HHS Public Access

Author manuscript

J Cancer Res Clin Oncol. Author manuscript; available in PMC 2023 December 07.

Published in final edited form as:

J Cancer Res Clin Oncol. 2023 September ; 149(11): 8255–8265. doi:10.1007/s00432-023-04778-z.

Use of weight loss medications in relation with prostate, colorectal and male breast cancers among older men: SEER-Medicare 2007–2015

David S. Lopez[1], **Hyunkyoung Kim**[1], **Efstathia Polychronopoulou**[1], **Luisa E. Torres-Sanchez**[2], **Alejandro Villasante-Tezanos**[1], **Jacques Baillargeon**[1], **Steven Canfield**[3], **Yong-Fang Kuo**[1]

[1]School of Public and Population Health, The University of Texas Medical Branch (UTMB), 301 University Blvd., Galveston, TX 77555-1153, USA

[2]Instituto Nacional de Salud Publica, Mexico City, Mexico

[3]Division of Urology, UTHealth McGovern Medical School, Houston, TX, USA

Abstract

Background—The association of weight loss medications with prostate (PCa), colorectal (CRC) or male breast cancers, including assessment of these cancers combined (HRCs, hormone-associated cancers) remain poorly understood. Testosterone replacement therapy (TTh) is reported to be inversely associated with obesity, PCa and CRC, but it is unclear whether TTh modifies the association of weight loss medications with HRCs.

Methods—In 49,038 men (≥ 65 years) of SEER-Medicare, we identified 15,471 men diagnosed with PCa, 4836 with CRC, and 141 with male breast cancers. Pre-diagnostic prescription of weight loss medications and TTh was ascertained for this analysis. Weighted multivariable-adjusted conditional logistic and Cox proportional hazards (mortality) models were conducted.

Results—We found an inverse association between use of weight loss medications and incident PCa (OR 0.59, 95% CI 0.57–0.62), CRC (OR 0.86, 95% CI 0.80–0.92), and HRCs (OR 0.65, 95% CI 0.62–0.68). Similar associations were observed for advanced stage at diagnosis of PCa and CRC. Effects of weight loss medications on PCa and HRC remained significant irrespective of the use of TTh but were only suggestive with CRC with positive TTh use. No associations were observed with male breast cancer and HRCs mortality.

Conclusion—Pre-diagnostic use of weight loss medications reduced the incidence of PCa, CRC, and HRCs. These associations persisted in the same direction irrespective of the history of TTh

✉David S. Lopez, davlopez@utmb.edu.

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

Author contributions DSL, YFK, HK, EP, SC: conception and design, and writing original draft. DSL, HK, YFK: methodology and statistical analysis. DSL, KH, EP, YFK: interpretation of data, statistical analysis, biostatistics, and computational analysis. All the authors: interpretation, writing review and editing.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-023-04778-z.

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

use. Future studies are needed to confirm these findings and to identify underlying biological mechanisms of weight loss medications and TTh on the risk of cancer.

Keywords

Weight loss medication; Prostate; Colorectal; Male breast cancer

Introduction

Approximately, 78.4% of American men age ≥ 60 are classified as overweight (BMI ≥ 25 kg/m^2) and 37.1% are classified as obese (body mass index ≥ 30 kg/m^2) (Malenfant and Batsis 2019). Obesity has been previously associated with prostate (PCa) (Wilson et al. 2012), colorectal (CRC) (Keum and Giovannucci 2019) or male breast cancers (Humphries et al. 2015), but the effect of weight loss medications—one of the treatment options for obesity—on these cancers remain understudied (Andrade et al. 2021; Tak and Lee 2021a). Interestingly, a recent survey of 102 geriatric patients who were overweight or obese reported that 57.4% would like to discuss weight loss medications as a treatment option (MacMillan et al. 2016).

The safety of weight loss medications used in older adults is still unclear (MacMillan et al. 2016). Few medications, such as orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, lorcaserin, and including metformin (Day et al. 2019; Seifarth et al. 2013), have been associated with weight loss at 12 months or greater (Day et al. 2019; Seifarth et al. 2013; Bipartisan Policy Center 2022; Khera et al. 2016). The effects of these medications on PCa, CRC, or male breast cancers among older men are still poorly understood (Andrade et al. 2021; Tak and Lee 2021a). However, lorcaserin use was recently linked with an increased risk of total cancer and cancer-related mortality, which prompted the FDA to issue an official warning to voluntary remove this medication from the market in February 2020 (US Food and Drug Administration 2020).

