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Metformin and testosterone replacement therapy inversely associated with hormone-associated cancers (prostate, colorectal and male breast cancers) among older White and Black men

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Abstract

Background: The independent and joint association of metformin and testosterone replacement therapy (TTh) with the incidence of prostate, colorectal, and male breast cancers remain poorly understood, including the investigation of the risk of these cancers combined (HRCs, hormone-associated cancers) among men of different racial and ethnic background.

Methods: In 143,035 men (≥ 65 yrs old) of SEER-Medicare 2007–2015, we identified White (*N* = 110,430), Black (*N* = 13,520) and Other Race (*N* = 19,085) men diagnosed with incident HRC. Pre-diagnostic prescription of metformin and TTh was ascertained for this analysis. Weighted multivariable-adjusted conditional logistic and Cox proportional hazards models were conducted.

Results: We found independent and joint associations of metformin and TTh with incident prostate (odds ratio $[OR]_{joint} = 0.44$, 95% confidence interval [CI]: 0.36–0.54) and colorectal cancers ($OR_{joint} = 0.47$, 95% CI: 0.34–0.64), but not with male breast cancer. There were also inversed joint associations of metformin and TTh with HRCs ($OR_{joint} = 0.45$, 95% CI: 0.38–0.54). Similar reduced associations with HRCs were identified among White, Black, and Other Race men.

Conclusion: Pre-diagnostic use of metformin and TTh were, independently and jointly, inversely associated with incident prostate and colorectal cancers. The risk of HRCs was also reduced among White, Black and Other Race men. Greatest reduced associations of prostate and colorectal cancers and HRCs were mainly observed in combination of metformin and TTh. Larger studies are needed to confirm the independent and joint association of metformin plus TTh with these cancers in understudied and underserved populations.

Yong-Fang Kuo and Steven Canfield contributed equally as senior authors.

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KEYWORDS
hormone-associated cancers, metformin, testosterone

1 | INTRODUCTION

The effect of metformin on the reduction of overall cancer risk has been previously observed, but it merits a further observation with prostate, colorectal and male breast cancers, stage and grade at diagnosis, and cancer site-specific mortality.[1–3] Because endogenous testosterone has been previously associated with prostate, colorectal and male breast cancer, they will be referred as hormone-associated cancers, HRCs, when they are combined.[4–11] Colorectal cancer is investigated as a hormone-associated cancer and not as a hormone-dependent or hormone-caused cancer; therefore, this potential hormone-cancer relationship has potential translational applications for preventive diagnosis, risk stratification and treatment.[6,8,9,11] A retrospective cohort study that emulated an intent-to-treat analysis on 95,820 participants found a similar incidence of total cancer, prostate, colorectal and postmenopausal breast cancers among those who used metformin compared with those who used sulfonylureas.[1] A recent meta-analysis of 18 cohort studies did not show an association between metformin and prostate cancer.[12] However, a recent retrospective study of 76,733 males reported that the use of metformin alone was associated with lower risk of prostate cancer in Hispanics compared with White men, but not between Black and White men.[13] There is a research gap about the effects of metformin on prostate, colorectal or male breast cancers among Black men and other races and ethnic groups (herein we will refer as Other Race composed of Asian, Native American, and Hispanic men).

Similarly, the association of TTh with prostate, colorectal, or male breast cancer in large studies remains poorly understood.[4–10] The use of TTh in the United States increased from 0.81% in 2001 to 2.9% in 2011. However, it decreased from 2013 to 2016 due to a FDA safety bulletin issued between 2013 and 2014. A meta-analysis of 11 randomized controlled trials (RCT) based on 20 incident prostate cancer cases concluded that testosterone supplementation for symptomatic hypogonadism did not increase the risk of prostate cancer,[14] but the power of this study to make conclusions was minimal. Recent observational studies have linked serum testosterone levels with colorectal cancer[6,8,9,11,15] and breast cancer in men,[7,10] but as of to date no RCT has been designed to investigate these associations. 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 underserved and understudied populations.

It is plausible that metformin and TTh can work together as the prevalence of testosterone deficiency and diabetes has increased among older men, and subsequently their treatment with TTh and metformin.[16–18] Previous studies have suggested a biological interaction between low levels of testosterone and type II diabetes,[19,20] and subsequently between TTh and metformin.[18,21]

Therefore, the objectives of this study are to investigate the independent and joint effects of metformin and TTh on the incidence of prostate, colorectal, or male breast cancers and HRCs, and to examine whether associations with HRCs vary among White, Black and Other Race men.

