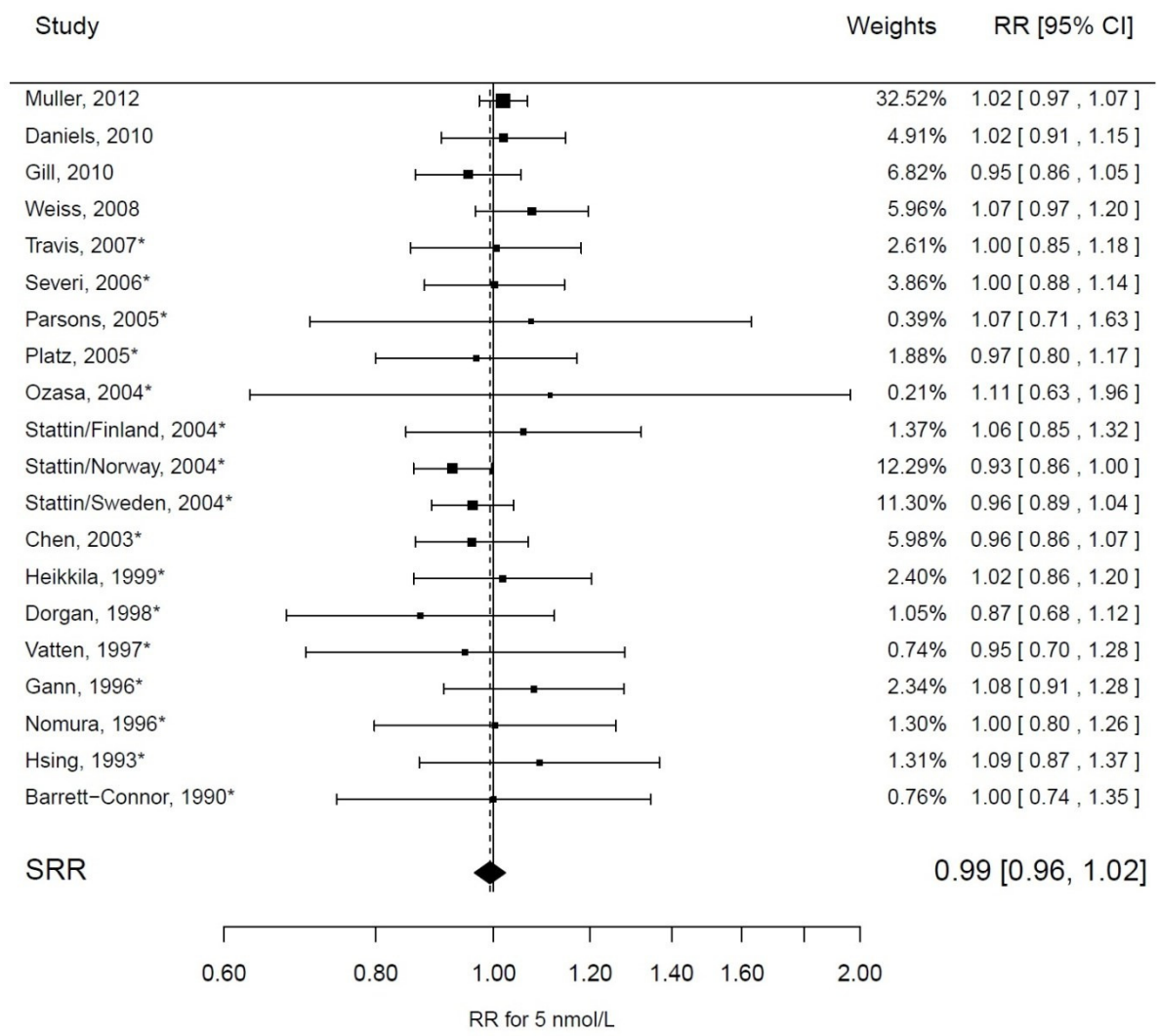
TD=Transdermal (includes testosterone patches or testosterone gels); IM = Intramuscular; NR=Not Reported; MS = Metabolic syndrome; T2DM = type 2 diabetes mellitus; T NOS= Testosterone not otherwise specified; TU = Testosterone undecanoate; TE = testosterone enanthate; TC = testosterone cypionate; CHF = chronic heart failure; BPH = benign prostate hypertrophy; * range 20-75

