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ORIGINAL REPORT

# Testosterone Replacement Therapy and Risk of Favorable and Aggressive Prostate Cancer

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## ABSTRACT

### Purpose
The association between exposure to testosterone replacement therapy (TRT) and prostate cancer risk is controversial. The objective was to examine this association through nationwide, population-based registry data.

### Methods
We performed a nested case-control study in the National Prostate Cancer Register of Sweden, which includes all 38,570 prostate cancer cases diagnosed from 2009 to 2012, and 192,838 age-matched men free of prostate cancer. Multivariable conditional logistic regression was used to examine associations between TRT and risk of prostate cancer (overall, favorable, and aggressive).

### Results
Two hundred eighty-four patients with prostate cancer (1%) and 1,378 control cases (1%) filled prescriptions for TRT. In multivariable analysis, no association was found between TRT and overall prostate cancer risk (odds ratio [OR], 1.03; 95% CI, 0.90 to 1.17). However, patients who received TRT had more favorable-risk prostate cancer (OR, 1.35; 95% CI, 1.16 to 1.56) and a lower risk of aggressive prostate cancer (OR, 0.50; 95% CI, 0.37 to 0.67). The increase in favorable-risk prostate cancer was already observed within the first year of TRT (OR, 1.61; 95% CI, 1.10 to 2.34), whereas the lower risk of aggressive disease was observed after > 1 year of TRT (OR, 0.44; 95% CI, 0.32 to 0.61). After adjusting for previous biopsy findings as an indicator of diagnostic activity, TRT remained significantly associated with more favorable-risk prostate cancer and lower risk of aggressive prostate cancer.

### Conclusion
The early increase in favorable-risk prostate cancer among patients who received TRT suggests a detection bias, whereas the decrease in risk of aggressive prostate cancer is a novel finding that warrants further investigation.

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## INTRODUCTION

Since the discovery of the testosterone dependence of prostate cancer in the 1940s,[1] medical or surgical castration has been a first-line treatment of advanced prostate cancer. Conversely, this has led to the concern that testosterone replacement therapy (TRT) increases prostate cancer risk; however, no evidence has shown that high levels of circulating levels of androgens increase the risk of prostate cancer.[2] Recent meta-analyses found no increased risk of prostate cancer in men who received TRT,[3,4] but the individual studies included in the meta-analyses had substantial limitations, such as small sample size (range, six to 307 patients who received TRT), short trial duration, and lack of a control group.

Given the rapid increase in the administration of TRT in recent years,[5] an association with the risk of prostate cancer has important implications. Our objective was to examine the association between TRT and risk of prostate cancer by using population-based data from the Prostate Cancer Database Sweden (PCBaSe). We hypothesized that if TRT promotes prostate cancer then patients who received TRT would have an increased risk of overall prostate cancer, a longer duration of adherent TRT would be associated with greater risk, and patients who received TRT would have a greater risk of aggressive prostate cancer.

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## METHODS

We performed a nested case-control study to examine the association between TRT and prostate cancer risk by using data from nationwide, population-based Swedish registries. The National Prostate Cancer Register of Sweden includes detailed, high-quality clinical data on 98% of all prostate cancer patients compared with the Cancer Register to which registration is mandated by law.[6-8] In the PCBaSe 3.0, each patient with prostate cancer has been matched to five men without prostate cancer on the basis of birth year and county of residence. The participants' unique personal identity number was used to link them to other health care registries and demographic databases in Sweden, including the Prescribed Drug Register—which holds data on all filled prescriptions since July 1, 2005—to determine the number of filled prescriptions for TRT, type of administration, and treatment adherence.[9]

Detailed data on prostate cancer features contained in the National Prostate Cancer Register, including prostate-specific antigen (PSA), stage, and grade, were used to classify men into risk categories, as previously described[10,11]: low risk (clinical local stage T1 to T2, PSA $<$ 10 ng/mL, Gleason score $\leq$ 6, not N1, not M1); intermediate risk (T1 to T2, Gleason score of 7, PSA of 10 to 20 ng/mL, not N1, not M1); local high risk (T1 to T2, Gleason score of 8 to 10, 20 $>$ PSA $<$ 50 ng/mL, not N1, not M1); locally advanced (T3, PSA $<$ 50 ng/mL, not N1, not M1); regionally metastatic (T4, 50 $<$ PSA $<$ 100 ng/mL, N1, not M1); and metastatic (metastases on bone imaging or PSA $>$ 100 ng/mL). For the purpose of this study, we dichotomized these classifications into two prognostic categories: favorable-risk (low- and intermediate-risk prostate cancer) and aggressive (high-risk, locally advanced, regional, and distant metastatic prostate cancer).