2 | PATIENTS AND METHODS

2.1 | Data source

We analyzed data from Surveillance, Epidemiology and End Results (SEER)-Medicare 2007–2015, a linkage of population-based cancer registries with Medicare administrative data. We used the Summarized Denominator file to collect information on the 5% sample of non-cancer patients. The SEER program collects clinical, demographic and survival information from American cancer patients ≥65 years. Part A includes hospital care, skilled nursing facility and hospice information. Part B includes outpatient care, physician and provider care, and home health care information. Part D includes prescription medication data. Institutional Review Board of UTMB approved this study.

2.2 | Study cohort

In this retrospective cohort study, all males (n = 344,103) aged ≥65 years with at least 1 year of continuous enrollment in Part D, before any cancer diagnosis, anytime between 2007 and 2015 were eligible for inclusion in the study. The cancer cohort included patients (n = 145,704) with a confirmed primary diagnosis of prostate, colorectal or male breast cancers and HRCs between January 2008 and December 2015. Eligible subjects were divided in two groups; the exposed, including those that received any testosterone or metformin prescription between 07/2007 and 06/2015 and the unexposed who did not receive any of the two drugs during the same period. Exposed subjects were excluded from consideration if they were younger than 65 years old at the time of the first drug prescription (index date), if they had less than 6 months continuous part A and B enrollment before the index date or if the index date was less than 6 months before the prostate, colorectal and male breast cancers and HRCs diagnosis date (if any). Unexposed subjects that were at least 65 years old and had at least 6 months of part A and B enrollment at any time during the study period formed the pool of eligible matched participants. Unexposed subjects were randomly matched 4:1 on birth year with the exposed group and were assigned the same index date as their match, while ensuring they had at least 6 months of continuous Medicare parts A, B and D enrollment before their assigned index date, and the index date was at least 6 months before any HRCs cancer site diagnosis (Figure 1).

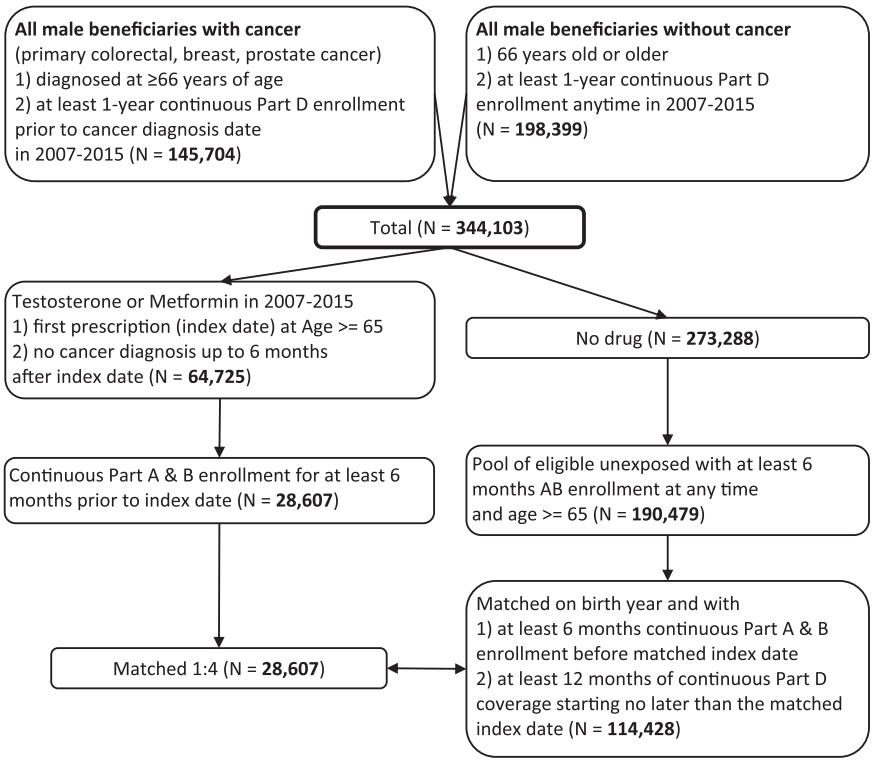

FIGURE 1 Flow chart of cohort derivation.

2.3 | Prediagnostic use of metformin and TTh

Prescriptions of TTh and use of metformin were established from Medicare Part D using National Drug Codes (NDC) and Current Procedural Terminology (CPT) codes. The primary exposures were metformin (Yes/No), term use of metformin, TTh (Yes/No), and number of TTh injections. The combined use of both TTh and metformin was based on the use of TTh (Yes/No) or metformin (Yes/No), we categorized individuals in four groups: No TTh plus No metformin (reference group), metformin alone, TTh alone, and both (TTh plus metformin). The index date was defined as the date of the first prescription within the study period. For patients who used both TTh and metformin, at least 6 months between the later of the two dates and prostate, colorectal and male breast cancers and HRC diagnosis (if any) was required. These criteria also applied to metformin and TTh only groups, including cancer-specific sites and HRCs mortality analysis. For the outcome of cancer-specific sites and HRCs-specific mortality, we evaluated TTh and metformin use at any time during the study period and conducted to time-to-event analysis.

