The role of testosterone replacement therapy and statin use, and their combination, in prostate cancer

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Abstract (250 words)

Purpose: Previous studies have reported conflicting results in the associations of testosterone replacement therapy (TTh) and statins use with prostate cancer (PCa). However, the combination of these treatments with PCa stage and grade at diagnosis and prostate cancer-specific mortality (PCSM) and by race/ethnicity remains unclear.

Methods: We identified non-Hispanic White (NHW, N=58576), non-Hispanic Black (NHB, N=9703) and Hispanic (N=4898) men diagnosed with PCa in SEER-Medicare data 2007-2011. Pre-diagnostic prescription of TTh and statins was ascertained for this analysis. Multivariable-adjusted logistic and Cox proportional hazards models were used to evaluate the association of TTh and statins use with PCa stage and grade and PCSM.

Results: 22.5% used statins alone, 1.2% used TTh alone, and 0.8% used both. TTh and statins were independently, inversely associated with PCa advanced stage and high grade. TTh plus statins was associated with 44% lower odds of advanced-stage PCa (OR = 0.56, 95% CI: 0.35 – 0.91). **As expected, similar inverse associations were present in NHWs as the overall cohort is mostly comprised of NHW men.** In Hispanic men, statin use with or without TTh was inversely associated with aggressive PCa.

Conclusions: Pre-diagnostic use of TTh or statins, independent or in combination, was inversely associated with aggressive PCa, including in NHW and Hispanics men, but was not with PCSM. The findings for use of statins with aggressive PCa are consistent

with cohort studies. Future prospective studies are needed to explore the independent inverse association of TTh and the combined inverse association of TTh plus statins on fatal PCa.

Key words: testosterone therapy, statins, race, ethnicity, and prostate cancer

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Declarations

Funding information: David S. Lopez was supported by the National Institutes of Health (NIH) and National Institute on Aging, Grant #: P30 AG059301. Dr. Platz was supported by the National Cancer Institute, Grant #: P30 CA006973

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: The protocols for the conduct of this study were approved by the Institutional Review Board of the University of Texas Medical Branch that also include consent for publication.

Informed Consent: We conducted a secondary data analysis using data from Seer-Medicare.

Submission declaration and verification: This work has not been published previously and it is not under consideration for publication elsewhere. The publication is approved by all authors and, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including

Authors Contributions: DSL, EAP and KM contributed to the study design, interpretation of the data, writing and critical discussion of manuscript draft. DH contributed to the statistical analysis of the study. All other authors contributed in the interpretation, discussion and editing of the manuscript draft.

Availability of data and material: All data generated or analysed during this study are included in this published article [and its supplementary information files]. For further data inquiries, please contact the corresponding author.

"This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and

Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database."

Introduction

Prostate cancer (PCa) is a hormone-related cancer and its association with the use of testosterone replacement therapy (TTh) remains poorly understood [1-3]. The use of TTh in the United States (U.S.) increased from 0.81% in 2001 to 2.9% in 2011 [4, 5]. However, Baillargeon *et al*. reported that the percentage of US men receiving testosterone prescriptions decreased from 2013 through 2016 due to a FDA safety bulletin issued between 2013-2014 addressing a relationship between TTh use and myocardial infarction [6-8]. A recent meta-analysis of eight randomized-controlled trials (RCTs) reported that TTh did not promote the incidence and progression of PCa [9]. Subsequently, a larger meta-analysis of 11 RCTs based on 20 PCa cases concluded that TTh for symptomatic hypogonadism did not increase the risk of PCa [10]. Although RCTs represent the most rigorous study design in terms of reducing confounding and selection bias, they often have small cohort samples with limited generalizability to non-Hispanic Blacks (NHB) and Hispanics [11].

Similarly, the use of statins in the prevention of PCa remains inconclusive, especially among NHB and Hispanic men. Two meta-analysis, Tan *et al.* 2016 (11 observational studies) and Mei *et al.* (12 observational studies) found an inverse association between use of statins and high grade, advanced stage PCa and prostate cancer-specific mortality (PCSM) [12, 13], whereas Tan *et al.* 2017 did not find significant associations between any type of statin and incident PCa [14]. It is important to note that the aforementioned meta-analyses did not explore the association of statins with PCa among NHB and Hispanic men.

It is plausible that TTh and statins can work or interact together as the prevalence of testosterone deficiency and hypercholesterolemia has increased among older men, and subsequently their treatment with TTh and statins [5, 6, 15-17]. Approximately 21% of TTh users have also reported use of statins [18]. There is biological plausibility in the interaction between levels of testosterone and cholesterol, and potentially with their treatments, TTh and statins, because cholesterol is a required intermediate precursor in steroidogenesis [19-21]. To the best of our knowledge, this is the first study that investigates the combination of pre-diagnostic TTh and statins with PCa stage and grade at diagnosis and with PCSM, including among NHB and Hispanic men. Identifying the independent and combined association of medications with low toxicity and cost, such as TTh and statins, will provide insight in the design and development of future studies and clinical interventions to prevent and/or reduce the risk and progression of PCa among men of different racial and ethnic backgrounds. Therefore, the objectives of this study are to investigate, in men diagnosed with PCa, the independent and combined association of TTh and statins use with PCa stage and grade at diagnosis and PCSM, and to examine whether these associations vary among non-Hispanic White, non-Hispanic Black and Hispanic men.

Methods

Data Source

We analyzed data from Surveillance, Epidemiology and End Results (SEER)-Medicare, a linkage of population based cancer registries from 19 SEER regions, which cover approximately 30% of the population of the US, with Medicare administrative data [22].

Approximately 95% of patients recorded in the SEER registry with incident cancer cases have been linked to their Medicare claims for covered health related services. The SEER program collects clinical, demographic and survival information from American cancer patients 65 years or older [23]. Medicare claims are linked through unique SEER identifiers covering the time of Medicare eligibility until death.