In parallel, the relationship between body fatness (measured by BMI ≥ 30 kg/m, waist circumference ≥ 102 cm, percent body fat ≥ 25%, or increased adipose tissue) and low levels of testosterone remains controversial. Several studies suggest an inverse association between body fatness and low levels of testosterone as shown in cross-sectional studies (Rohrmann et al. 2011; Abate et al. 2002), prospective cohort studies (Derby et al. 2006; Travison et al. 2007), and a systematic review and meta-analysis with observational studies (Brand et al. 2014). Yet, another body of literature suggests that there is a bidirectional relationship between these two factors (Kelly and Jones 2015; Mammi et al. 2012). Furthermore, the use of testosterone replacement therapy (TTh) has been shown to increase lean mass (Corona et al. 2016; Neto et al. 2015), reduce fat mass (Corona et al. 2016; Neto et al. 2015) and BMI (Corona et al. 2016), as shown in a systematic review and meta-analysis of 8 randomized placebo-controlled trials in men over 60 years old with serum testosterone ≤ 550 ng/mL (Neto et al. 2015), and a comprehensive meta-analyses of 32 observational studies with a total of 4513 patients (Corona et al. 2016). Therefore, there is a general observation that obese men are presenting with low levels of testosterone, and it is through these conditions

that there is a biological plausibility that weight loss medications and TTh can potentially interact when men use these medications concomitantly.

Previous studies have reported that endogenous testosterone is associated with PCa, CRC, or male breast cancers; so herein they will be referred as hormone-associated cancers (HRCs) when combined (Claps et al. 2018; Wang et al. 2020; Yang et al. 2019; Brinton et al. 2015; Lin et al. 2013; Hang et al. 2021; Dimitrakakis 2011; Harbs et al. 2022). Colorectal cancer is investigated as a hormone-associated cancer and not as a hormone-dependent cancer, so this relationship has potential translational applications for preventive diagnosis, risk stratification and treatment (Yang et al. 2019; Lin et al. 2013; Hang et al. 2021; Harbs et al. 2022). In this study, we hypothesize that weight loss medications have the potential to reduce these cancers, including in the presence of TTh.

Therefore, we investigated the association of weight loss medications with incident PCa, CRC, or male breast cancers, including HRCs combined. In addition, we examined whether these associations varied by concomitant use of TTh.

Patients and methods

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 (Warren et al. 2002). 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 (Zippin et al. 1995). The Institutional Review Board of UTMB (Galveston, TX) approved this study.

Study cohort

In this retrospective cohort study, all males (n = 441,333) aged ≥ 65 years with at least 1 year of continuous enrollment in Part D, prior to any cancer diagnosis, anytime between 2007 and 2015 were eligible for inclusion in the study. The exposed group included patients (n = 24,519) with a confirmed primary diagnosis of PCa, CRC, or male breast cancers and HRCs between January 2008 and September 2015. Eligible subjects were divided in two groups; the exposed, including those that received any weight loss medication and TTh 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 prior to the index date or if the index date was less than 12 months prior to the PCa, CRC, or male breast cancer diagnosis date (if any). Unexposed subjects who were at least 65 years old and had at least 6 months of part A, B and D enrollment at any time during the study period formed the pool of eligible matched participants. These patients were matched 1:1 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 and B enrollment before their assigned index date, and the index date was at least 12 months before any HRCs cancer site diagnosis (Fig. 1).

Pre-diagnostic use of weight loss medications and TTh prescription

Prescription of weight loss medications and TTh were identified before PCa, CRC, or male breast cancers diagnosis from Medicare Part D using National Drug Codes (NDC) and Current Procedural Terminology (CPT) codes. We included orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, lorcaserin, and metformin as weight loss medications (Tak and Lee 2021a, 2021b; Day et al. 2019; Seifarth et al. 2013; Bipartisan Policy Center 2022). The primary exposure was weight loss medications (Yes/No). TTh (Yes/No) was investigated as an effect modifier. We further categorized long-term use of weight loss medications in four groups: No use (reference group), < 1 year, 1–3 years, > 3 years. The index date was defined as the date of the first prescription within the study period. For patients who used both weight loss medications and TTh, at least 6 months between the later of the two dates and PCa, CRC, and male breast cancers diagnosis (if any) was required. For the outcome of cancer-specific mortality, we evaluated weight loss medications and TTh use at any time during the study period and conducted to time-to-event analysis.

Prostate (PCa), colorectal (CRC) or male breast cancers

The outcomes of interest for this study were incident PCa, CRC, or breast male breast and HRCs, localized (stage I and II), advanced stage (AJCC stage III and IV) (Edge and Compton 2010), 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 (Albertsen et al. 2000). Cancer mortality was censored at the administrative end of the calendar year (December 31, 2016) and for those who died due to non-cancer causes of death.

Covariates

Patient characteristics included in the model were age at diagnosis, race and ethnicity, 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) (Charlson et al. 1987). We used the NCI-CCI from 6 months prior to the index date to determine comorbidity burden. In addition to the 12-month period required between first medication date and HRCs (prostate, colorectal and male breast cancers) 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.