2.4 | Prostate, colorectal or male breast cancers outcomes

The outcomes of interest of this study were incident prostate, colorectal and breast male breast and HRCs, localized (stage I and II), advanced-stage (AJCC Stage III and IV),[22] high-tumor grade (undifferentiated and poorly differentiated tumors), and cancer mortality. Causes of cancer 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. Cancer mortality was censored upon loss-to-follow-up because of discontinuation of enrollment or the administrative end of calendar year (31 December 2016) and for those who died of other causes.

2.5 | Covariates

Patient characteristics included in the model were age at diagnosis, race (White, Black and Other Race), level of education, number of primary care physician (PCP) visits, and number of prostate-specific antigen (PSA) tests, breast cancer screening, colorectal colonoscopy, and NCI-Charlson Comorbidity Index (CCI). We used the NCI-CCI from 6 months before the index date to determine comorbidity burden. In addition to the 6-months period required between first medication date and HRCs diagnosis date, all covariates were ascertained in the period of at least 6 months preceding first index date. Clinical indicators identified from Medicare claims using NDC and CPT codes included hypogonadism, hyperlipidemia, hypertension, diabetes, use of insulin, muscular wasting and disuse atrophy, malaise and fatigue, osteoporosis, erectile dysfunction, depressive disorder, and anterior pituitary disorder.

3 | STATISTICAL ANALYSIS

Patient characteristics, clinical indicators, and census tract socioeconomic status variables were compared by drug group (TTh plus metformin) using Chi-square tests for categorical variables (n[%]) and

F-tests for continuous variables (mean[SD]). Non-cancer cohort were sampled from the Medicare population, whereas cancer patients were not (SEER). To account for this difference, we applied weights to extrapolate to full population of men (65+ years old) to be able to estimate the incidence of prostate, colorectal and male breast cancers and HRCs (as well as grade and stage), and to conduct weighted multivariable-adjusted conditional logistic models. Independent associations of TTh and metformin with incident, prostate, colorectal, or male breast cancers and HRCs, stage and grade at diagnosis were assessed by conducting weighted multivariable conditional logistic regression models using *a priori knowledge*[23] to identify potential confounders as previously described in the Covariates Section. These weighted multivariable adjusted models compared the odds of incident HRCs (prostate, colorectal and breast cancers), high-grade HRCs, or advanced-stage HRCs versus non-cancer cohort. Multivariable adjusted Cox proportional hazards models estimated hazard ratios for HRCs mortality adjusting for stage and grade at diagnosis. Scaled Schoenfeld residuals were used to test the proportional hazards assumption.[24] We conducted stratified analysis to determine whether the association between TTh plus metformin use and HRCs outcomes was different in White, Black, and Other Race men.[25] Statistical analyses were performed using SAS (SAS Institute v.9.4). *p*-values were considered significant at ≤.05.

4 | RESULTS

We identified 110,430 White, 13,520 Black, and 19,085 Other Race men diagnosed with any primary HRCs (prostate, breast, or colorectal cancer) in SEER-Medicare data 2007-2015. Mean age was 75 years old, and the median follow-up time from diagnosis of HRCs to death or end of study was 5.5 years (12/31/2015). Table 1 shows patient characteristics by combination of TTh and metformin. Approximately 18.1% of men used metformin alone, 1.48% used TTh alone, and 0.50% used both TTh plus metformin. Compared to men with no TTh plus no metformin, users of TTh alone, metformin alone or their combination were less likely to report <12 years of education and lower percentage below poverty line, but more likely to be younger, White, hypertensive, diabetic, reported muscular wasting and malaise and fatigue, reported erectile dysfunction, higher score of CCI comorbidity, hypogonadism, osteoporosis, depressive disorder, pituitary disorder, higher use of insulin, and minimally higher number of PCP visits, breast cancer screenings, colonoscopies, and PSA tests (Table 1).

Tables 2–4 showed the independent and joint associations of metformin and TTh with prostate, colorectal and male breast cancers, respectively. Due to power sample size, we were able only to conduct independent associations of metformin use and TTh with incident male breast cancer (Table 4). For prostate cancer (Table 2), independent associations of metformin use and TTh with incident prostate cancer, high grade and advanced stage at diagnosis were significantly, inversely associated. For colorectal cancer (Table 3), there were inverse independent and joint inverse associations of metformin use and TTh mainly with incident colorectal cancer. The associations with high grade and advanced stage at diagnosis were not consistent. For incident male breast cancer, there were no significant associations with metformin and TTh (Table 4). In general, the combination of metformin and TTh showed greater reduced effects for prostate and colorectal cancers than the independent associations of metformin and TTh with those cancers. No significant associations with cancer mortality were found.