Study Cohort

Using SEER-Medicare linked data we identified 89346 NHW, NHB, and Hispanic men ≥ 65 years diagnosed with incident PCa (site recode 28010) between 2007-2011. Men were excluded if diagnosed at death or autopsy, were not enrolled continuously in the Prescription Drug Event File (PDE) and both Medicare A and B, were enrolled in a health maintenance organization (HMO) from 6 months prior to diagnosis with incident PCa and were from racial/ethnic groups other than NHW, NHB and Hispanic (Figure 1). Additional exclusion criteria included: men who were diagnosed with American Joint Committee on Cancer (AJCC Manual 7th edition)[24] stage III, or had unknown stage, and had missing diagnosis month. After eligible patients were identified from the Patient Entitlement and Diagnosis Summary File (PEDSF), their medical claims were extracted from the Outpatient (OUTSAF), Inpatient (Medical Provider Analysis and Review [MEDPAR]), National Claims History (NCH) files and PDE.

Prediagnostic use of testosterone replacement therapy (TTh) and statin prescription

Prescription of TTh was identified before PCa diagnosis from Medicare Part D file using national drug codes (NDC) and from outpatient and physician claims utilizing the Healthcare Common Procedure Coding System (HCPCS) and Current Procedural

Terminology (CPT) codes (relevant HCPCS/CPT and ICD-9 codes are listed in Appendix Supplemental Table S1. Similarly, use of statin was identified from Part D-NDC file (Appendix Supplemental Table S2). Based on the use of TTh (Yes/No) or statin (Yes/No), PCa patients were categorized into four groups: No TTh plus No statin (reference group), statin alone, TTh alone, and TTh plus statin. The index date was defined as the date of the first prescription within the study period. For patients who used both TTh and statin, at least 6 months between the later of the two dates and PCa diagnosis (if any) was required. These criteria also applied to statin and TTh only groups, including PCSM analysis. For the outcome **of PCSM** we evaluated TTh and statins use at any time during the study period (before or after diagnosis).

Prostate cancer stage, grade and mortality

The PCa outcomes of interest of this study were advanced stage PCa, high tumor grade and PCSM. The comparison group for advanced stage was localized PCa and for high-grade was low grade PCa. Advanced stage PCa was defined as AJCC stage IV definition, and localized PCa was defined with stages 0-II. The SEER grading system indicates that “Well Differentiated” corresponds to Gleason scores 2-4, “Moderately Differentiated” corresponds with Gleason scores 5-7, and “Poorly Differentiated” corresponds with Gleason scores 8-10 [25]. We defined high tumor grade as Gleason score 8-10. PCSM was available from SEER database through December 31, 2015. Causes of PCa death in the SEER record were based on the underlying causes of death in the death certificate, which has a high agreement (87%-92%) with medical record review [26]. PCSM was censored upon loss-to-follow-up because of

discontinuation of enrollment or the administrative end of calendar year and for those who died of other causes. Stage information was extracted from the PEDSF file.

Covariates

Patient characteristics included in the model were age at diagnosis, race and ethnicity (NHW, NHB, Hispanic), marital status (currently married or currently not married), number of primary care physician (PCP) visits, number of prostate-specific antigen (PSA) tests, and Charlson Comorbidity Index (CCI) [27]. We used the NCI-Charlson Comorbidity index (CCI) from 6 months prior to the index date to determine comorbidity burden. In fact, in addition to the 6-months period required between first medication date and PCa diagnosis date, all covariates were ascertained in the period at least six months preceding first index date to avoid ascertainment bias in those being worked up for a prescription compared with the referent group of no prescription. Clinical indicators identified from Medicare claims using NDC and HCPCS/CPT codes included hypogonadism, hypertension, diabetes, use of insulin, muscular wasting and disuse atrophy, malaise and fatigue, osteoporosis, erectile dysfunction, depressive disorder, anterior pituitary disorder, and decreased libido. No data were available on laboratory findings (e.g. serum testosterone), occupational, environmental, nutritional and/or several lifestyle factors. We also included in the model, US Census tract socioeconomic status that were measured the percentage of persons older than 25 years with less than 12 years education and the percentage of adults below the poverty line in the census tract.

Statistical Analysis

Patient characteristics, clinical indicators, census tract socioeconomic status variables, medical resources use were compared by localized and advanced prostate cancer at diagnosis using *Chi-square* tests for categorical variables and *t-test* for continuous variables. Per Seer-Medicare guideline publications, a sample size less than 11, should be reported as <11 as shown in Tables. The *a-priori* research objective of this study doesn't include a statistical comparison of the measures of association for NHW vs NHB vs Hispanic, as suggested by Ward et al. 2019, due to the sample size of the study [28]. Independent associations of TTh and statins with PCa stage and grade at diagnosis were assessed by conducting multivariable logistic regression models using *a priori knowledge* [29] to identify potential confounders, namely age at diagnosis, race and ethnicity, marital status, PCP visits, PSA tests, CCI, hypogonadism, hypertension, diabetes, use of insulin, muscular wasting and disuse atrophy, malaise and fatigue, osteoporosis, erectile dysfunction, depressive disorder, anterior pituitary disorder, decreased libido, and census tract socioeconomic status. These multivariable adjusted models compared the odds of high grade PCa *versus* low grade, and the odds of advanced stage PCa *versus* localized PCa. In a similar manner, the association of the combination of TTh and statin use (No TTh plus No statin was the reference group) with PCA stage and grade at diagnosis was assessed by conducting multivariable logistic regression models after adjusting for the aforementioned potential confounders. The multivariable adjusted Cox proportional hazards models estimated hazard ratios for PCSM adjusting for stage and grade at diagnosis. Scaled Schoenfeld residuals were used to test the proportional hazards assumption [30]. We conducted stratified analysis to determine whether the association between TTh plus statin use and PCa outcomes

varies by race and ethnicity [31]. Multiplicative interactions terms were incorporated into the models and tested using the Wald test. All statistical analyses were performed using SAS (SAS Institute v.9.4, Cary, NC). All *P*-values were considered significant at ≤ 0.05.