We examined possible associations between TRT and prostate cancer risk overall and by prognostic category. Separate analyses were performed to examine gel versus other types of TRT administration, timing of TRT, and duration of TRT. On the basis of the starting date for the Prescribed Drug Register (July 1, 2005), we chose January 1, 2009 as the starting date for our study to include men with $\geq$ 3 years of TRT exposure.

Data on education level, income, and marital status were obtained from the Swedish longitudinal integration database for health insurance and labor market studies—LISA.[12] Data from the Patient Register on discharge diagnosis (International Classification of Diseases, 10th Revision, coding) of hospital admissions up to 10 years before the date of diagnosis for patients with prostate cancer (and for the control group, the date for their index case) were used to calculate a Charlson comorbidity index (CCI),[13] as previously described.[14]

Multivariable conditional logistic regression analyses were performed to estimate odds ratios (ORs) and adjusted for age, CCI, marital status (married *v* not married, divorced, separated, or widowed), and education level (low [$<$ 10 years], intermediate [10 to 12 years], or high [$>$ 12 years, university or equivalent]). Subset analysis was also performed to estimate ORs for prostate cancer in men with $>$ 1 year of adherent TRT (defined as $>$ 75% drug adherence per year on the basis of the defined daily dose) and among men exposed to TRT within 1 year of prostate cancer diagnosis versus $>$ 1 year before prostate cancer diagnosis. Less than 2% of data were missing overall, and multiple imputation was used to handle missing values for covariates in the multivariable model.

The study was approved by the research ethics board at Umeå University Hospital and received exempt status for participant consent. Analysis was performed with SAS 9.2 (SAS Institute, Cary, NC) and R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) statistical software. The significance level was set to $P < .05$, and all tests were two-sided.

## RESULTS

In PCBaSe, 38,570 men who were diagnosed with prostate cancer between 2009 and 2012 were compared with 192,838 men free of prostate cancer in a matched control group. Table 1 lists the demographics of the overall study population; Table 2 lists clinicopathologic characteristics of prostate cancer cases. Compared with men in the control group, men with prostate cancer had lower comorbidity, were more often married than not, had higher education and income, and were more likely to have had a previous negative prostate biopsy.

Of the 38,570 patients with prostate cancer, 284 (1%) had filled prescriptions for TRT as did 1,378 (1%) of the 192,838 men in the control group (crude OR, 1.03; 95% CI, 0.91 to 1.17). Of the number of filled TRT prescriptions, gel was the most common form of administration; most men had filled more than three TRT prescriptions.

In multivariable analysis (Table 3), no significant difference was found in prostate cancer risk on the basis of TRT exposure (OR, 1.03; 95% CI, 0.90 to 1.17). Lower CCI, being married, and having a higher education level were all associated with significantly more favorable-risk and overall prostate cancer, although these factors were not associated with the risk of aggressive prostate cancer. Small interaction effects existed between education and both comorbidity and marital status, but they did not influence the overall model (data not shown).

**Table 1.** TRT Exposure and Demographics in PCBaSe 3.0, 2009 to 2014

| Exposure and Demographics | Participants, No. (%) | |
|---|---|---|
| | Case (n = 38,570) | Control (n = 192,838) |
| TRT exposure | | |
| No prescriptions | 38,286 (99) | 191,460 (99) |
| Any prior prescriptions | 284 (1) | 1,378 (1) |
| Age at diagnosis (years) | | |
| Median (IQR) | 69 (63-75) | 69 (63-75) |
| Charlson comorbidity index | | |
| 0 | 28,775 (75) | 140,566 (73) |
| 1 | 4,903 (13) | 25,926 (13) |
| 2+ | 4,892 (13) | 26,346 (14) |
| Marital status* | | |
| Married | 25,684 (67) | 121,279 (63) |
| Not married | 12,871 (33) | 71,344 (37) |
| Missing data | 15 (0) | 215 (0) |
| Education level† | | |
| Low | 13,534 (35) | 71,622 (37) |
| Middle | 15,086 (39) | 74,318 (39) |
| High | 9,648 (25) | 44,080 (23) |
| Missing data | 302 (1) | 2,818 (1) |
| Disposable income‡ | | |
| 1%-25% | 8,060 (21) | 48,019 (25) |
| 26%-50% | 9,422 (24) | 48,001 (25) |
| 51%-75% | 9,997 (26) | 47,967 (25) |
| 76%-100% | 11,010 (29) | 48,003 (25) |
| Missing data | 81 (0) | 848 (0) |
| Prior negative biopsy§ | | |
| No | 34,170 (89) | 186,667 (97) |
| Yes | 4,400 (11) | 6,171 (3) |

