Testosterone therapy and cancer risks among men in the SEER-Medicare linked database

Eboneé N. Butler[1,2✉], Cindy Ke Zhou[3], Michael Curry[4], Úna McMenamin[5], Christopher Cardwell[5], Marie C. Bradley[1], Barry I. Graubard[6] and Michael B. Cook[3]

BACKGROUND: We examined associations between two forms of testosterone therapy (TT) and risks of seven cancers among men.
METHODS: SEER-Medicare combines cancer registry data from the Surveillance, Epidemiology, and End Results programme with Medicare claims. Our population-based case–control study included incident cancer cases diagnosed between 1992–2015: prostate ($n = 130{,}713$), lung ($n = 105{,}466$), colorectal ($n = 56{,}433$), bladder ($n = 38{,}873$), non-Hodgkin lymphoma ($n = 17{,}854$), melanoma ($n = 14{,}241$), and oesophageal ($n = 9116$). We selected 100,000 controls from a 5% random sample of Medicare beneficiaries and used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI).
RESULTS: TT was associated with lower risk of distant-stage prostate cancer (injection/implantation OR = 0.72, 95% CI: 0.60–0.86; topical OR = 0.50, 95% CI: 0.24–1.03). We also observed inverse associations for distant-stage colorectal cancer (injection/implantation OR = 0.75, 95% CI: 0.62–0.90; topical OR = 0.11, 95% CI: 0.05–0.24). Risks of distant-stage colorectal and prostate cancers decreased with time after initiating TT by injection/implantation. By contrast, TT was positively associated with distant-stage melanoma (injection/implantation OR = 1.70, 95% CI: 1.37–2.11). TT was not associated with bladder cancer, oesophageal cancer, lung cancer or non-Hodgkin lymphoma.
CONCLUSION: TT was inversely associated with distant-stage prostate and colorectal cancers but was positively associated with distant-stage melanoma. These observations may suggest an aetiologic role for TT or the presence of residual confounding.

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BACKGROUND

Beginning around 40 years of age, testosterone (T) levels in men decline ~1% per year [1–3]. When total concentrations fall below purportedly normal physiologic thresholds (typically in the range of 200–400 ng/ml), men may experience decreased quality of life resulting from lowered libido, fatigue and other conditions linked to low or declining T [4]. Notably, many of these ailments afflict younger men with clinically diagnosed hypogonadism but are also a natural consequence of ageing. Thus, what constitutes normal T varies between individuals and differs across age groups [1]. Testosterone therapy (TT) has been used in both young and older populations to increase circulating levels of the hormone, thereby helping to reverse the adverse effects of its decline. Indeed, the use of TT for off-label indications increased during the early 2000s following the US Food and Drug Administration (FDA) approval of self-administered topical forms of the medication in the mid-1990 s and subsequent marketing campaigns targeted to men experiencing conditions associated with low T [5]. However, following reports from observational studies describing a link between TT and myocardial infarction risk, the FDA issued a safety communication in 2014, which led to a gradual decline in TT prescriptions [6, 7].

An elevated *endogenous* testosterone concentration has historically been *hypothesised* to be associated with an increased risk of prostate cancer, though past studies of pre-diagnostic concentrations have yielded null results [8, 9]. Meanwhile, studies of *exogenous* TT exposure have largely reported null or inverse associations with prostate cancer risk [10–19]. These observations have spurred debates surrounding TT as a potential protective factor for the disease or, alternatively, may suggest confounding by indication; men with clinically low endogenous T levels (i.e., those who are hypogonadal)—and who are subsequently prescribed TT—could have a lower baseline risk of the disease when compared with eugonadal men. Indeed, a recent pooled case–control study demonstrated that lower circulating free T levels were associated with decreased prostate cancer risk [20]. Notwithstanding, T and its derivatives are also thought to play a role in the carcinogenesis of organ sites other than the prostate. Several studies have examined endogenous T concentrations in relation to risks of gastric, colorectal, and liver cancers [21–24];

[1]Integrative Tumor Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA. [2]University of North Carolina at Chapel Hill, Department of Epidemiology, Chapel Hill, NC, USA. [3]Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA. [4]Information Management Services, Inc, Calverton, MD, USA. [5]Cancer Epidemiology Research Group, Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland, UK. [6]Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA. ✉email: ebonee@unc.edu

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these studies hypothesised that observed sex differences in incidence could be explained by variations in endogenous hormone exposures. Indeed, males experience a 20% higher overall cancer incidence relative to females [25]; thus, it is conceivable that cancers with a higher incidence in males that have no known hormonal etiologies could be linked to endogenous or exogenous T exposure. To our knowledge, no prior study has examined the relationship between exogenous TT and cancers other than those of the prostate.