Results

We identified 58576 NHW, 9703 NHB and 4898 Hispanic men diagnosed with PCa in SEER-Medicare data 2007-2011. Mean age was 74 years old, and the **median follow-up** time from diagnosis of PCa to death or end of study was 5.6 years (12/31/2015). Table 1 shows patient characteristics by combination of TTh and statin use. Approximately 22.5% of men used statin alone, 1.2% used TTh alone, and .78% used both TTh plus statin. Compared to men with no TTh plus no statin, users of TTh alone, statin alone and their combination were less likely to report a higher CCI index score, but more likely to be relatively older, NHW, married, hypertensive, diabetic, report muscular wasting and malaise and fatigue, reported erectile dysfunction, hypogonadism, osteoporosis, depressive disorder, decreased libido, higher use of insulin, and higher number of PCP visits (≥3) and PSA tests (≥2).

Table 2 shows the multivariable-adjusted independent and combined associations of TTh plus statin use with high grade PCa, advanced stage PCa and PCSM. Compared with no TTh use, TTh was independently inversely associated with advanced stage PCa (OR = 0.69, 95% CI, 0.51-0.91, *P* = <0.01). Compared with no statin use, statin use was independently inversely associated with high grade PCa (OR = 0.87, 95% CI, 0.81-0.93, *P* = <0.01). Compared with no TTh plus no statins use, statin alone was inversely associated with high grade PCa (OR = 0.86, 95% CI, 0.81-0.92, *P* = <0.01). **Similarly, TTh plus statins** use was inversely associated with advanced stage PCa (OR = 0.56,

95% CI, 0.34-0.91, *P* = 0.02). However, there was no evidence of statistical interaction TTh and statins use with advanced stage ($P_{interaction}$ = *0.41)* or high grade ($P_{interaction}$ = *0.25).* Adjusting for stage and grade, no independent or combined associations were observed with PCSM.

The independent and combined associations of TTh and statins use with PCa stage and grade and PCSM by race and ethnicity are shown in Tables 3-5. Among NHW men (Table 3), the results were similar to overall. Compared with no TTh use, TTh use was independently inversely associated with advanced stage PCa (OR = 0.66, 95% CI, 0.48-0.90, *P* = 0.01). Compared with no statin use, statin use was independently inversely associated with high grade PCa (OR = 0.86, 95% CI, 0.81-0.93, *P* < 0.01). **Compared with no TTh plus no statins use among, statin alone was inversely associated with high grade PCa (OR = 0.86, 95% CI, 0.80-0.92, *P* < 0.01). Similarly, TTh plus statins use was inversely associated with advanced stage PCa (OR = 0.51, 95% CI, 0.29-0.89, *P* = 0.01).** However, there was no evidence for statistical interaction between TTh and statin with advanced stage ($P_{interaction}$ = *0.27)* or high grade ($P_{interaction}$ = *0.31).* Adjusting for stage and grade, no independent or combined associations were observed with PCSM.

Among Hispanic men (Table 4), compared with no statin use, statin was independently inversely associated with advanced stage (OR = 0.74, 95% CI, 0.57-0.95, *P* = 0.01) and high grade PCa (OR = 0.74, 95% CI, 0.58-0.95, *P* = 0.02). Compared with no TTh plus no statins use among Hispanics, use of statin was also associated with both advanced stage (OR = 0.74, 95% CI, 0.58-0.96, *P* = 0.02) and high grade PCa (OR = 0.74, 95% CI, 0.58-0.95, *P* = 0.01). However, there was no evidence for statistical interaction

between TTh and statin with advanced stage ($P_{interaction}$ = *0.30)* or high grade ($P_{interaction}$ = *0.73).* Adjusting for stage and grade, no independent or combined association were observed with PCSM.

Among NHB men (Table 5), compared with no TTh use, TTh use was not associated with high-grade PCa (OR = 0.73, 95% CI, 0.34-1.57) and advanced stage PCa (OR = 0.79, 95% CI, 0.31-2.00). Compared with no statin use, statin use was not associated with high-grade PCa (OR = 0.99, 95% CI, 0.81-1.20) and advanced stage PCa (OR = 0.95, 95% CI, 0.78-1.17). Similar, non-significant associations were observed for statin alone and TTh alone. In the combination of TTh plus statins use, there was no significant association with high-grade PCa (OR = 0.95, 95% CI, 0.31-2.93) and advanced stage PCa (OR = 1.49, 95% CI, 0.43-5.09). There was also no evidence for statistical interaction between TTh and statin with advanced stage ($P_{interaction}$ = *0.19)* or high grade ($P_{interaction}$ = *0.56).* Adjusting for stage and grade, no independent or combined associations were observed with PCSM.

Discussion

Overall, we found independent inverse associations between pre-diagnostic TTh use and advanced stage PCa and between pre-diagnostic statin use and high grade PCa in older men. However, the statistical interactions between TTh and statins were not significant. Compared with not taking either medication, the use of statin alone was inversely associated with high grade PCa, and the combination of TTh plus statin was associated with advanced PCa. ***As expected, similar inverse associations were present in NHWs as the overall cohort is mostly comprised of NHW men*****.** Among

Hispanic men, use of statin was independently inversely associated with advanced stage PCa and high grade PCa. Compared with not taking either medication among Hispanics, statin alone was associated with advanced stage PCa and high grade PCa. No significant association was found among NHB. Neither medication individually or in combination was associated with PCSM overall or by race/ethnicity. To our knowledge, this is the first large epidemiological study to quantify the association of the independent and combined associations of TTh and statin use with PCa stage and grade at diagnosis and PCSM by race and ethnicity. Our findings for use of statins with aggressive disease characteristics is consistent with prospective cohort studies, with the exception of the non-statistical significant interactions of TTh and statins. Future prospective cohort studies are needed to explore the independent inverse association of TTh and the combined inverse association of TTh plus statin on risk of fatal PCa, including larger sample sizes to test interactions. These future studies should also include lethal PCa.