Statistical analysis

Demographic, clinical and cancer characteristics were compared by use of weight loss medications using Chi-square tests for categorical variables and F-tests for continuous variables. Non-cancer cohort was sampled from the Medicare population, whereas cancer patients were all cancer patients from the SEER cancer registry. To account for this difference, we applied weights to extrapolate to full population of men (65+ years) in

the SEER program to be able to estimate the incidence of PCa, CRC, and male breast cancers and HRCs. Our eligibility criteria were applied first, and it was applied for both exposed and non-exposed groups, and we subsequently matched both groups on birthdate. We conducted weighted multivariable-adjusted conditional logistic models using a priori *knowledge* (Hernan et al. 2002) to identify potential confounders (the Covariates Section). These weighted multivariable-adjusted models compared the odds of incident HRCs (prostate, colorectal and breast cancers), high grade or advanced stage at diagnosis *versus* non-cancer cohort.

Multivariable-adjusted Cox proportional hazards models estimated hazard ratios for cancer mortality (prostate, colorectal and HRCs) adjusting for stage and grade at diagnosis. Scaled Schoenfeld residuals were used to test the proportional hazards assumption (Therneau 2000). We conducted stratified analysis to determine whether the association between weight loss medications and cancer outcomes was different among men who used TTh (Yes/No) (VanderWeele 2009). Statistical analyses were performed using SAS (SAS Institute v.9.4, Cary, NC). *P*-values were considered significant at ≤ 0.05.

Results

We identified 49,038 men (≥ 65 years) from SEER-Medicare of whom 15,471 were diagnosed with any primary PCa, 4836 with CRC, or 141 with male breast cancer. 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 use of weight loss medication (No/Yes [< 1 year, 1–3 years, > 3 years]). Approximately, 57.33% of men did not use weight loss medications, and 42.66% did. Of those men who used weight loss medications, 30.33% used them < 1 year, 29% used them between 1 and 3 years, and 40.65% use them for > 3 years. Compared to men who did not use weight loss medications, users of weight loss medications were less likely to: be White, report hypogonadism, osteoporosis, erectile dysfunction, pituitary disorder, and have received colonoscopies, but more likely to be relatively younger, to report < 12 years of education and higher percentage of adults below poverty line, to be Black, Hispanic, reported hyperlipidemia, be hypertensive, diabetic, reported muscular wasting and malaise and fatigue, higher score of CCI comorbidity, depressive disorder, higher use of insulin, and higher number of PCP visits, breast cancer screenings, and PSA tests (Table 1).

Tables 2, 3, and 4 show the associations of weight loss medications, and their years of use with PCa, CRC, and male breast cancers, respectively. Weight loss medications were inversely associated with incident PCa, including high grade and advanced stage at diagnosis (Table 2). Similar inversed associations were observed for years of use of weight loss medications. There were inverse associations of weight loss medication with incident and advanced stage at diagnosis for CRC, but not with high grade (Table 3). These significant and inverse associations remained with years of use of weight loss medications and incident CRC. No significant associations with male breast cancer (Table 4), and cancer mortality (prostate and colorectal) were found (Supplemental Table 1).

Table 5 shows the association of weight loss medications, and their years of use, with incident HRCs, high grade and advanced stage at diagnosis. In general, weight loss medication reduced the risk of HRCs, high grade and advanced stage at diagnosis. Similar patters were observed for years of use of weight loss medications. No significant association with HRCs mortality was found (Supplemental Table 1).

In stratified analysis with positive and negative use of TTh, the association of weight loss medications with HRCs was significantly inversed (Tables 6 and 7). Similar significant inverse associations were observed with incident PCa (Supplemental Tables 2, 3), and CRC (Supplemental Tables 4, 5, only suggestive among positive TTh users, OR 0.74, 95% CI 0.55–1.01). There were similar associations with high grade and advanced stage mainly with PCa and HRCs. We did not find significant associations with male breastcancer (Supplemental Tables 6, 7). Sensitivity analysis was conducted for a second drug, unrelated to the investigated HRCs (Supplemental Table 8).

Discussion

Overall, we observed an inverse association between pre-diagnostic use of weight loss medications and risk of PCa, CRC and HRCs, including advanced stage at diagnosis of these cancers. Stratifying by history of TTh use (positive and negative), showed similar associations between weight loss medications, PCa and HRCs, and only a suggestive inverse association with incident CRC. In general, there were no significant associations with male breast cancer and cancer mortality. The innovative component of this study is the reduction of incident PCa, CRC and HRCs in relation with weight loss medications, including in the presence of a positive use of TTh. These findings seem to agree with our previous hypothesis. Yet, further studies are needed to tease out the null findings we observed between weight loss medications, male breast cancer and cancer mortality.