Table 3: heterogeneity analyses

Analysis	Endogenous testosterone		TRT PSA		TRT PCA	
	# Studies	Summary estimate RR per 5 nmol/L** (95% CI)	# Studies	Summary estimate PSA: absolute difference (ng/mL) (95% CI)	# Studies	Summary estimate MH-OR (95% CI)
Main analysis (all studies)	20	0.99 (0.96; 1.02)	26	0.10 (-0.28; 0.48)	11	0.87 (0.30; 2.50)
Sensitivity analysis: high vs. low serum testosterone approach	20	0.98 (0.88; 1.09)				
Sensitivity analysis: studies from EHPCCG	16	0.97 (0.93; 1.01)				
Sensitivity analysis: include study with no SD assuming SD = 1 [34]			27	0.10 (-0.27; 0.48)		
Sensitivity analysis: include cases occurring during open-label phase, or additional follow-up, etc					13	0.84 (0.31; 2.25
Studies conducted in the USA	11	1.01 (0.98; 1.05)	13	0.34 (-0.41; 1.10)	7	1.32 (0.33; 5.25)
Studies conducted in Europe	7	0.95 (0.90; 1.01)	10	0.09 (-0.58; 0.76)	4	0.24 (0.01; 8.77)
Age at baseline < 65 years	15	0.99 (0.95; 1.02)	10	0.11 (-0.47; 0.69)	3	2.04 (0.01; 461.7)
Age at baseline ≥ 65 years	5	1.02 (0.93; 1.11)	15	0.30 (-0.41; 1.00)	8	0.74 (0.22; 2.54)
Short Follow-up *	12	0.99 (0.96; 1.03)	15	0.07 (-0.41; 0.55)	7	0.58 (0.14; 2.41)
Long Follow-up *	8	1.00 (0.93; 1.09)	11	0.17 (-0.57; 0.91)	4	2.15 (0.12; 37.46)
Baseline Testosterone ≤ 11 nmol/L			17	0.07 (-0.37; 0.51)	8	0.75 (0.22; 2.54)
Baseline Testosterone > 11 nmol/L			9	0.25 (-0.70; 1.20)	3	2.05 (0.01; 469.8)
Studies conducted in healthy subjects			15	0.08 (-0.43; 0.58)	7	0.63 (0.17; 2.39)
Studies conducted in subjects with comorbidities			11	0.14 (-0.52; 0.81)	4	2.98 (0.07; 122.67)
Administration: transdermal			13	0.20 (-0.41; 0.81)	7	2.57 (0.31; 21.16)
Administration: intramuscular			9	0.21 (-0.56; 0.98)	3	0.61 (0.03; 11.38)
Administration: oral			4	-0.21 (-1.40; 0.98)	1	NR
Testosterone undecanoate			8	-0.12 (-0.78; 0.55)	2	NR
Testosterone enhanthate			4	0.61 (-1.42; 2.63)	2	NR
Testosterone: other and unspecified			13	0.20 (-0.41; 0.81)	7	2.57 (0.31; 21.16)

TRT: testosterone replacement therapy; MH-OR: Mantel-Haenzel odds ratio; *Short Follow-up: ≤ 10 years for cohort studies, ≤ 1 year for randomized controlled trials; *Long Follow-up: > 10 years for cohort studies, >1yr year for randomized controlled trials; **except for the high vs. low analysis