Abbreviations: IQR, interquartile range; PCBaSe, Prostate Cancer Data Base Sweden 3.0; TRT, testosterone replacement therapy.
*Married includes registered partnership.
†Low (compulsory school, $<$ 10 years); middle (upper secondary school, 10-12 years); high (college or university, $>$ 12 years).
‡Cutoffs for quartiles are based on distribution among control cases free of prostate cancer.
§Excludes biopsies performed within 6 months before prostate cancer diagnosis.

**Table 2.** Characteristics of Patients With Prostate Cancer in PCBaSe Diagnosed 2009 to 2014

| Characteristic | Patients, No. (%) | |
|---|---|---|
| | All Patients (n = 38,570) | Patients Exposed to TRT (n = 284) |
| Serum PSA (ng/mL) | | |
| < 10 | 20,327 (53) | 220 (77) |
| 10-20 | 7,346 (19) | 35 (12) |
| 20-50 | 4,785 (12) | 15 (5) |
| 50-100 | 2,013 (5) | 5 (2) |
| 100+ | 2,548 (7) | 3 (1) |
| Missing data | 1,536 (4) | 6 (2) |
| Stage (T/N/M) | | |
| Not T3+/N1/M1 | 29,212 (76) | 251 (88) |
| T3+/N1/M1 | 8,353 (22) | 25 (9) |
| Missing data | 1,005 (3) | 8 (3) |
| GS | | |
| ≤ 6 | 15,361 (40) | 145 (51) |
| 7 | 13,965 (36) | 99 (35) |
| 8-10 | 8,083 (21) | 36 (13) |
| Missing data | 1,161 (3) | 4 (1) |
| Risk category* | | |
| Favorable-risk | | |
| Low | 10,762 (28) | 127 (45) |
| Intermediate | 11,806 (31) | 99 (35) |
| Aggressive | | |
| High | 8,484 (22) | 38 (13) |
| Regionally metastatic | 2,116 (5) | 3 (1) |
| Distant metastases | 4,397 (11) | 9 (3) |
| Missing data | 1,005 (3) | 8 (3) |

Abbreviations: GS, Gleason score; PCBaSe, Prostate Cancer Data Base Sweden 3.0; PSA, prostate-specific antigen; TRT, testosterone replacement therapy.
*Favorable: low risk (clinical risk category T1-T2, PSA < 10 ng/mL, GS ≤ 6, not N1, not M1) and intermediate risk (T1-T2, GS of 7, PSA of 10-20 ng/mL, not N1, not M1). Aggressive: local high risk (T1-T2, GS of 8-10, 20 > PSA < 50 ng/mL, not N1, not M1); locally advanced (T3, PSA < 50 ng/mL, not N1, not M1); regionally metastatic (T4, 50 < PSA < 100 ng/mL, N1, not M1); and metastatic (metastases on bone imaging or PSA > 100 ng/mL).

On the basis of route of administration, neither gel (OR, 1.06; 95% CI, 0.90 to 1.24) nor other forms (OR, 0.97; 95% CI, 0.78 to 1.21) were significantly associated with prostate cancer risk. No significant difference was found in risk of prostate cancer on the basis of timing or duration of adherent TRT. Results were similar when months of adherent exposure were taken into consideration as a continuous variable.

Figures 1A to 1C show the results by risk category, grade, and stage. Patients who received TRT had more favorable-risk prostate