Total cancer

The CAMELLIA-TIMI 61 trial (462 cancer cases in lorcaserin group/423 in placebo group) reported that the overall rate ratio for total cancer was 1.09 (95% CI 0.96–1.24), and for malignant neoplasms (excluding skin cancers) was 1.16 (95% CI 0.98–1.36) (Andrade et al. 2021; Sharretts et al. 2020). After this trial, a new systematic review and meta-analysis of 4 trials that included 476 cancer cases in 10,342 participants in the lorcaserin group and 438/9429 participants in the placebo group found that the relative risk was for total cancer was 1.08 (95% CI 0.96–1.26) (Andrade et al. 2021). None of these previous trials has reached statistical significance. Our findings with HRCs (combined prostate, colorectal or male breast cancer) do not seem to be in the same direction as with previous studies, which is possible that our large sample size (7354 cancer cases in the weight loss medication group), retrospective cohort study design, and older population are contributing to these differences.

PCa, CRC or male breast cancers

A few basic science studies have explored the role of weight loss medications, such as orlistat and liraglutide, on PCa in mouse models (Tyan et al. 2021) or PCa cell lines (Wright

et al. 2017; Eftekhari et al. 2020) with a potential benefit of inducing apoptosis. Metformin has been suggested to promote weight loss (Day et al. 2019; Seifarth et al. 2013), and it has been previously reported to be inversely associated with incident PCa (Tsilidis et al. 2014). In CRC research, the CAMELLIA-TIMI 61 trial reported that CRC was found in 23 individuals treated with lorcaserin and in 12 subjects in the placebo group (RR 1.92; 95% CI 0.95–3.85), but the risk was not significant, and due to a small sample size in these groups, the power to make conclusions is minimal (Andrade et al. 2021; Sharretts et al. 2020) Another study, a large European matched retrospective cohort study (n = 33,625 on orlistat group; 160,374 on placebo; n = 57 CRC cases) did not find a significant association between orlistat and CRC (HR 1.11, 95% CI 0.84–1.47) (Hong et al. 2013). On the other hand, a recent meta-analysis reported that metformin may be a protective factor for CRC (Wang and Shi 2021). In male breast cancer research, there is still a paucity of high-quality data on the relationship between weight loss medications and male breast cancer. Yet, it is important to note that studies have shown an increased incidence of male breast cancer among obese individuals (Humphries et al. 2015).

It was previously reported that TTh use could reduce fat mass (Corona et al. 2016; Neto et al. 2015) and BMI (Corona et al. 2016) in a meta-analysis of RCTs (men ≥ 60 years) (Neto et al. 2015), and another meta-analyses of observational studies (Corona et al. 2016). In addition, other studies have reported that TTh use reduced the risk of PCa (Boyle et al. 2016; Cui et al. 2014), and endogenous testosterone reduced the risk of CRC (Yang et al. 2019; Harbs et al. 2022), but it remains poorly understood the role of endogenous and exogenous testosterone with male breast cancer (Brinton et al. 2015; Dimitrakakis 2011). Therefore, leveraging from the findings of previous studies, we hypothesized that TTh use could influence the interplay between weight loss medications and HRCs. However, our general observation from our findings is that the association between weight loss medication and HRCs remained in the same significant direction irrespective of the history of TTh use.

Strengths and limitations

Our study has strengths. This investigation included a large sample of men with incident prostate and colorectal cancers, HRCs, stage and grade at diagnosis, and large enough sample to be able to investigate the association of weight loss medications with HRCs, and to determine whether TTh use modified this association. This study also included a long period of follow-up, detailed information on patient's exposures to weight loss medication and TTh based on filled prescriptions and inclusion of clinically relevant comorbidities.

Yet, the present study has limitations as well. First, although we had the power and sample size to investigate the association of weight loss medications with incident male breast cancer, including stratification by TTh use, there were other specific analysis we could not conduct due to the small number of cases (e.g., male breast cancer mortality). Our analyses related to duration use of weight loss medications should only be considered as exploratory as sample size and power to conduct statistical analysis were more limited. 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 (Platz 2010). Third, there are general limitations of retrospective analysis based on Medicare claims data, such as possible coding errors, omissions of claims (Warren et al. 2002), or use of medications prior to 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). However, due to the different PSA guidelines throughout the years, this could influence the number of prostate cancer cases. 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. In addition, the 12-month period between index date and cancer diagnosis was conducted to mitigate potential confounding by indication and protopathic biases. Yet, it is possible that this 12-month criterion has a minimal effect on the high 5-year survival rates for prostate (90%) and colorectal (80%) cancers. Fifth, although we adjusted for several potential risk factors for HRCs, we cannot rule out potential residual confounding by these factors. SEER-Medicare indicates that laboratory results or other environmental, and nutritional/lifestyle (e.g., smoking) factors are incompletely reported with low sensitivity. This includes data for body mass index (≥ 30 kg/m^2), a strong risk factor for colorectal cancer. However, we further adjusted our multivariable models by including obesity, and the results remained nearly identical to the ones without obesity. We adjusted for strong factors associated with obesity such as diabetes, hypertension, CCI comorbidity score, hypogonadism, and use of insulin, and it is possible that some levels of obesity were captured and adjusted for (Hernan et al. 2002), yet residual confounding may remain. In sensitivity analysis, we further conducted propensity score matching to ensure comparability of exposed and non-exposed groups, and the main effect analysis remained similar. Sixth, to 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 weight loss medication after HRCs diagnosis is about the same across groups, (b) aligned prescription and follow-up at the same time, and (c) we conducted time-to-event analysis for cancer mortality. A previous study reported that in the presence of immortal time bias there is a significant reduced risk of cancer mortality (Emilsson et al. 2018), but our findings with cancer mortality were null, including a previous case-only analysis with SEER-Medicare. Due to the nature of the retrospective cohort study, we cannot imply causality from this study. Therefore, the odds ratios provided in these analyses were obtained from weighted conditional logistic regression models that consider incident cancer cases and an exposure (weight loss medication) that preceded the cancer diagnosis; therefore, they are only approximations to hazard ratios. Finally, our study population included ≥ 65 years old patients with Medicare claims, so our results may not be generalizable to research cohorts using other types of insurance, no insurance at all, or a younger population. Furthermore, future studies should focus on more obesity-related cancers.