Table 5 shows the multivariable-adjusted independent and joint effects of metformin and TTh on the incidence of HRCs, high grade and advanced stage at diagnosis and mortality. In combination, when we compared with no TTh plus no metformin use, TTh plus metformin showed a greater reduced odds ratio of incident HRCs (OR = 0.45, 95% CI, 0.38–0.54). In general, similar significant associations were found with high grade and advanced stage at diagnosis. Additionally, there was no significant association with HRCs-specific mortality.

Among White men (Table S1), the largest cohort of the overall population, the findings were similar like with the overall population. In combination, TTh plus metformin showed a greater reduced odds ratio of incident HRCs (OR = 0.44, 95% CI, 0.36–0.53).

Among Black men (Table S2) and men from Other Race (Table S3), there were significant inverse associations with HRCs. In general, the results for stage and grade at diagnosis of HRCs among Black and Other Race men were limited in sample size; therefore, those findings should be interpreted with caution.

In exploratory analysis, we also investigated the effects of time of use of metformin (1–3 years vs. No Use) and number of injections of TTh (1–2 and >2 injections vs. No Use) on prostate and colorectal cancers and HRCs, stage and grade at diagnosis, cancer-specific site, and by race (Tables S4–S9). In general, the direction of the associations was inversed and significant.

5 | DISCUSSION

Overall, we found independent and inverse associations between pre-diagnostic use of metformin and TTh with incident prostate and colorectal cancers (mainly incident disease) and HRCs in older men, including stage and grade at diagnosis. Similar associations were observed with the combination of TTh plus metformin. Among White men, the direction of these associations remained similar like in the overall population, but among Black and Other Race men the independent and joint effects were observed mainly on the risk of HRCs. In general, the combination of metformin use and TTh showed greater reduced effects of prostate and colorectal cancers and HRCs than the independent associations of metformin and TTh. No associations with any cancer mortality was found. The innovative component of this study is the quantification of the joint effects of metformin and TTh on the incidence of prostate and colorectal cancers and

TABLE 1 Baseline characteristics of men 65+ years old with prostate, colorectal and male breast cancers (HRC) by current use of testosterone therapy (TTh) and/or metformin with a median follow-up (HRC mortality) of 5.5 years in the SEER-Medicare 2007–2015

Characteristic	Drug Group[a] None	Metformin alone	TTH alone	Both (TTh plus metformin)	*p* value
Total	114,428 (80.0)	25,819 (18.1)	2,123 (1.48)	665 (0.50)	
Incident HRC	55,078 (48.1)	9,768 (37.8)	807 (38.0)	201 (30.2)	
Colorectal	12,705 (23.1)	2,891 (29.6)	158 (19.6)	40 (19.9)	
Prostate	42,037 (76.3)	6,805 (69.7)	>638 (>79.9)	>150 (>77.1)	
Male breast	336 (0.6)	72 (0.7)	<11 (<0.5)	<11 (<3.0)	
HRC stage[c]					<.0001
Localized	38,556 (77.3)	6,544 (75.0)	605 (81.7)	147 (80.3)	
Advanced	11,302 (22.6)	2,176 (25.0)	135 (18.2)	36 (19.7)	
HRC grade[d]					<.0001
Low	26,751 (48.6)	4,843 (49.6)	452 (56.0)	118 (58.7)	
High	28,327 (51.4)	4,925 (50.4)	355 (44.0)	83 (41.3)	
HRC mortality	6,931 (12.6)	1,355 (13.9)	60 (7.4)	15 (7.5)	<.0001
Age					<.0001
65–70	54,886 (48.0)	12,272 (47.5)	1,055 (49.7)	421 (63.3)	
70–75	29,889 (26.1)	6,780 (26.3)	525 (24.7)	141 (21.2)	
75–80	17,282 (15.1)	3,932 (15.2)	316 (14.9)	75 (11.3)	
80+	12,371 (10.8)	2,835 (11.0)	227 (10.7)	28 (4.2)	
Race					<.0001
White	89,054 (77.8)	18,925 (73.3)	1,883 (88.7)	568 (85.4)	
Black	10,976 (9.6)	2,386 (9.2)	112 (5.3)	46 (6.9)	
Other Race	14,398 (12.6)	4,508 (17.5)	128 (6.0)	51 (7.7)	
CCI Comorbidity					<.0001
0	75,285 (65.8)	14,833 (57.4)	1,104 (52.0)	403 (60.6)	
1	20,018 (17.5)	5,627 (21.8)	535 (25.2)	134 (20.2)	
2	9,815 (8.6)	2,805 (10.9)	234 (11.0)	68 (10.2)	
3+	9,310 (8.1)	2,554 (9.9)	250 (11.8)	60 (9.0)	
Hypogonadism	1,403 (1.2)	444 (1.7)	1,426 (67.2)	198 (29.8)	<.0001
Hypertension	57,388 (50.2)	19,366 (75.0)	1,411 (66.5)	507 (76.2)	<.0001
Muscle wasting	736 (0.6)	203 (0.8)	30 (1.4)	16 (2.4)	<.0001
Malaise/fatigue	12,243 (10.7)	3,862 (15.0)	829 (39.0)	172 (25.9)	<.0001
Osteoporosis	2,276 (2.0)	494 (1.9)	139 (6.5)	23 (3.5)	<.0001
Erectile dysfunction	4,996 (4.4)	1,054 (4.1)	736 (34.7)	124 (18.6)	<.0001
Depression	3,429 (3.0)	986 (3.8)	148 (7.0)	29 (4.4)	<.0001
Pituitary disorder	95 (0.1)	27 (0.1)	55 (2.6)	13 (2.0)	<.0001
Diabetes	16,869 (14.7)	22,161 (85.8)	429 (20.2)	497 (74.7)	<.0001
Use of insulin	2,545 (2.2)	1,817 (7.0)	91 (4.3)	46 (6.9)	<.0001