**Table 3.** ORs for Prostate Cancer According to Exposure to TRT

| Variable | Overall Prostate Cancer | | Favorable-Risk Prostate Cancer* | | Aggressive Prostate Cancer† | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| TRT exposure | | | | | | |
| No prescriptions | 1.00 | Ref | 1.00 | Ref | 1.00 | Ref |
| Any prior prescriptions | 1.03 | 0.90 to 1.17 | 1.35 | 1.16 to 1.56 | 0.50 | 0.37 to 0.67 |
| Charlson comorbidity index | | | | | | |
| 0 | 1.00 | Ref | 1.00 | Ref | 1.00 | Ref |
| 1 | 0.93 | 0.90 to 0.96 | 0.87 | 0.83 to 0.91 | 1.00 | 0.96 to 1.06 |
| 2+ | 0.91 | 0.88 to 0.94 | 0.75 | 0.71 to 0.79 | 0.96 | 0.92 to 1.01 |
| Marital status‡ | | | | | | |
| Married | 1.00 | Ref | 1.00 | Ref | 1.00 | Ref |
| Not married | 0.86 | 0.84 to 0.88 | 0.78 | 0.76 to 0.81 | 0.99 | 0.95 to 1.02 |
| Education level§ | | | | | | |
| Low | 1.00 | Ref | 1.00 | Ref | 1.00 | Ref |
| Middle | 1.07 | 1.05 to 1.10 | 1.13 | 1.09 to 1.17 | 1.01 | 0.97 to 1.05 |
| High | 1.15 | 1.11 to 1.18 | 1.27 | 1.22 to 1.32 | 0.98 | 0.93 to 1.03 |

NOTE. Conditional logistic regression with ORs and 95% CIs.
Abbreviations: OR, odds ratio; Ref, reference; TRT, testosterone replacement therapy.
*Favorable: low risk (clinical risk category T1-T2, prostate-specific antigen [PSA] < 10 ng/mL, Gleason score [GS] ≤ 6, not N1, not M1) and intermediate risk (T1-T2, GS of 7, PSA of 10-20 ng/mL, not N1, not M1).
†Aggressive: local high risk (T1- T2, GS of 8-10, 20 > PSA< 50 ng/mL, not N1, not M1); locally advanced (T3, PSA < 50 ng/mL, not N1, not M1); regionally metastatic (T4, 50 < PSA < 100 ng/mL, N1, not M1); and metastatic (metastases on bone imaging or PSA > 100 ng/mL).
‡Married includes registered partnership.
§Low (compulsory school, < 10 years); middle (upper secondary school, 10 to 12 years); high (college or university, > 12 years).

  

cancer (OR, 1.35; 95% CI, 1.16 to 1.56) and a lower risk of aggressive cancer (OR, 0.50; 95% CI, 0.37 to 0.67). Similar patterns were observed in models stratified separately by grade and stage. Subset analysis by timing demonstrated that the increase in favorable-risk cancer was observed already during the first year of a patient's TRT, whereas the reduction in aggressive prostate cancer only became apparent with exposure beginning > 1 year before diagnosis. In separate analyses, the interaction between TRT and