Conclusion

In summary, in this large SEER-Medicare claims-based analysis, we found that pre-diagnostic use of weight loss medications reduced the incidence of prostate, colorectal cancers, and HRCs. These inversed associations persisted irrespective of the history of TTh

use. No significant associations were observed with incident male breast cancer or cancer mortality. Further research is warranted to investigate the specific biological mechanism (s) that underly the possible protective effects of weight loss medications on the risk of HRCs.

Data availability

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The collection of cancer incidence data used in this study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN2612018000032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute. The ideas and opinions expressed herein are those of the author(s) and do not necessarily reflect the opinions of the State of California, Department of Public Health, the National Cancer Institute, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors.

Funding

David S. Lopez was supported by the National Institutes of Health (NIH) and National Institute on Aging, Grant #: P30 AG059301; and Cancer Prevention and Research Institute of Texas (CPRIT), Grant #: RP210130.

Conflict of interest

The authors declare no potential 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.

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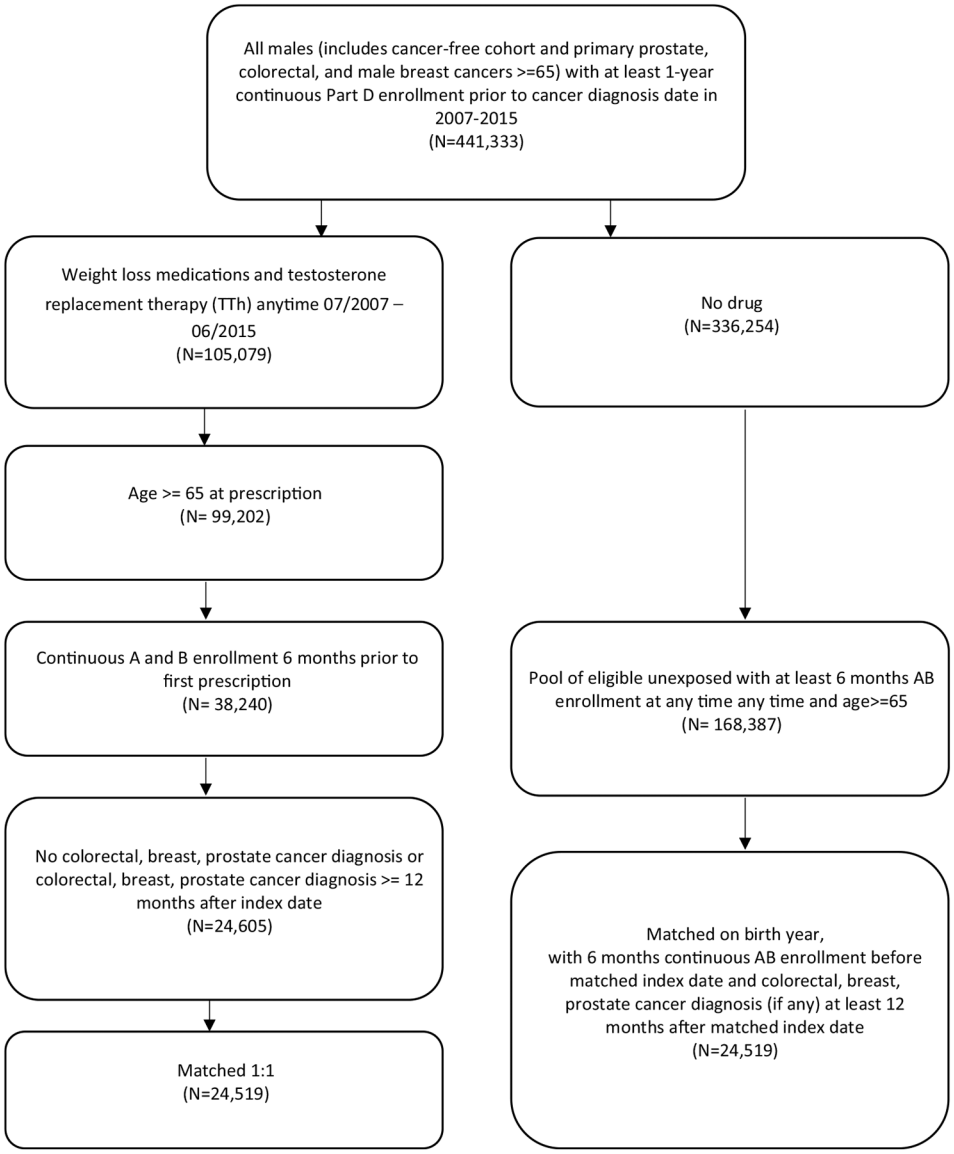