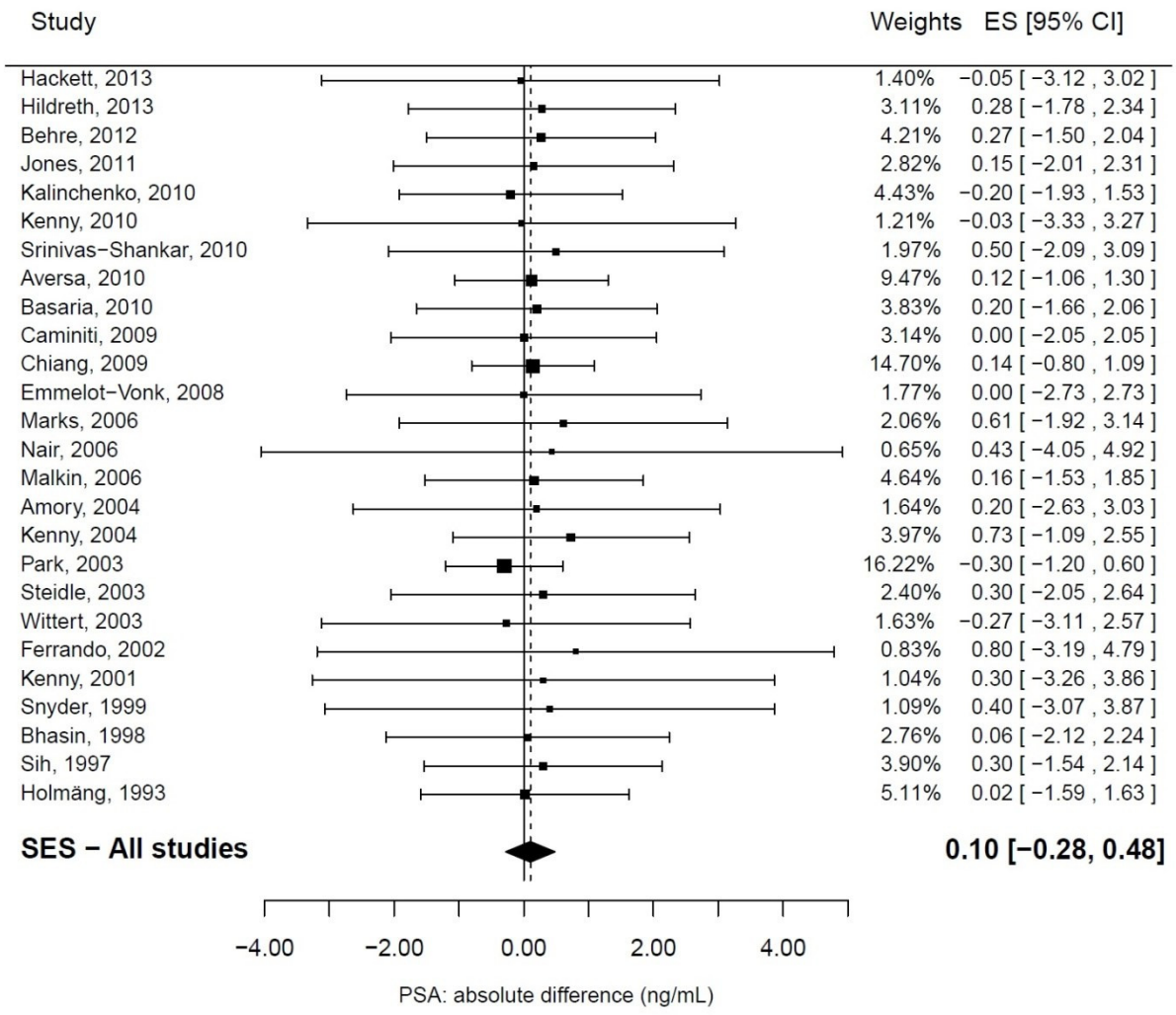
FIGURES



**: study included in EHPCCG pooled analysis*

Heterogeneity: I^2 = 0% [0%; 19%]; Q = 12.20, df = 19 (p = 0.88)
Publication bias: Begg = 0.16 (p = 0.87); Egger = −0.79 (p = 0.17);
Macaskill = −0.41 (p = 0.69)