TTh use and PCa outcomes

A number of studies and reviews have previously addressed the independent association of TTh [9, 10, 32] with risk of developing PCa and have reported conflicting results. While we did not investigate the risk of developing PCa, our significant inverse associations with high grade and advanced stage PCa seem to concur with the direction of the inverse associations found in two meta-analysis of randomized clinical trials that investigated risk of developing PCa in relation to TTh use, albeit findings from these meta-analyses did not reach statistical significance [9, 10]. Yet, it is important to note that in those meta-analyses transdermal was the most common delivery method, but in

our analyses, we combined injections and use of gels of testosterone therapy. Similarly, three recent retrospective population-based studies found no increased risk of high grade PCa in men with TTh use [33-35]. Two of these studies, Kaplan *et al*. 2013 and Yassin *et al*. 2017, further investigated the relationship between TTh use and likelihood to be diagnosed with advanced stage PCa (clinical stage T4) reporting protective effects [34, 35]. The direction of our measures of association seem to be agreement with these previous studies investigating PCa high grade and advanced stage. We did not find any significant association with PCSM, but a recent population-based cancer registry study showed a risk reduction of PCSM in relation to TTh use [36]. Specifically, this latter study capitalized on the SEER-Medicare 1991-2007 database reporting a significant 41% lower risk of dying of PCa [36]. However, compared to our study, this latter study[36] did not adjust for PCa stage and grade at diagnosis. It is possible that our findings differ from this previous study due to the larger inclusion of Part D data in our study, including a larger racially and ethnically diverse population. We further adjusted for use of statins in the independent association of TTh with PCa stage and grade, which to our knowledge no other study has conducted similar analysis due to the widely used of statins.

Statin use and PCa outcomes

A number of prospective cohort studies and reviews have addressed the association between taking statins and risk of developing PCa, lethal disease, fatal disease, and in men with a PCa diagnosis, risk of PCSM [12-14]. There is growing evidence that the use of statin is significantly inversely associated with the risk of aggressive disease, including a lower risk of high-grade (RR= 0.83, 95% CI: 0.66-0.99) and advanced stage

(RR = 0.87, 95% CI: 0.82-0.91) PCa, as shown in a meta-analysis of 6 randomized trials and 36 observational studies [12]. While we did not investigate the risk of developing lethal or fatal disease PCa, our significant inverse association with high-grade disease appears to be consistent, whereas our null association for advanced disease is not consistent with prior prospective cohort studies. Evidence is also mounting that pre-diagnostic use of statins is inversely associated with PCSM; a meta-analysis of 12 cohort studies reported as summary HR of 0.43, 95% CI, 0.25-0.76.[13] The null association in our prospective analysis of pre-diagnostic use of statins and PCSM is not consistent with that meta-analysis summary association, although it is consistent with some individual studies that reported hazard ratios lower than 1, but they did not reach statistical significance [37, 38]. Some aspects can be attributed to the different results comparing our study to previous studies, however, they can't be test it within the scope of our study (e.g. influence of different study designs compared to other studies, different definitions of survivorship/mortality, and the sample size in our study compare with other studies).

The investigation of use of statins and its association with PCa among Hispanics remains significantly scarce. Our study is the first one that focused in investigating the role of statins in PCa stage and grade at diagnosis and risk of PCSM among Hispanics. One previous study investigated only the relationship of the combination of metformin plus statins with PCa among diabetic Hispanics reporting a significant inverse association [39].

Combined association of TTh plus statin use with PCa stage and grade and PCSM

To our knowledge no study has investigated the combination of TTh plus statin use in relation to PCa stage and grade and PCSM. Therefore, our findings may not seem comparable with other studies. However, it is important to note there are a number of studies that have explored the interplay between statins, endogenous and exogenous testosterone, and prostate cancer in different settings [40-42]. For instance, a previous study noted that co-use of both medications had the possibility of confounding each other's effect [43]. A meta-analysis of randomized controlled trials and an individual cohort study in humans showed that statins may lower testosterone levels [40, 41]. Another experimental study used human prostate cancer cell lines and found that simvastatin significantly increased testosterone levels [42]. Although our study and other studies are not comparable due to different settings, what remains to be determined is whether there is an epidemiologic [44] and biological plausibility in the interplay between low levels of testosterone/testosterone deficiency and hypercholesterolemia and their treatment with TTh and statins. Recently, it was reported that the prevalence of both, testosterone deficiency and hypercholesterolemia, has increased and subsequently their treatment medications, especially TTh and statins [5, 6, 15-17]. We previously identified in a US commercial claims database of 189 491 men aged 40-69 years that 21% of TTh users have also reported statin use [18]. Furthermore, a review article by Mokarram et al. 2017 suggested the biological mechanistic interconnection between testosterone metabolism and the mevalonate pathway, which is required for the generation of several fundamental end-products including cholesterol that is a required precursor in steroidogenesis [20, 21, 45]. However, our multiplicative interactions between TTh and statins and their associations

with PCa stage and grade and PCMS were not statistically significant. Therefore, more epidemiological studies with larger sample sizes are warranted to determine whether the use of TTh and statin is associated with the risk and progression of PCa.

Strengths and Limitations

Our study has a number of strengths. This study included a large racially and ethnically diverse cohort, a large number of men with PCa stage and grade, and a large enough sample to be able to investigate men who have used both TTh and a statin. This study also include a long follow-up data, detailed information on patient's exposures to TTh and statin use on the basis of filled prescriptions and inclusion of clinically relevant comorbidities. These strengths increased our statistical power for the categorical comparison groups and generalizability for studies with similar PCa populations. In addition, they also reduced residual confounding because of our well-characterized modifiable factors.