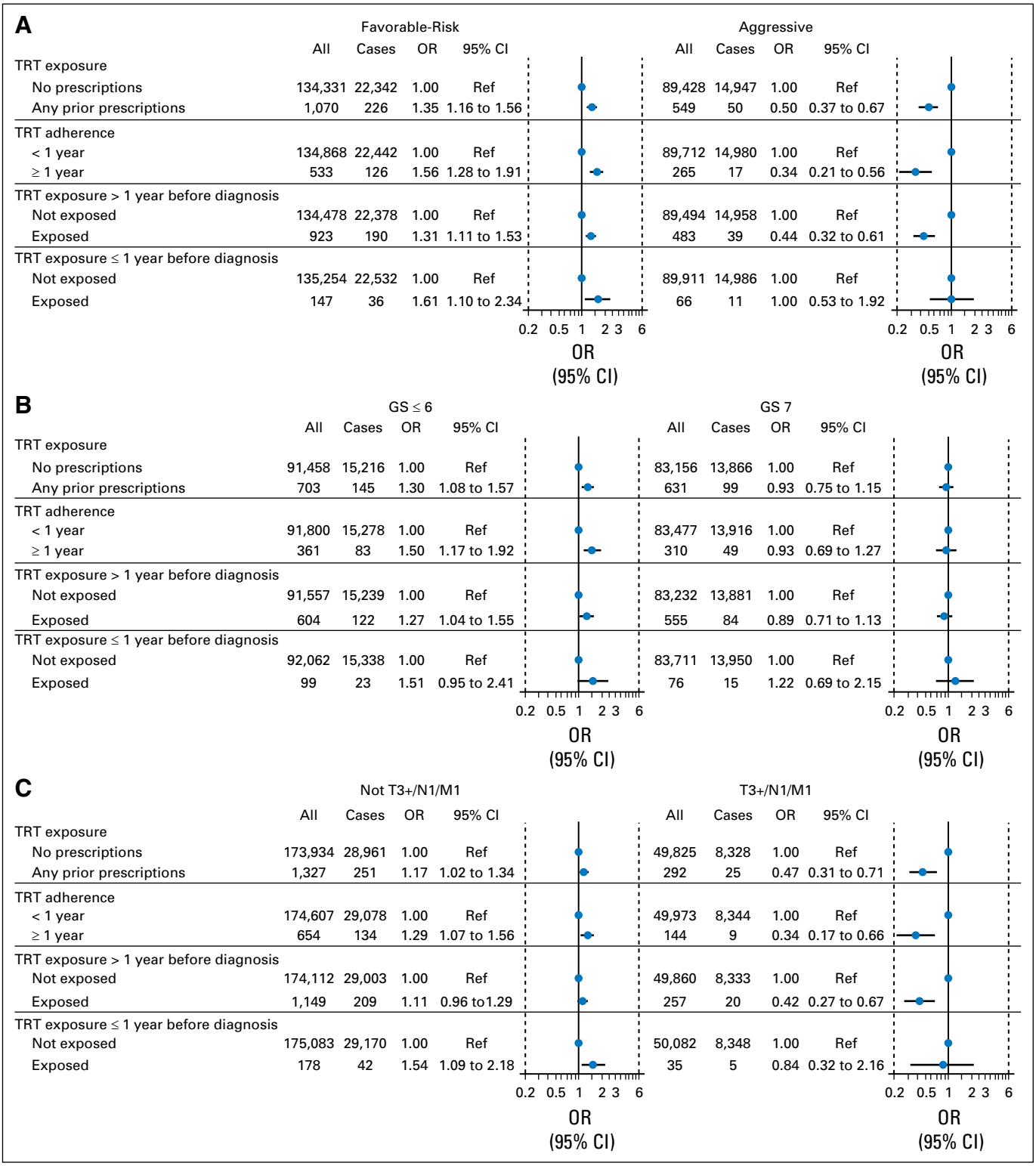


**Fig 1.** Odds ratios (ORs) with 95% CIs for prostate cancer according to exposure to testosterone replacement therapy (TRT) on the basis of three classifications of cancer aggressiveness: (A) favorable-risk versus aggressive cancer, (B) Gleason score (GS) ≤ 6 versus GS 7, and (C) not clinical T3+/N1/M1 versus T3+/N1/M1. Ref, reference.

previous biopsy findings on favorable-risk and aggressive prostate cancer was investigated. Men who had previously undergone a biopsy but were not taking TRT had more favorable-risk cancer (OR, 5.01; 95% CI, 4.75 to 5.29) than aggressive cancer (OR, 2.73; 95% CI, 2.55 to 2.93).

## DISCUSSION

In this population-based study, we found that patients who received TRT did not have an increased risk of overall prostate cancer, a longer duration of adherent TRT was not associated with greater risk, and patients who received TRT had a significantly lower risk of aggressive prostate cancer. Although there was more favorable-risk prostate cancer among men who received TRT, this finding may reflect physician-recommended prostate cancer screening in men who take TRT.

These findings are important given the recent increased use of TRT and the ongoing debate about the benefits and risks of TRT. A uniform increase in the prescription of TRT products worldwide was observed between the years 2000 and 2010.[5] This trend was most pronounced in the United States and reached a peak in 2011 with > 5% of US men ages 60 to 70 years using a testosterone product.[15] The increase in TRT prescriptions in the United States ended shortly thereafter because of changes in insurance coverage and safety concerns, among a number of other factors. The decreased use of TRT was also driven by two reports in 2013 that addressed cardiac safety[16,17] and persisting concerns about an increased risk of prostate cancer. The US Food and Drug Administration statement on both cardiac safety and appropriateness of testosterone prescription issued in January 2014 likely contributed further to this decline.[17a]

TRT has benefits for men with hypogonadism, and a recent randomized trial showed significantly improved sexual activity, sexual desire, and erectile function for men age ≥ 65 years with testosterone levels < 275 ng/dL who received TRT.[18] Testosterone deficiency is associated with numerous health issues, including increased risk of bone fracture (as a result of low bone mineral density), poor sleep quality, and fatigue.[19]