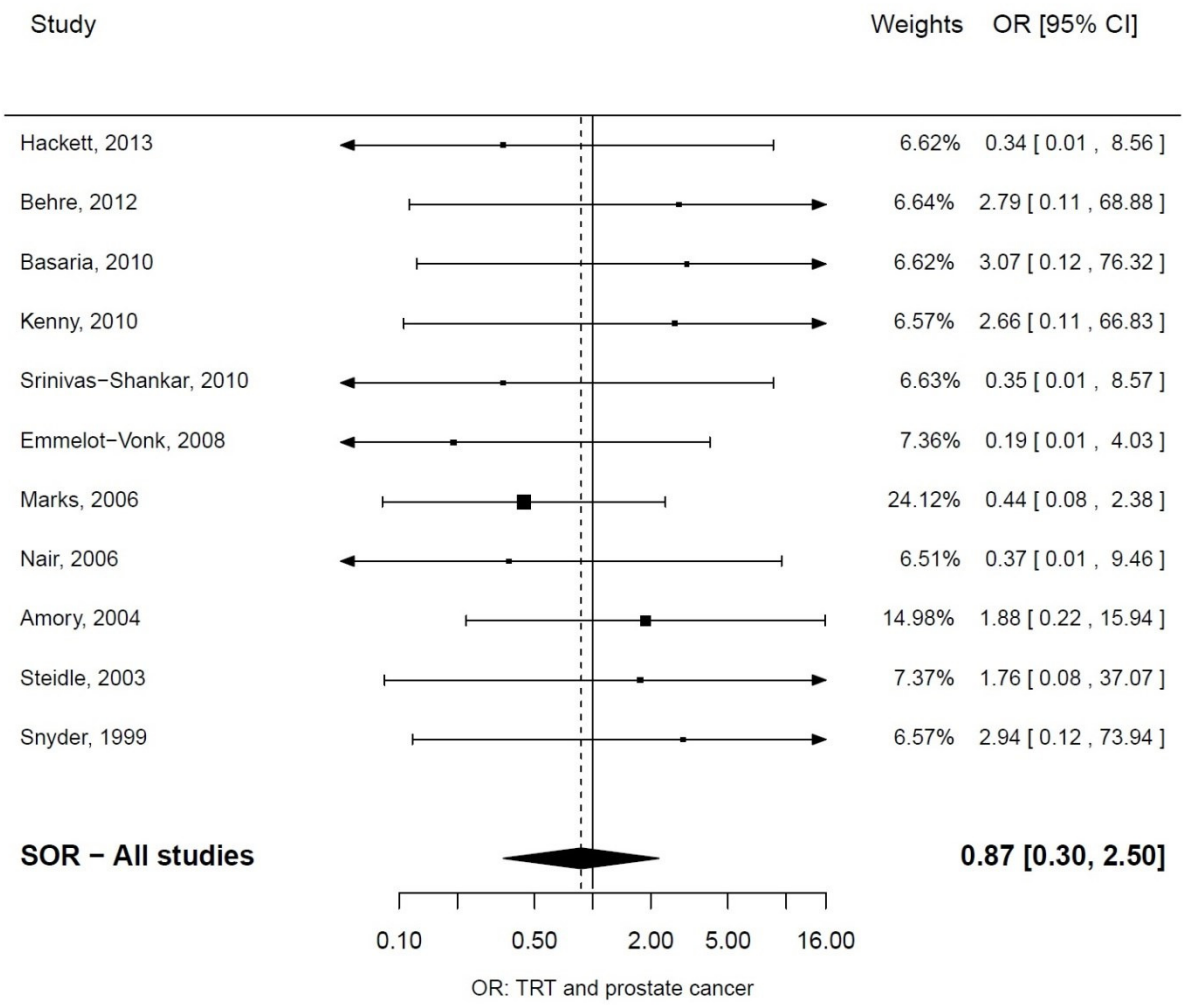
Figure 1



SES: Summary effect size

Heterogeneity: I^2 = 0% [0%; 0%]; Q = 2.03, df = 25 (p = 1.00)
Publication bias: Begg = 0.15 (p = 0.88); Egger = 0.48 (p = 0.01);
Macaskill = 0.65 (p = 0.52)

Figure 2

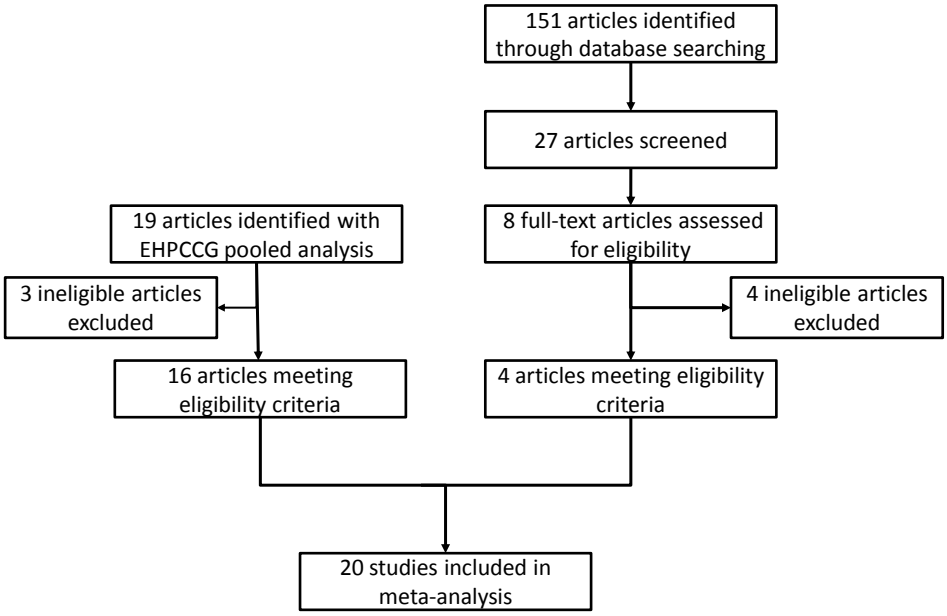


SOR: Summary odds ratio

Heterogeneity: I^2 = 0% [0%; 25%]; Q = 5.29, df = 10 (p = 0.87)
Publication bias: Begg = 0.23 (p = 0.82); Egger = 0.93 (p = 0.26);
Macaskill = 0.40 (p = 0.70)