Examining associations between TT and cancer risks for multiple organ sites may help to clarify the potential role of TT in cancer aetiology. Therefore, we performed a case–control study in the SEER-Medicare linked database to examine the association between TT and prostate cancer as well as six cancers with higher incidence among men, namely: bladder, colorectal, oesophageal, lung and bronchus, melanoma and non-Hodgkin lymphoma.

METHODS

SEER-Medicare

The Surveillance, Epidemiology, and End Results (SEER) programme collects cancer registry data for incident cases diagnosed across 18 geographic regions, representing 28% of the US population [26]. Medicare is the primary health insurer for US citizens and permanent residents aged 65 years and older and is organised into four parts that provide healthcare coverage based on the beneficiary's preferences and needs. All Medicare beneficiaries are entitled to Medicare Part A, which provides coverage for inpatient costs or hospital services. Ninety-six percent of those who elect to receive coverage for outpatient services under a fee-for-service model pay a monthly premium for Medicare Part B. In 2006, prescription drug coverage became available through Medicare Part D; the proportion of beneficiaries served under Part D has increased with each calendar year and ranged between 45 and 61% of beneficiaries during our study period. SEER-Medicare successfully matches cancer registry data to insurance claims for 94% of patients in SEER who are Medicare-eligible and who represent ~25% of the total Medicare population. In addition, the SEER-Medicare-linked database includes a 5% random sample of Medicare beneficiaries who reside in the SEER catchment, which can be used to select a control comparison group.

Study design and study population

We used a population-based case–control study design to examine the associations between TT and seven cancers among men, namely: prostate, bladder, colorectal, oesophageal, lung & bronchus, melanoma, and non-Hodgkin lymphoma. Cases were identified through SEER, diagnosed between 1992 and 2015, aged 66 years or older, and had at least 13 months of continuous coverage through Medicare Parts A and B. The period for continuous Medicare coverage among cases is defined as the time between first observation in the SEER-Medicare linkage and date of diagnosis. Cases with health management organisation (HMO) coverage (i.e., Medicare Part C) were excluded. We identified the first primary malignant cancer diagnoses using International Classification of Disease for Oncology (ICD-O-3) codes (Supplemental Table 1). We excluded death certificate-only or autopsy-only diagnosed cancer cases.

To the total case population, we frequency-matched 100,000 controls from the 5% sample (excluding cancers of interest) on a 5-year age group and calendar year of selection/diagnosis [27]. Eligible controls were cancer-free up until the midpoint of the calendar year of selection and could be sampled multiple times across the study period, but no more than once for any given calendar year. As with cases, controls were required to have at least 13 months of continuous coverage through Medicare Parts A and B and no HMO. The period for continuous Medicare coverage among controls is defined as the time between first observation in the SEER-Medicare linkage and date of control selection.

Testosterone therapy

Our study included two calendar periods of interest. During the first period (January 1, 1992 through December 31, 2015), we examined the associations between ever-use of older forms of TT exposure (injection or implantation) and cancer risks. Medical procedures for inpatient or outpatient administrations of TT were identified via healthcare common procedure coding system (HCPCS) codes. For the second calendar period of interest (January 1, 2008 through December 31, 2015), we examined ever-use of newer forms of TT exposure (topical application). Topical gel or cream TT prescriptions were identified using national drug codes (NDC) recorded in the Part D Event (PDE) Medicare file. Beneficiaries were ineligible to be selected as cases or controls if they received any form of TT during the baseline period, defined as their first year of observation in the SEER-Medicare linkage.