Yet, the present study has limitations as well. First, our retrospective cohort design doesn't allow us to conclude whether these medications decrease the occurrence of advanced diseases or increase the occurrence of non-advanced disease, which both scenarios lead to an OR < 1 [46]. Similarly, due to the nature of our retrospective analysis for PCSM, we cannot infer causality; therefore, these findings should be interpreted with caution. Second, there are general limitations of retrospective analysis based on Medicare claims data, such as possible coding errors or omissions of claims. For instance, comorbidities were identified using ICD-9-CM codes, possibly resulting in incorrect capture of medical conditions due to under-coding, upcoding or miscoding, leading to classification bias in those comorbidities at baseline [22, 47]. It is also

possible that some of the non-users might have used TTh or statins prior to 2007, the earliest year of available Part D data. However, this potential inaccurate capture of information will be considered nondifferential misclassification because they were collected before the disease developed, which in general influence associations to the null (1.0). Third, limiting the pre-index period to six months did not allow to capture full medical history; for instance, patients may have had the comorbidity of interest before the start of the pre index period. Fourth, evidence of a filled prescription with pharmaceutical data did not confirm actual use of a medication and over-the-counter medications could not be identified. Given the perceived social stigma associated with receiving TTh, some men may choose to seek treatment outside their usual health care setting. Fifth, our database did not include important confounders such as body mass index and waist circumference measurements that have been associated with advanced stage PCa and testosterone (endogenous and exogenous) [48, 49]. Also, although we adjusted for hypogonadism and age in the multivariable analysis, we cannot rule out potential residual confounding by these factors. Another potential confounding in our analysis is that our statin 'non-user' group is possibly mixed with men with different cholesterol levels and treatment status (with and without high cholesterol and with and without treatment with high cholesterol medications other than statins). However, Seer-Medicare does not include laboratory results to be able to identify men with hypercholesterolemia. Furthermore, it is important to note although we found an inverse relationship between use of statin alone and combination of TTh plus statin with aggressive disease, the results of our multiplicative interactions models are not significant (combined use of these medications are not different than what would be

expected from their combined use), which suggest a potential residual confounding; therefore, measures of association found in this paper should be interpreted with caution." Sixth, our study only included men 65+ years old; therefore, we can't know what the PCSM association would like in a younger population of men. In addition, **most of the cohort is comprised of NHW men (80%) that any comparison between the overall cohort and NHWs will not provide new insight**. Seventh, **because of the** small sample size in some of the categories among NHB and Hispanic men, the a-priori research objective of the study did not include the statistical comparison of measures of association for NHW, NHB and Hispanic. **Due to the small sample size among Hispanic and NHB men, the findings of this study should be viewed as exploratory and not conclusive for the power to make conclusions is minimal; therefore, they should be interpreted with caution** [28]. Finally, **to our knowledge, there is no biological explanation why use of statins was associated with high-grade PCa in NHW and Hispanics, but not among NHB men. It is also possible that this may be due to residual confounding or chance. In addition, there is no serum testosterone and total and LDL-cholesterol data available in SEER-Medicare database that can provide insight in the interaction between these serum markers and the use of TTh and statins and determine their effect on high-grade PCa.** Further, our study population only included patients with Medicare claims; therefore, our results may not be generalizable to patients with PCa using other types of insurance or no insurance at all. Although our study has a large sample size, there was a still a small number of PCa events among men who took both TTh and statin.

Conclusion

In summary, in this large racially and ethnically diverse SEER-Medicare claims based analysis, we found that pre-diagnostic use of TTh or statins, independent or in combination, was inversely associated with aggressive PCa, including in NHW and Hispanics men, but was not with PCSM. Future prospective cohort studies are needed to explore the independent inverse association of TTh and the combined inverse association of TTh plus statin on risk of fatal PCa (and lethal PCa), including larger sample sizes to test interactions.

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Table 1. Baseline characteristics of men 65+ years old with PCa by current use of testosterone therapy (TTh) and/or statin, SEER-Medicare 2007-2011

	No TTh/No Statin	Statin alone	TTh alone	TTh+Statin	*P*
Cancer Stage†β					<0.01
N	67468	20106	1071	701	
Localized	91.7	93.2	95.9	97.4	
Advanced	8.3	6.8	4.1	2.6	
Cancer Grade‡					<0.01
N	29665	11296	526	478	
Low grade	77.5	80.7	85.9	85.4	
High grade	22.5	19.3	14.1	14.6	
PCSM¥					<0.01
N	**4506**	**1078**	**38**	**27**	
Age, %					<0.01
<65	6.0	6.6	9.4	11.3	
65-69	28.6	27.9	24.0	27.9	
70-74	27.6	30.0	30.4	29.4	
75-79	19.6	19.9	21.0	21.3	
80-84	11.3	10.4	9.9	7.6	
>=85	7.0	5.3	5.3	2.6	
Race/ Ethnicity					<0.01
White	80.1	78.8	84.2	86.0	
Black	13.5	11.2	11.1	7.4	
Hispanic	6.4	10.0	4.6	6.6	
Married	74.4	72.7	77.5	75.2	<0.01
Percent persons 25+ with <12 year education Mean (SD)	18.3	20.0	16.7	17.7	<0.01
Census Tract Poverty (% of adults < poverty line)					<0.01
0%-5%	25.8	23.6	22.6	23.8	
5% to <10%	26.6	25.6	30.3	27.5	
10% to <20%	27.7	28.1	27.4	28.2	
20% to 100%	19.3	22.1	19.4	20.3	
Unknown	0.6	0.6	0.3	0.3	
Charlson Comorbidity Index (CCI), %					<0.01
0	70.3	54.8	61.3	51.4	
1	18.1	25.3	22.1	23.8	