Characteristic	Drug Group[a] None	Metformin alone	TTH alone	Both (TTh plus metformin)	*p* value
Drug Group[b]					
Number of PSA tests	0.38 (0.7)	0.42 (0.6)	0.74 (0.7)	0.56 (0.7)	<.0001
Number of breast screening	0.00 (0.03)	0.00 (0.03)	0.00 (0.06)	0.00 (0.04)	<.0001
Number of colonoscopies	0.05 (0.2)	0.05 (0.2)	0.07 (0.3)	0.07 (0.3)	<.0001
Number PCP Visits	8.16 (9.7)	9.94 (9.3)	13.40 (10.2)	11.61 (9.9)	<.0001
Percent adults <12 yrs education	14.87 (10.9)	16.61 (11.8)	14.04 (10.2)	15.63 (10.6)	<.0001
Percent adults below poverty	14.32 (9.5)	15.16 (9.7)	14.40 (8.9)	15.48 (9.4)	<.0001

Note: SEER-Medicare guideline presentation has been followed and all counts less than 11 have been suppressed.

Abbreviations: CCI, Charlson Comorbidity Index; HRC, hormone-associated cancer; PCP, primary care physician; PSA, prostate-specific antigen; SD, standard deviation; SEER, Surveillance, Epidemiology, and End Results.

[a]Data are presented as *N* (%).

[b]Data are presented as mean (±SD).

[c]Advanced stage HRC cases were consistent with AJCC Stage III and IV definition where localized HRC cases were defined with Stages I–II.

[d]High tumor grade was defined with Grade III–IV (undifferentiated and poorly differentiated tumors) and low-grade (I–II).

HRCs, stage and grade at diagnosis, and cancer-specific mortality in Seer-Medicare 2007–2015.

5.1 | TTh use and prostate, colorectal and breast cancers and HRCs

5.1.1 | Prostate cancer

The association of TTh with risk of developing prostate cancer remains conflicted.[14,26–28] Our significant inverse associations with incident prostate cancer, high-grade and advanced stage at diagnosis are in the same direction as previously found in two meta-analysis of randomized clinical trials that investigated risk of developing prostate cancer in relation to TTh use, albeit findings from these meta-analyses did not reach statistical significance.[14,26] Yet, it is important to note that in those meta-analyses transdermal was the most common delivery method, while in our analysis we combined injections and the use of gels of testosterone therapy. Furthermore, concurring with our findings two recent retrospective cohort studies conducted in U.S. commercial insurance claims data found an inverse association between TTh and incident prostate cancer.[27,28] Findings related to aggressive disease, three recent retrospective population-based studies found no increased risk of high-grade prostate cancer in men with TTh use,[29–31] and protective effects for advanced stage.[30,31]

5.1.2 | Colorectal cancer

A pooled analysis of two large observational and two randomized controlled trials reported that higher levels of testosterone were associated with a lower risk of colorectal cancer in men.[8] Subsequently, this pooled analysis reported that higher circulating levels of free testosterone were associated with lower risk of overall and possibly colorectal cancer-specific mortality.[6] More recently, a 2022 large European nested-case control study concluded that there is suggestive evidence for the association between testosterone and male colon cancer development. Our findings related to the use of TTh were similar to those studies showing a reduced risk on colorectal cancer with endogenous testosterone. However, some other studies reported that endogenous levels of testosterone were not associated with colorectal cancer risk.[15,32,33] For male breast cancer, the role of endogenous and exogenous testosterone remains unclear.[7,10] This may be due, in part, to small sample size studies, and our study can be an example as we couldn't conduct the joint effects of TTh plus metformin on male breast cancer cases.