Fig. 1.
Flow chart of cohort derivation

Table 1

Baseline characteristics of men 65+ years old with prostate, colorectal or male breast cancers by current time of use of weight loss medications[a] in the SEER-Medicare 2007–2015

	No—weight loss medication (*N*=20,921)	Yes—weight loss medication (*N*=20,921)			*P*
		< 1 year (*n* = 6346)	1–3 years (*n* = 6070)	> 3 years (*n* = 8505)	
Incident HRC, *N* (%)	11,687 (55.86)	2062 (32.49)	1804 (29.72)	3488 (41.01)	< 0.0001
Colorectal	2507 (21.45)	617 (29.92)	607 (33.65)	850 (24.37)	
Prostate	9115 (77.99)	1426 (69.16)	1183 (65.58)	2609 (74.80)	
Male breast	65 (0.56)	19 (0.92)	14 (0.78)	29 (0.83)	
HRC stage[†], *N* (%)					< 0.0001
Localized	8074 (32.93)	1261 (71.72)	1099 (68.77)	2412 (78.15)	
Advanced	2390 (9.75)	497 (28.27)	499 (31.22)	674 (21.84)	
HRC grade[‡], *N* (%)					< 0.0001
Low	6279 (25.61)	1052 (59.06)	964 (60.59)	1846 (58.23)	
High	4289 (17.49)	729 (40.93)	627 (39.40)	1324 (41.76)	
HRC mortality, *N* (%)	1109 (4.52)	347 (5.47)	309 (5.09)	239 (2.81)	< 0.0001
Age, *n* (%)					< 0.0001
65–70	9798 (39.96)	2328 (36.68)	2399 (39.52)	3633 (42.72)	
70–75	7156 (29.19)	1710 (26.95)	1690 (27.84)	2692 (31.65)	
75–80	4194 (17.11)	1134 (17.87)	1063 (17.51)	1384 (16.27)	
≥ 80	3371 (13.75)	1174 (18.5)	918 (15.12)	796 (9.36)	
Race, *n* (%)					< 0.0001
Black	2462 (10.04)	654 (10.31)	599 (9.87)	645 (7.58)	
Hispanic	645 (2.63)	302 (4.76)	338 (5.57)	381 (4.48)	
Other	2032 (8.29)	621 (9.79)	696 (11.47)	922 (10.84)	
White	19,380 (79.04)	4769 (75.15)	4437 (73.1)	6557 (77.1)	
Hyperlipidemia, *n* (%)	11,389 (46.45)	4163 (65.6)	4170 (68.7)	6080 (71.49)	< 0.0001
Hypogonadism, *n* (%)	218 (0.89)	317 (5.00)	209 (3.44)	150 (1.76)	< 0.0001
Hypertension, *n* (%)	12,356 (50.39)	4805 (75.72)	4617 (76.06)	6389 (75.12)	< 0.0001
Muscular wasting and disuse atrophy, *n* (%)	186 (0.76)	129 (2.03)	102 (1.68)	86 (1.01)	< 0.0001
Malaise and fatigue, *n* (%)	2371 (9.67)	1521 (23.97)	1090 (17.96)	1155 (13.58)	< 0.0001

J Cancer Res Clin Oncol. Author manuscript; available in PMC 2023 December 07.