Figure 3

Supplementary figures



PubMed keywords: "serum testosterone", "prostate cancer", "cohort", "prospective", "randomized controlled trial"

Figure S1: Literature search flowchart for study selection: endogenous testosterone and prostate cancer

Figure 1b: PRISMA for Exogenous testosterone and prostate cancer

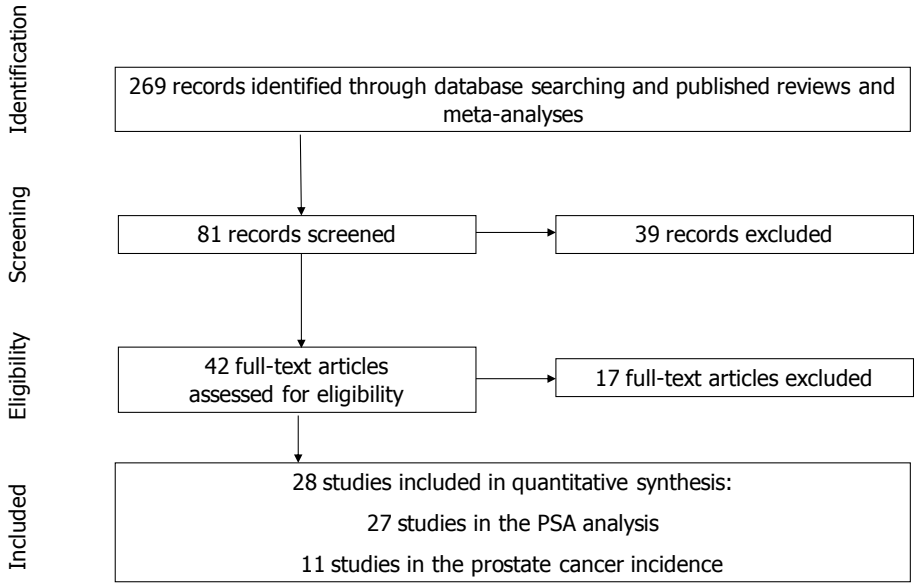


Figure S2: Literature search flowchart for study selection: Exogenous testosterone, Prostate Specific Antigen, and prostate cancer

Supplementary methods: PLCO Study

Most studies reported only baseline (B_{PSA}) and end of study (E_{PSA}) PSA with corresponding standard deviations, but not the average difference (Δ_{PSA}) and corresponding standard deviation. The average difference was therefore estimated as the difference of the average PSA at the end of study minus the average PSA at baseline. However, it would have been erroneous to consider the two measurements of PSA as independent in the computation of the variance of the difference and we needed to estimate the covariance between measurements. The following formula was used to compute the variance of the difference:

$$Var(\Delta PSA) = var(B_{PSA}) + var(E_{PSA}) - 2r\sqrt{(Var(B_{PSA}) * var(E_{PSA}))}$$

The coefficient r represents the correlation between the two measurements. It was computed from the PLCO study with dataset as of August 2012 [1].

Interpretation of changes in PSA (particularly in low ranges i.e. ≤ 4 ng/mL) is not straightforward and PSA testing has been shown to induce substantial over-diagnosis of prostate cancer, mainly due to poor specificity of the test. To help understand the occurrence and magnitude of variations of PSA levels in men with initially low levels of PSA, a detailed analysis of subjects participating in the intervention arm of the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Cancer Screening Trial who had an initial PSA level ≤ 4 ng/mL was conducted.

Data were abstracted from the PLCO study [1] on all men in the intervention arm with two tests performed in a period of less than two years and with an initial result of the first test ≤ 4 ng/mL. The range of variation of the second test compared to initial level was examined.

Among the 38,340 men participating to the intervention arm, 31,286 men had two PSA tests performed within two years and with an initial value ≤ 4 ng/mL. From these data, a correlation coefficient r of 0.64 was estimated and used in our analysis.

Reference

[1] Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst. 2012 Jan 18: **104**:125-32