TABLE 2 **Only prostate cancer (PCa)**: Independent and joint effect of metformin and TTh on incident PCa, grade and stage at diagnosis, and PCa mortality among men 65+ years old in SEER-Medicare 2007–2015[a]

	Incidence[b]		High grade[b]		Advanced stage[b]		PCa mortality[b,c]	
	Events/*n*	OR (95% CI)	Events/n	OR (95% CI)	Events/n	OR (95% CI)	Events/n	HR (95% CI)
Metformin								
No	42,682/1,256,002	REF	20,919/1,234,239	REF	6,200/1,219,520	REF	3124/42,682	REF
Yes	6960/337,260	0.62 (0.60–0.65)	3435/333,735	0.61 (0.57–0.64)	1015/331,315	0.73 (0.66–0.80)	548/6960	1.05 (0.93–1.17)
TTh								
No	48,842/1,556,862	REF	24,016/1,532,036	REF	7,128/1,515,148	REF	3649/48,842	REF
Yes	800/36,400	0.65 (0.58–0.72)	338/35,938	0.58 (0.50–0.67)	87/35,687	0.57 (0.45–0.72)	23/800	0.81 (0.52–1.25)
TTh & Metformin								
None	42,037/1,229,037	REF	20,642/1,207,642	REF	6,132/1,193,132	REF	3107/42,037	REF
Met alone	6805/327,825	0.62 (0.59–0.65)	3374/324,394	0.61 (0.57–0.64)	996/322,016	0.72 (0.66–0.79)	542/6805	1.05 (0.93–1.17)
TTh alone	645/26,965	0.63 (0.56–0.71)	277/26,597	0.58 (0.49–0.68)	68/26,388	0.54 (0.41–0.72)	17/645	0.78 (0.47–1.30)
Both	155/9435	0.44 (0.36–0.54)	61/9341	0.36 (0.27–0.47)	19/9299	0.47 (0.30–0.72)	<11/155	0.92 (0.41–2.06)

Note: SEER-Medicare guideline presentation has been followed and all counts less than 11 have been suppressed.

Abbreviations: CI, confidence interval; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results; TTh, testosterone therapy.

[a]Cancer incidence [events/n] in this study are extrapolated to the whole SEER-Medicare program.

[b]Multivariable analysis adjusted for age, race/ethnicity, hypogonadism, hypertension, diabetes, use of insulin, muscular wasting, malaise and fatigue, osteoporosis, erectile dysfunction, depression, anterior pituitary disorder, 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 metformin.

[c]Additionally adjusted for stage and grade.

TABLE 3 **Only colorectal cancer (CRC)**: Independent and joint effect of metformin and TTh on incident CRC, grade and stage at diagnosis, and CRC mortality among men 65+ years old in SEER-Medicare 2007–2015[a]

	Incidence[b]		High grade[b]		Advanced stage[b]		CRC mortality[b,c]	
	Events/*n*	OR (95% CI)	Events/n	OR (95% CI)	Events/n	OR (95% CI)	Events/n	HR (95% CI)
Metformin								
No	12,863/1,226,183	REF	1941/1,215,261	REF	2325/1,215,645	REF	3,826/12,863	REF
Yes	2931/333,231	0.79 (0.75–0.84)	432/330,732	0.76 (0.66–0.87)	500/330,800	0.88 (0.77, 1.01)	815/2931	0.99 (0.90–1.09)
TTh								
No	15,596/1,523,616	REF	2344/1,510,364	REF	2788/1,510,808	REF	4589/15,596	REF
Yes	198/35,798	0.75 (0.63–0.88)	29/35,629	0.76 (0.50–1.15)	37/35,637	0.88 (0.61, 1.27)	52/198	1.14 (0.84–1.56)
TTh & Metformin								
None	12,705/1,199,705	REF	1919/1,188,919	REF	2295/1,189,295	REF	3783/12,705	REF
Met alone	2891/323,911	0.80 (0.75–0.85)	425/321,445	0.76 (0.66–0.87)	493/321,513	0.89 (0.78, 1.02)	806/2891	1.00 (0.91–1.10)
TTh alone	158/26,478	0.82 (0.67–0.99)	22/26,342	0.79 (0.48–1.28)	30/26,350	1.00 (0.66–1.52)	43/158	1.28 (0.90–1.81)
Both	40/9320	0.47 (0.34–0.64)	<11/9287	0.53 (0.26–1.08)	<11/9287	0.56 (0.26–1.20)	<11/40	0.80 (0.41–1.54)

Note: SEER-Medicare guideline presentation has been followed and all counts less than 11 have been suppressed.

Abbreviations: CI, confidence interval; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results; TTh, testosterone therapy.

[a]Cancer incidence [events/n] in this study are extrapolated to the whole SEER-Medicare program.