	No—weight loss medication (*N*=20,921)	Yes—weight loss medication (*N*=20,921)			*P*
		< 1 year (*n* = 6346)	1–3 years (*n* = 6070)	> 3 years (*n* = 8505)	
Osteoporosis, *n* (%)	445 (1.81)	180 (2.84)	131 (2.16)	151 (1.78)	< 0.0001
Erectile dysfunction, *n* (%)	903 (3.68)	384 (6.05)	303 (4.99)	367 (4.32)	< 0.0001
Depression disorder, *n* (%)	1010 (4.12)	953 (15.02)	612 (10.08)	517 (6.08)	< 0.0001
Anterior pituitary disorder, *n* (%)	23 (0.09)	20 (0.32)	12 (0.20)	< 11 (0.12)	< 0.0001
Diabetes, *n* (%)	4345 (17.72)	4423 (69.7)	5139 (84.66)	7308 (85.93)	< 0.0001
Charlson comorbidity, *n* (%)					< 0.0001
0	19,963 (81.42)	3066 (48.31)	2683 (44.2)	3939 (46.31)	
1	2541 (10.36)	1767 (27.84)	2013 (33.16)	3226 (37.93)	
2	1014 (4.14)	762 (12.01)	790 (13.01)	928 (10.91)	
3 or more	1001 (4.08)	751 (11.83)	584 (9.62)	412 (4.84)	
Use of insulin, *n* (%)	481 (1.96)	689 (10.86)	613 (10.10)	538 (6.33)	< 0.0001
Number of PSA[b] tests, mean (SD)	0.32 (0.55)	0.42 (0.62)	0.40 (0.61)	0.44 (0.60)	< 0.0001
Number of breast cancer screening, mean (SD)	0 (0.02)	0 (0.02)	0 (0.02)	0 (0.02)	0.7993
Number of colonoscopies, mean (SD)	0.02 (0.14)	0.02 (0.16)	0.02 (0.14)	0.02 (0.13)	0.0112
Number of PCP[c] visits, mean (SD)	7.01 (8.34)	12.28 (11.72)	10.18 (9.53)	8.79 (8.08)	< 0.0001
Percent of adults with < 12 years education, mean (SD)	19.39 (12.54)	22.15 (13.73)	21.73 (13.47)	20.93 (13.22)	< 0.0001
Percent of adults below poverty, mean (SD)	11.72 (8.67)	13.35 (9.18)	12.72 (8.91)	12.19 (8.73)	< 0.0001

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

[†]Advanced stage HRCs cases were consistent with AJCC stage III and IV definition where localized HRCs cases were defined with stages I–II

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

[a]This table does not include the number of Yes—TTh users (*N* = 3598), which is reflected in Fig. 1 with weight loss medication plus TTh users (20,921 + 3,598 = 24,519), and age-matched no weight loss medication and TTh users (24,519)

[b]Prostate-specific antigen (PSA)

[c]Primary care physician (PCP)

Table 2

Only prostate cancer (PCa)—effect of weight loss medication, and years of use, on incident PCa, grade and stage at diagnosis among men 65+ years old in SEER-Medicare 2007–2015[a]

	Incidence[†]			High grade[†]			Advanced stage[†]		
	Events/*n*	**OR**	**95% CI**	**Events/*n***	**OR**	**95% CI**	**Events/*n***	**OR**	**95% CI**
Weight loss medication (yes vs. no)	5218/278694	**0.59**	0.57, 0.62	2345/275821	**0.63**	0.60,0.67	803/274279	0.66	0.61, 0.71
No use	10253/313554	1		4383/307,684	1		1548/304849	1	
<1 year	1426/87742	0.55	0.51, 0.59	617/86,933	0.56	0.51, 0.61	235/86551	0.65	0.58, 0.73
1–3 years	1183/87124	0.43	0.40, 0.47	526/86,467	0.46	0.42, 0.50	214/86155	0.56	0.49, 0.63
> 3 years	2609/103828	0.76	0.72, 0.81	1202/102421	0.83	0.77, 0.89	354/101573	0.74	0.67, 0.83
P for trend	< 0.0001			< 0.0001			< 0.0001		

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

[†]Multivariable analysis adjusted for age, race/ethnicity, hypogonadism, obesity, 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

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

Table 3

Only colorectal cancer (CRC)—effect of weight loss medication, and years of use, on incident CRC, grade and stage at diagnosis among men 65+ years old in SEER-Medicare 2007–2015[a]

	Incidence[†]			High grade[†]			Advanced stage[†]		
	Events/*n*	**OR**	**95% CI**	**Events/*n***	**OR**	**95% CI**	**Events/*n***	**OR**	**95% CI**
Weight loss medication (yes vs. No)	2074/278694	0.86	0.80, 0.92	317/276937	0.97	0.84, 1.13	853/277473	0.85	0.80, 0.90
No use	2762/313554	1		399/311191	1		1056/311848	1	
< 1 year	617/87742	0.84	0.76, 0.93	104/87229	1.04	0.85, 1.28	259/87384	0.98	0.85, 1.13
1–3 years	607/87124	0.80	0.72, 0.88	100/86617	0.98	0.79, 1.21	282/86799	1.01	0.88, 1.17
> 3 years	850/103828	0.92	0.84, 1.00	113/103091	0.91	0.73, 1.12	312/103290	0.90	0.78, 1.03
P for trend	< 0.0001			0.750			0.404		

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

[†]Multivariable analysis adjusted for age, race/ethnicity, hypogonadism, obesity, 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

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

Table 4

Only male breast cancer—effect of weight loss medication, and years of use, on incident male breast cancer, grade and stage at diagnosis among men 65+ years old in SEER-Medicare 2007–2015[a]