2	6.7	10.6	8.2	13.4	
3 or more	5.0	9.3	8.5	11.4	
Hypogonadism, %	0.6	0.5	33.1	33.6	<0.01
Hypertension, %	22.8	34.3	28.6	35.3	<0.01
Diabetes, %	15.8	27.7	21.5	33.5	<0.01
Muscular wasting and disuse atrophy, %	0.1	0.2	0.3	0.3	0.02
Malaise and fatigue, %	3.4	4.4	9.2	8.2	<0.01
Osteoporosis, %	1.1	1.3	2.1	3.9	<0.01
Erectile dysfunction organic, %	1.8	2.1	13.5	13.2	<0.01
Depressive disorder, %	1.0	1.5	2.9	3.0	<0.01
Anterior pituitary disorder, %	0.0	0.0	0.7	1.5	<0.01
Decreased libido, %	0.0	0.0	0.5	0.5	<0.01
Use of Insulin, %	1.2	8.0	3.0	13.4	<0.01
No. PCP visits, %					<0.01
0	8.9	2.0	1.7	1.1	
1	6.1	3.5	1.6	2.1	
2	7.7	6.2	3.1	2.5	
>=3	77.3	88.2	93.6	94.3	
No. PSA Tests, %					<0.01
0	21.4	11.7	8.6	6.2	
1	17.3	15.6	12.4	10.0	
>=2	61.4	72.6	79.0	83.8	

[†]Advanced stage PCa cases were consistent with AJCC stage IV definition where localized PCA cases were defined with stages 0-II.
[β]Stage III was not included in this analysis.
[‡]High tumor grade was defined with Gleason score 8-10 and low-grade Gleason score 2-7.
[¥]Prostate cancer-specific mortality

Table 2. Independent and combined association of TTh and statin use with prostate cancer grade and stage at diagnosis and prostate cancer specific mortality among men 65+ years old with a prostate cancer diagnosis in SEER-Medicare 2007-2011

	High grade prostate cancer†			Advanced stage prostate cancer†			Prostate cancer mortality (adjusted for stage and grade at diagnosis)†		
N=89346	**Events/N**	**OR**	**95% CI**	**Events/N**	**OR**	**95% CI**	**Events/PY¥**	**HR**	**95% CI**
TTh Use									
No TTh	8848/40961	1.0		6995/87574	1.0		5584/491777	1.0	
Yes TTh	144/1004	0.82	0.66,1.02	62/1772	0.69	0.51,0.91	65/9787	1.02	0.63,1.66
Statin Use									
No Statin	6740/30191	1.0		5666/68539	1.0		4544/388775	1.0	
Yes Statin	2252/11774	0.87	0.81,0.93	1391/20807	0.96	0.89,1.03	1105/112790	1.03	0.90,1.18
TTh & Statin Use‡									
No TTh/No Statin	6666/29665	1.0		5622/67468	1.0		4506/382699	1.0	
Statin alone	2182/11296	0.86	0.81,0.92	1373/20106	0.96	0.90,1.03	1078/109078	1.02	0.88,1.17
TTh alone	74/526	0.76	0.57,1.03	44/1071	0.75	0.53,1.05	38/6075	0.82	0.47,1.61
TTh+Statin	70/478	0.84	0.62,1.13	18/701	0.56	0.34,0.91	27/3712	1.35	0.71,2.58

†Multivariable analysis adjusted for age, race/ethnicity, Charlson Comorbidity Index (CCI), hypogonadism, hypertension, diabetes, use of insulin, muscular wasting and disuse atrophy, malaise and fatigue, osteoporosis, erectile dysfunction, depressive disorder, anterior pituitary disorder, decreased libido, education (percentage of persons older than 25 years with less than 12 years education), percentage of adults below poverty line at census tract level, patients' primary care (PCP), prostate-specific antigen (PSA), and mutual adjustment for TTh and statin.
‡Interaction term for TTh and statin use and its association with PCa stage ($P_{interaction} = 0.41$) and grade ($P_{interaction} = 0.25$).
¥Person-years

Table 3. **NWH men**- Independent and combined association of TTh and statin use with prostate cancer grade and stage at diagnosis and prostate cancer specific mortality among NHW men 65+ years old with a prostate cancer diagnosis in SEER-Medicare 2007-2011

	High grade prostate cancer†			Advanced stage prostate cancer†			Prostate cancer mortality (adjusted for stage and grade at diagnosis)†		
N=58576	**Events/N**	**OR**	**95% CI**	**Events/N**	**OR**	**95% CI**	**Events/PY¥**	**HR**	**95% CI**
TTh Use									
No TTh	6521/30177	1.0		5163/66153	1.0		4211/371787	1.0	
Yes TTh	125/804	0.85	0.67,1.07	51/1452	0.66	0.48,0.90	55/8026	0.95	0.54,1.67
Statin Use									
No Statin	5034/22466	1.0		4205/52282	1.0		3434/296827	1.0	
Yes Statin	1612/8515	0.86	0.80,0.93	1009/15323	0.98	0.90,1.06	832/82986	1.04	0.89,1.21
TTh & Statin Use‡									
No TTh/No Statin	4969/22044	1.0		4168/51403	1.0		3401/291841	1.0	
Statin alone	1552/8133	0.86	0.80,0.92	995/14750	0.99	0.91,1.07	810/79945	1.03	0.88,1.20
TTh alone	65/422	0.79	0.57,1.08	37/879	0.75	0.52,1.08	33/4985	0.71	0.31,1.62
TTh+Statin	60/382	0.8	0.62,1.18	14/573	0.51	0.29,0.89	22/3041	1.29	0.62,2.68

†Multivariable analysis adjusted for age, Charlson Comorbidity Index (CCI), hypogonadism, hypertension, diabetes, use of insulin, muscular wasting and disuse atrophy, malaise and fatigue, osteoporosis, erectile dysfunction, depressive disorder, anterior pituitary disorder, decreased libido, education (percentage of persons older than 25 years with less than 12 years education), percentage of adults below poverty line at census tract level, patients' primary care (PCP), prostate-specific antigen (PSA), and mutual adjustment for TTh and statin.