[b]Multivariable analysis adjusted for age, race/ethnicity, hypogonadism, hypertension, diabetes, use of insulin, muscular wasting, malaise and fatigue, osteoporosis, erectile dysfunction, depression, anterior pituitary disorder, 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), colorectal cancer screening, and mutual adjustment for TTh and metformin.

[c]Additionally adjusted for stage and grade.

TABLE 4 **Only male breast cancer**. Independent associations of metformin and TTh with male breast cancer among men 65+ years old in SEER-Medicare 2007–2015[a]

	Incidence[b]	
	Events/*n*	OR (95% CI)
Metformin		
No	340/1,213,660	REF
Yes	78/330,378	0.77 (0.56–1.07)
TTh		
No	408/1,508,428	REF
Yes	<11/35,610	1.01 (0.48–2.11)

Note: SEER-Medicare guideline presentation has been followed and all counts less than 11 have been suppressed.

Abbreviations: CI, confidence interval; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results; TTh, testosterone therapy.

[a]Cancer incidence [events/n] in this study are extrapolated to the whole SEER-Medicare program.

[b]Multivariable analysis adjusted for age, race/ethnicity, hypogonadism, hypertension, diabetes, use of insulin, muscular wasting, malaise and fatigue, osteoporosis, erectile dysfunction, depression, anterior pituitary disorder, 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), colorectal cancer screening, and mutual adjustment for TTh and metformin.

5.2 | Metformin use and prostate, colorectal and breast cancers and HRCs

Metformin has been associated with cancer, but this interplay is poorly understood in relation to HRCs (prostate, colorectal and male breast cancer) and among men of different racial backgrounds.[3,12,34,35] Our findings are in agreement with a previous study retrospective cohort study that significant associations between metformin and incident prostate and colorectal cancers.[1] However, a meta-analysis of 18 cohort studies did not show an association between metformin and prostate cancer,[12] prostate cancer mortality,[2] and another study did not show improvement in survival in women with breast cancer.[34] These differences may be mainly driven by the study design. Of note, these meta-analyses[12,36] did not analyze Black or any other racial/ethnic group as a separate group. A more recent meta-analysis in the relation between metformin and colorectal cancer reported that metformin may be a protective factor for colorectal cancer.[36]

5.3 | Joint association of TTh plus metformin use with HRC

To our knowledge no study has investigated the combination of TTh plus metformin in relation to incident HRCs, stage and grade at diagnosis, and HRCs specific mortality. However, it is important to note there are some studies that have explored the interplay between metformin, endogenous and exogenous testosterone in different settings that may provide insight to our findings.[18,37] For instance, Krysiak et al. reported that testosterone had a beneficial effect on risk factors of cardiovascular disease in patients with hypogonadism receiving metformin than sulfonylurea, suggesting that testosterone may bring more clinical effects to metformin than sulfonylurea treatment.[18] Yet, the network meta-analysis of randomized controlled trials reported that metformin was associated with a substantial reduction in testosterone levels among women.[37]

5.4 | Strengths and limitations

Our study has strengths. This investigation included a large racially diverse cohort, a large number of men with incident prostate and colorectal cancers, HRCs, stage and grade at diagnosis, and a large enough sample to be able to investigate men who have used both TTh and metformin. This study also included a long period of follow-up, detailed information on patient's exposures to TTh and metformin on the basis of filled prescriptions and inclusion of clinically relevant comorbidities.

Yet, the present study has limitations as well. First, we had a small sample size for male breast cancers; therefore, we couldn't conduct specific analysis with the joint association of metformin and TTh. This included a limited sample size among racial groups this is why we conducted analysis mainly among HRCs, and not the specific cancer sites. Second, our retrospective cohort design does not allow us to conclude whether these medications decrease the occurrence of advanced diseases (high grade and advanced stage) or increase the occurrence of non-advanced disease, which both scenarios lead to an OR < 1.[38] Third, there are general limitations of retrospective analysis based on Medicare claims data, such as possible coding errors, omissions of claims,[39] or use of medications before 2007 (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 influences associations to the null (1.0). Fourth, limiting the pre-index period to 6 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.

Fifth, although we adjusted for hypogonadism, age, CCI, and insulin users and diabetes in the multivariable analysis, we cannot rule out potential residual confounding by these factors. Seer-Medicare does not include laboratory results (serologic or diagnostic indications), so we can't define hypo- or hyperglycemia, or other occupational, environmental, nutritional and/or several lifestyle factors. This includes no available data for obesity (body mass index ≥ 30 kg/m^2), a strong risk factor for colorectal cancer. Although we adjusted for strong factors associated with obesity such as diabetes, hypertension, CCI comorbidity score, hypogonadism, and use of insulin, it is possible that some levels of obesity were captured and adjusted for,[23] yet residual confounding may remain. Sixth, to