	Incidence[†]			High grade[†]			Advanced stage[†]		
	Events/*n*	**OR**	**95% CI**	**Events/*n***	**OR**	**95% CI**	**Events/*n***	**OR**	**95% CI**
Weight loss medication (yes vs. No)	141/278694	0.88	0.61, 1.27	45/278650	0.67	0.35, 1.29	29/278646	1.28	0.65, 2.54
No use	79/313554	1		27/313502	1		15/313490	1	
< 1 year	19/87742	0.90	0.54, 1.50	< 11/87731	1.04	0.45, 2.43	< 11/87726	0.81	0.30, 2.18
1–3 years	14/87124	0.71	0.39, 1.29	< 11/87111	0.15	0.02, 1.12	< 11/87113	0.89	0.26, 3.10
> 3 years	29/103828	1.00	0.62, 1.62	< 11/103808	0.77	0.32, 1.84	< 11/103807	2.09	0.90, 4.86
P for trend	0.696			0.292			0.257		

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

[†]Multivariable analysis adjusted for age, race/ethnicity, hypogonadism, obesity, 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

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

Table 5

Only HRCs—effect of weight loss medication, and years of use, on incident HRCs, grade and stage at diagnosis among men 65+ years old in SEER-Medicare 2007–2015[a]

	Incidence[†]			High grade[†]			Advanced stage[†]		
	Events/*n*	**OR**	**95% CI**	**Events/*n***	**OR**	**95% CI**	**Events/*n***	**OR**	**95% CI**
Weight loss medication (yes vs. no)	7354/278694	0.65	0.62, 0.68	2680/274020	0.66	0.62, 0.69	1670/273010	0.78	0.73, 0.82
No use	13094/313554	1		4809/305269	1		2619/303079	1	
< 1 year	2062/87742	0.61	0.57, 0.65	729/86409	0.60	0.56, 0.65	497/86177	0.78	0.71, 0.85
1–3 years	1804/87124	0.51	0.48, 0.54	627/85947	0.49	0.46, 0.54	499/85819	0.74	0.68, 0.81
> 3 years	3488/103828	0.79	0.80, 0.91	1324/101664	0.83	0.78, 0.89	674/101014	0.81	0.75, 0.87
P for trend	< 0.0001			< 0.0001			< 0.0001		

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

[†]Multivariable analysis adjusted for age, race/ethnicity, hypogonadism, obesity, 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

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

Table 6

Stratified by positive use of TTh the association of weight loss medication, and years of use, with incident HRCs, and high grade at diagnosis among men 65+ years old in SEER-Medicare 2007–2015[a]

	Incidence[†]			High grade[†]		
	Events/*n*	**OR**	**95% CI**	**Events/*n***	**OR**	**95% CI**
Weight loss medication (yes vs. no)	340/16380	0.65	0.55, 0.76	114/16154	0.59	0.47, 0.75
No use	1407/45227	1		520/44340	1	
< 1 year	227/10107	0.72	0.60, 0.87	78/9958	0.66	0.50, 0.88
1–3 years	68/4048	0.52	0.39, 0.70	23/4003	0.51	0.33, 0.81
> 3 years	45/2225	0.55	0.38, 0.81	13/2193	0.40	0.21, 0.77
P for trend	< 0.0001			< 0.0001		

SEER-Medicare guideline presentation has been followed and all counts less than 11 have been suppressed. No advanced stage at diagnosis of HRC was included due to limited power sample size

[†]Multivariable analysis adjusted for age, race/ethnicity, hypogonadism, obesity, 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

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

Table 7

Stratified by negative use of TTh the association of weight loss medication, and years of use, with incident HRCs, grade and stage at diagnosis among men 65+ years old in SEER-Medicare 2007–2015[a]

	Incidence[†]			High grade[†]			Advanced stage[†]		
	Events/*n*	**OR**	**95% CI**	**Events/*n***	**OR**	**95% CI**	**Events/*n***	**OR**	**95% CI**
Weight loss medication (yes vs. no)	7014/262314	0.64	0.61, 0.67	4289/260929	0.65	0.61, 0.70	1608/256908	0.77	0.71, 0.83
No use	11,687/268327			4289/76451			2390/259030		
<1 year	1835/5625	0.60	0.56, 0.65	651/76451	0.59	0.54, 0.65	462/76262	0.80	0.71, 0.89
1–3 years	1736/5803	0.50	0.47, 0.54	604/81944	0.49	0.44, 0.54	476/81816	0.72	0.64, 0.80
> 3 years	3443/8351	0.78	0.73, 0.82	1311/99471	0.82	0.76, 0.89	670/98830	0.80	0.72, 0.88
P for trend	< 0.0001			< 0.0001			< 0.0001		

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

[†]Multivariable analysis adjusted for age, race/ethnicity, hypogonadism, obesity, 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

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