‡Interaction term for TTh and statin use and its association with PCa stage ($P_{interaction} = 0.27$) and grade ($P_{interaction} = 0.31$).

¥Person-years

Table 4. **Hispanic men**- Independent and combined association of TTh and statin use with prostate cancer grade and stage at diagnosis and prostate cancer specific mortality among NHW men 65+ years old with a prostate cancer diagnosis in SEER-Medicare 2007-2011*

	High grade prostate cancer†			Advanced stage prostate cancer†			Prostate cancer mortality (adjusted for stage and grade at diagnosis)†		
N=4898	**Events/N**	**OR**	**95% CI**	**Events/N**	**OR**	**95% CI**	**Events/PY¥**	**HR**	**95% CI**
TTh Use									
No TTh	543/2851	1.0		486/5629	1.0		345/32173	1.0	
Yes TTh	<11/62	0.58	0.23,1.43	<11/92	0.78	0.27,2.20	<11/462	1.22	0.35,4.19
Statin Use									
No Statin	378/1882	1.0		370/3925	1.0		264/22689	1.0	
Yes Statin	172/1031	0.74	0.58,0.95	122/1796	0.74	0.57,0.95	85/9946	0.78	0.44,1.37
TTh & Statin Use‡									
No TTh/No Statin	375/1854	1.0		365/3878	1.0		262/22433	1.0	
Statin alone	168/997	0.74	0.58,0.95	121/1751	0.74	0.58,0.96	83/9739	0.75	0.42,1.34
TTh alone	<11/28	0.53	0.14,2.02	<11/47	1.26	0.37,4.27	<11/255	0.96	0.22,4.30
TTh+Statin	<11/34	0.53	0.17,1.65	<11/45	0.28	0.03,2.15	<11/206	1.70	0.21,13.0

†Multivariable analysis adjusted for age, Charlson Comorbidity Index (CCI), hypogonadism, hypertension, diabetes, use of insulin, muscular wasting and disuse atrophy, malaise and fatigue, osteoporosis, erectile dysfunction, depressive disorder, anterior pituitary disorder, decreased libido, education (percentage of persons older than 25 years with less than 12 years education), percentage of adults below poverty line at census tract level, patients' primary care (PCP), prostate-specific antigen (PSA), and mutual adjustment for TTh and statin.

‡Interaction term for TTh and statin use and its association with PCa stage ($P_{interaction} = 0.30$) and grade ($P_{interaction} = 0.73$).

¥Person-years

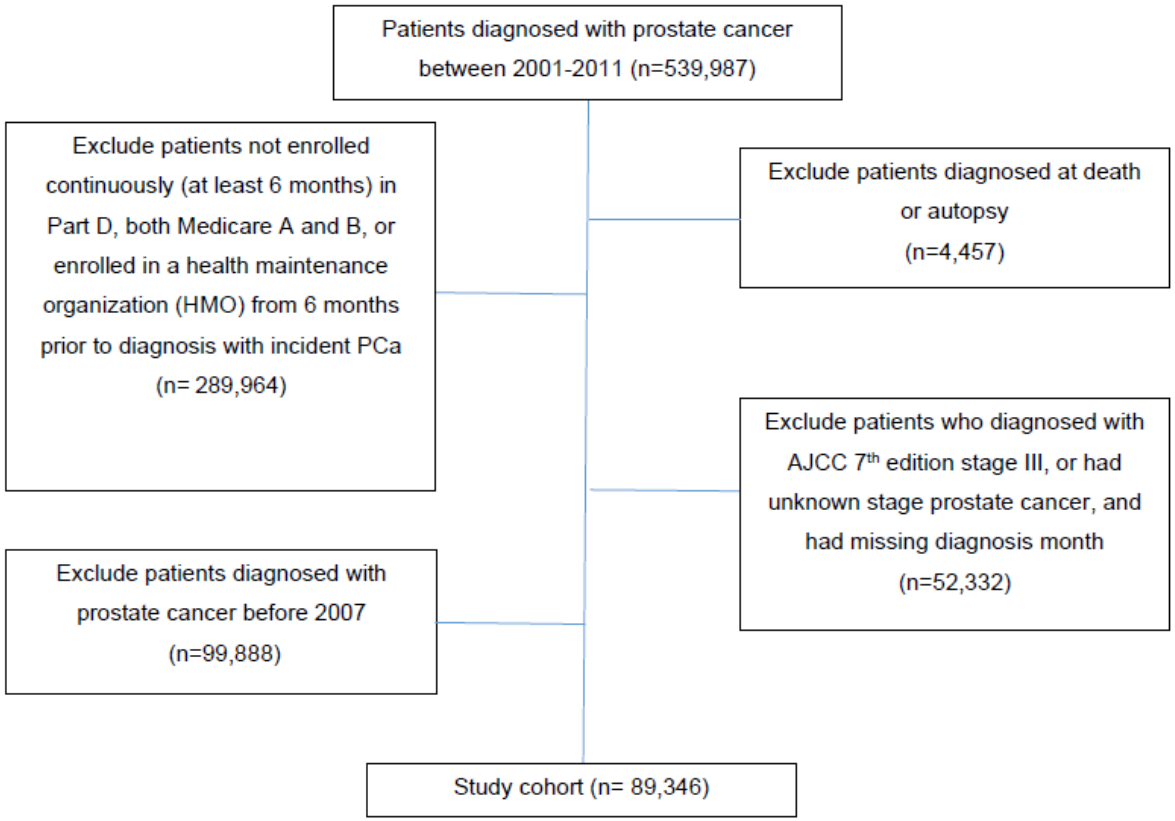
*Per Seer-Medicare guideline publications, a sample size less than 11, should be reported as <11.