TABLE 5 **Only HRCs**: Independent and joint effect of metformin and TTh on incident HRCs, grade and stage at diagnosis, and HRCs mortality among men 65+ years old in SEER-Medicare 2007–2015[a]

	Incidence[b]		High grade[b]		Advanced stage[b]		HRCs mortality[b,c]	
	Events/*n*	OR (95% CI)	Events/*n*	OR (95% CI)	Events/*n*	OR (95% CI)	Events/*n*	HR (95% CI)
Metformin								
No	55,885/1,269,205	REF	22,972/1,236,292	REF	8545/1,221,865	REF	6991/55,885	REF
Yes	9969/340,269	0.66 (0.64–0.69)	3891/334,191	0.62 (0.59–0.65)	1519/331,819	0.77 (0.71–0.83)	1370/9,969	1.02 (0.95–1.10)
TTh								
No	64,846/1,572,866	REF	26,492/1,534,512	REF	9940/1,517,960	REF	8286/64,846	REF
Yes	1008/36,608	0.66 (0.60–0.73)	371/35,971	0.59 (0.52–0.68)	124/35,724	0.63 (0.51–0.77)	75/1008	1.03 (0.80–1.32)
TTh & Metformin								
None	55,078/1,242,078	REF	22,671/1,209,671	REF	8447/1,195,447	REF	6931/55,078	REF
Met alone	9768/330,788	0.66 (0.64–0.69)	3821/324,841	0.62 (0.59–0.65)	1493/322,513	0.77 (0.71–0.83)	1355/9,768	1.03 (0.96–1.11)
TTh alone	807/27,127	0.66 (0.59–0.73)	301/26,621	0.59 (0.50–0.68)	98/26,418	0.63 (0.50–0.80)	60/807	1.14 (0.85–1.51)
Both	201/9481	0.45 (0.38–0.54)	70/9350	0.38 (0.29–0.49)	26/9306	0.49 (0.33–0.71)	15/201	0.80 (0.48–1.33)

Note: SEER-Medicare guideline presentation has been followed and all counts less than 11 have been suppressed.

Abbreviations: CI, confidence interval; HRC, hormone-associated cancer; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Results; TTh, testosterone therapy.

[a]Cancer incidence [events/n] in this study are extrapolated to the whole SEER-Medicare program.

[b]Multivariable analysis adjusted for age, race/ethnicity, hypogonadism, hypertension, diabetes, use of insulin, muscular wasting, malaise and fatigue, osteoporosis, erectile dysfunction, depression, anterior pituitary disorder, 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), breast cancer screening, and colorectal cancer screening, and mutual adjustment for TTh and metformin.

[c]Additionally adjusted for stage and grade at diagnosis.

reduce potential immortal time bias, we (a) restricted to the study population to those who survived at least 6 months so that the probability of initiating metformin and TTh after HRCs diagnosis is about the same across groups, (b) we aligned prescription and follow up at the same time, and (c) we conducted time-to-event analysis for cancer mortality. Previous study found that in the presence of immortal time bias there is a significant reduced risk of cancer mortality[40]; however, our findings with cancer mortality were null. Due to the nature of a retrospective cohort study, we can't imply causality from this study. The odds ratios provided in these analyses were obtained from weighted conditional logistic regression models that consider incident cancer cases and an exposure that preceded the cancer diagnosis, therefore, they are only approximations to hazard ratios. Finally, our study population only included patients with Medicare claims (≥65 years old); therefore, our results may not be generalizable to research cohorts using other types of insurance, no insurance at all, a younger population, or different racial and ethnic not included in this study.

6 | CONCLUSION

In summary, in this large racial and diverse SEER-Medicare claims-based analysis, we found that pre-diagnostic use of TTh or metformin, independent or in combination, was inversely associated with incident prostate and colorectal cancers and HRCs. Similar associations were observed among White, Black (mainly incident HRCs) and Other Race (mainly incident HRC). The greatest reduced association was observed with combined TTh and metformin. No associations were identified among prostate and colorectal and HRCs mortality. Future and larger studies need to confirm the independent inverse association of TTh and the joint inverse association of TTh plus metformin with these cancers in understudied populations.

AUTHOR CONTRIBUTIONS

DS. Lopez, I. Malagaris, E. Polychronopoulou, YF. Kuo, and S. Canfield: Conception and design, and writing original draft. DS. Lopez, I. Malagaris, and YF. Kuo: Methodology and statistical analysis. DS. Lopez, I. Malagaris, and YF. Kuo: Interpretation of data, statistical analysis, biostatistics, and computational analysis. All authors: interpretation, writing review, and editing.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest. 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.

DATA AVAILABILITY STATEMENT

The authors confirm that data used in developing this article are available upon reasonable request to the corresponding author.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The secondary data analysis was approved by Institutional Review Board at the UTMB, Galveston, TX.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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