With regard to prostate cancer, previous studies have shown a higher risk of aggressive disease in men with hypogonadism.[20,21] Of note, the prevalence of hypogonadism is approximately 30% of men with diabetes mellitus (DM), ten-fold higher than in the general population.[22] A study of the PCBaSe and the Swedish National Diabetes Register found that the proportion of men with aggressive prostate cancer was higher among those with type 2 DM than those without DM.[23]

These relationships may reflect several possible biologic mechanisms. Testosterone is important for epithelial cell differentiation and function in the normal prostate.[24,25] In prostate cells and prostate cancer cells, testosterone stimulates proliferation,[26-29] but the dependence of prostate cancer cell survival on androgens is more controversial. Most studies suggest a lower rate of apoptosis after castration in prostate cancer compared with normal prostate.[26-28,30]

In addition to stimulating cell differentiation and proliferation, testosterone also induces PSA production. These processes seem to be regulated, at least in part, by different mechanisms, given the observation in preclinical studies that their maximal stimulation occurs at different concentrations of testosterone,[31-33] with PSA production stimulated at higher testosterone concentrations than cell proliferation. If PSA is a marker of benign prostate cells and highly differentiated prostate cancer cells, then lower testosterone levels should correspond with lower PSA levels and more poorly differentiated cancer. A meta-analysis of prospective cohort studies by Roddam et al[2] found no association between high endogenous serum testosterone levels and prostate cancer risk. Serum levels of testosterone gradually decrease with age, whereas the risk of prostate cancer increases.[34,35] Speculatively, high or normal testosterone levels keep prostate cells and early prostate cancer cells in a differentiated state. In contrast, the gradual decrease of testosterone caused by aging may lead to a less-differentiated cancer phenotype. In combination with increased cellular proliferation, further progression of prostate cancer lesions may be triggered within a certain androgen concentration range.[36] Further support of the concept of testosterone as a differentiating agent for prostate cancer comes from the observation that high-dose testosterone treatment of men with castration-resistant prostate cancer transforms cancer cells into a more differentiated phenotype sensitive to further androgen deprivation therapy.[37] These observations support the biologic plausibility of the current finding of a decreased risk of poorly differentiated prostate cancer in men who receive TRT. Similarly, a previous case-by-case analysis from the United States showed a lower proportion of high-grade disease among patients with prostate cancer who received TRT before diagnosis compared with those who did not.[38]

Strengths of this study included the use of high-quality, nationwide, population-based data from several Swedish national registries; these data are ideally suited to postauthorization surveillance studies. Comprehensive linkages provided complete and detailed data on patients' exposure to TRT on the basis of filled prescriptions, prostate cancer characteristics, and information on socioeconomic status and comorbidity. Thus, the data also allowed an assessment of possible associations between various types, timing, and adherence of TRT exposure, risk of prostate cancer by risk category, and adjustment for putative confounders. Accordingly, additional analysis from a multiple-response logistic regression of more-detailed risk categories showed significantly more low-risk prostate cancer and a significantly lower risk of high-risk, regionally metastatic, and distant metastatic disease (data not shown).

Limitations of this study included a lack of data on circulating testosterone levels, which precludes a direct assessment of the association between changes in sex hormone levels and prostate cancer risk. In addition, the data did not include the indication for TRT, and the use of TRT was not randomly assigned, so selection bias cannot be ruled out. We did not have data on the frequency of PSA testing and instead used registered prostate biopsy data as a proxy for intensity of screening and work-up. Men who received TRT were more likely to have undergone prior prostate biopsies, so the lower risk of aggressive disease in those who receive TRT may reflect more intensive screening. Nevertheless, among men without prior biopsy findings (and therefore similar levels for this proxy of diagnostic activity), those who receive TRT were more likely to be

  

diagnosed with favorable-risk prostate cancer than aggressive prostate cancer.

Prescribing patterns for TRT differ globally; rates of TRT in Sweden are lower than those reported in other countries.[5] Factors that contribute to this disparity may include legality of direct-to-consumer advertising, physician awareness of overt hypogonadism and moderately low androgen levels as a result of metabolic syndrome and other medical conditions among men, and differences in insurance coverage. Whether different indications for TRT use would modify the association with prostate cancer risk is unknown.

In conclusion, this population-based nested case-control register study showed no evidence of an association between men who received TRT and total prostate cancer risk. However, TRT was associated with a decreased risk of aggressive prostate cancer in men with exposure of $>1$ year. The findings suggest that from a prostate cancer perspective, TRT is safe in hypogonadal men.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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**Final approval of manuscript:** All authors
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