Table 5. **NHB men**- Independent and combined association of TTh and statin use with prostate cancer grade and stage at diagnosis and prostate cancer specific mortality among NHW men 65+ years old with a prostate cancer diagnosis in SEER-Medicare 2007-2011*

	High grade prostate cancer†			Advanced stage prostate cancer†			Prostate cancer mortality (adjusted for stage and grade at diagnosis)†		
N=9703	**Events/N**	**OR**	**95% CI**	**Events/N**	**OR**	**95% CI**	**Events/PY¥**	**HR**	**95% CI**
TTh Use*									
No TTh	1119/5028	1.0		1004/11076	1.0		801/60423	1.0	
Yes TTh	<11/93	0.73	0.34,1.57	<11/169	0.79	0.31,2.00	<11/942	1.22	0.23,6.43
Statin Use*									
No Statin	885/3947	1.0		849/9050	1.0		679/49863	1.0	
Yes Statin	244/1174	0.99	0.81,1.20	160/2195	0.95	0.78,1.17	128/11502	1.21	0.82,1.77
TTh & Statin Use‡									
No TTh/No Statin	879/3886	1.0		847/8932	1.0		676/49194	1.0	
Statin alone	240/1142	0.98	0.81,1.2	157/2144	0.94	0.77,1.16	125/11229	1.20	0.81,1.76
TTh alone	<11/61	0.62	0.22,1.71	<11/118	0.45	0.10,1.89	<11/668	0.94	0.10,8.81
TTh+Statin	<11/32	0.95	0.31,2.93	<11/51	1.49	0.43,5.09	<11/273	1.88	0.23,15.37

†Multivariable analysis adjusted for age, Charlson Comorbidity Index (CCI), hypogonadism, hypertension, diabetes, use of insulin, muscular wasting and disuse atrophy, malaise and fatigue, osteoporosis, erectile dysfunction, depressive disorder, anterior pituitary disorder, decreased libido, education (percentage of persons older than 25 years with less than 12 years education), percentage of adults below poverty line at census tract level, patients' primary care (PCP), prostate-specific antigen (PSA), and mutual adjustment for TTh and statin.
‡Interaction term for TTh and statin use and its association with PCa stage ($P_{interaction} = 0.19$) and grade ($P_{interaction} = 0.56$).
¥Person-years
*Per Seer-Medicare guideline publications, a sample size less than 11, should be reported as <11.

Figure 1: Study inclusion and exclusion criteria for identifying men with PCa stage and grade from Seer-Medicare files



Appendix Supplemental Table S1 codes TTh

INJECTION	NDC	00574082001	00009041701	00574082010	00591322126	00781307470	00009041702	00781307370	00781307471					
		00009034702	00143975001	62756001640	00143972601	62756001540	00574082710	00574082105	62756001740	00703612501				
		00703612101	00009052001	00009052010	00009008610	00009008601	54868021601	54868021600	00009008510	00591412879				
		54569530100	67979050140	54868361800	00182071363	35356005810	54396032840	54868361801						
		007813073	007813074	631870647	005740820	005740821	005740827	005913221	005913223	005914128				
		500900330	500900331	500900746	545691411	545692131	545695301	550452092	627780105	627780108				
		000090085	000090086	000090347	000090417	000090520	007036121	007036125	548680216	548683618	548683669			
		627560015	627560016	627560017	001439726	001439750								
	HCPCS/CPT	J0900	J1060	J1070	J1071	J1080	J1090	J2320	J3120	J3121	J3130	J3140	J3145	J3150
GEL	NDC	66993093430	00603783188	00832112142	00832112035	00832112005	00832112140	45802011639	00051846233					
		66887000105	00051845030	00051848888	63481018316	00051842530	00051846230	00051846231	00051842501	00051848833				
		00245087242	00051845001	54569633700	54868498900	54868481000								
		005912921	005913216	005913217	005914810	006037831	458020116	669930934	009321120	009321121				
SULOTION	NDC	00002197590	67979051143											
IMPLANT	NDC	43773100102	43773100104	43773100103										
PATCH	NDC	52544007730	52544007660	52544047030	52544046960	55056306001	52244003060	52544007654	52544046954					
		52544007754	52544047054	17314471703	62109913302									
POWDER	NDC	51927102700	51927432400	38779016309	38779016300	51552002905	38779016305	51927270600	62991215003					
		63275998305	38779016303	38779016308	63275998309	51927102600	38779016409	62991215005	51927102900	62991215001				
		51552002904	62991170703	00574046005	51552002902	63275998308	49452765001	00574046025	38779016504	62991215002				
		38779253608	63370097025	51552002901	51552002903	51552056405	00574046105	38779016403	51552002907	49452765203				
		51552056404	63370097035	63275998304	38779016505	49452765002	38779016503	38779253605	49452765202	51552003004				
		62991170702	63370097135	49452001101	62991170705	51552002906	49452766003	00574046125	49452766001	49452765003				
		38779253600	51552010404	63370097150	38779016404	63275998205	38779016408	51552010405	49452766002	38779253609				
		49452001102	38779253606	62991170701	38779253602	38779259809	51552010407	51552056402	63370097125	51552003002				
		62991141201	38779016508	51552003001	51552010402	63275998209	38779016506	62991141203	63370098050	63370098025				
		51552056407	62991141202	62991170704	63275998204	38779253604	49452765602	63370097050						
Tablet	NDC	00591322379												
	HCPCS/CPT	S0189												

Appendix Supplemental Table S1 codes Statin (Provided upon request since it is a long Excel file).