Other patient-level characteristics

We identified diagnoses of primary hypogonadism (i.e., testicular dysfunction) or secondary hypogonadism (i.e., disorders of the pituitary gland or androgen insensitivity) using ICD-9-clinical modification (CM) codes recorded in outpatient insurance claims. We also used ICD-9-CM codes to identify medical conditions that are associated with hypogonadism or cancer risks, including chronic fatigue, erectile dysfunction, benign prostatic hyperplasia (BPH), obesity, smoking and alcohol use. In addition, for each case and control, we examined the Charlson comorbidity score, average number of hospital visits per year, average number of outpatient visits per year, rurality/urbanicity (i.e., a proxy for population density), and median income by zip code [28]. Data on covariates, including medical conditions and potential confounders, were collected during the 12-month baseline period beginning at the start of observation.

Statistical analyses

We used logistic regression to assess the relationship between ever-use of TT (yes/no) and cancer risks modelled as a seven-level multinomial outcome. We used a Bonferroni correction to adjust for multiple testing ($P = 0.05/7 = 0.007$). For each mode of TT administration and calendar period of interest, we report odds ratios (ORs) and 95% confidence intervals (CI). We adjusted the variances for the ORs using the ROBUSTVARIANCE macro outlined by Engels et al. to account for multiple sampling of controls across calendar years and the use of individuals who were sampled as controls prior to developing cancer of interest [27]. All regression models were adjusted for matching factors (age and calendar year of selection), and multivariable models were additionally adjusted for the above-referenced medical conditions, risk factors and patient factors. Using a 12-month exposure lag, we examined associations between TT and cancer risks; we also examined associations stratified by clinical stage at diagnosis (localised/regional or distant) and hypogonadism. In addition, we examined associations within time windows of exposure (i.e., exposure 0–12, 12–24, 24–36 or 36+ months before case/control selection). Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

We identified 372,696 cancers of interest diagnosed between 1992 and 2015. The most commonly diagnosed cancer was prostate ($n = 130{,}713$) followed by lung & bronchus ($n = 105{,}466$), colorectal ($n = 56{,}433$), bladder ($n = 38{,}873$), non-Hodgkin lymphoma (NHL) ($n = 17{,}854$), melanoma ($n = 14{,}241$) and oesophageal ($n = 9116$). Compared with controls, bladder cancer and melanoma cases included slightly higher proportions of men aged 85 years and older (Table 1). Overall, cases and controls had similar proportions of obesity and alcohol use but differed according to other established cancer risk factors. Specifically, smoking prevalence was highest among men diagnosed with lung and bronchus, oesophageal and bladder cancers; and lung and bronchus cases had a higher proportion of men with comorbid conditions (4.7%). Fewer than 1% of cases (0.5%) or controls (0.6%) were characterised as hypogonadal. Cancer cases were similarly distributed across rural and urban regions. Across the cancer sites assessed, melanoma and non-Hodgkin lymphoma cases included the largest proportions of men in the highest income quintile.

For the analysis of TT by injection/implantation and cancer risks, cases and controls were observed for a median of 4.1 years [interquartile range (IQR): 3.9] and 4.3 years [IQR: 4.0], respectively; for the analysis of topical TT and cancer risks, cases and controls were observed for a median of 2.1 years [IQR: 2.8] and 1.5 years [IQR: 3.2], respectively. Cases and controls included in our analysis of topical TT and cancer risks were more likely to be classified as obese and had higher proportions of men with a Charlson

Table 1. Baseline characteristics of cancer cases and frequency-matched controls in the SEER-Medicare database, 1992–2015.

			Cancer site-specific cases													
	Controls		**Bladder**		**Colorectal**		**Oesophageal**		**Lung & bronchus**		**Melanoma**		**NHL**		**Prostate**	
Total	**100,000**		**38,873**		**56,433**		**9116**		**105,466**		**14,241**		**17,854**		**130,713**	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Year of diagnosis/selection																
1992–1995	18,178	18.2	5680	14.6	9754	17.3	953	10.5	12,967	12.3	1591	11.2	2080	11.7	34,721	26.6
1996–2000	16,796	16.8	6088	15.7	9989	17.7	1130	12.4	13,618	12.9	1959	13.8	2632	14.7	27,187	20.8
2001–2005	31,336	31.3	12,777	32.9	18,321	32.5	2681	29.4	31,638	30.0	4828	33.9	5767	32.3	40,779	31.2
2006–2010	22,806	22.8	9919	25.5	12,555	22.2	2580	28.3	28,800	27.3	4152	29.2	4800	26.9	22,190	17.0
2011–2015	10,884	10.9	4409	11.3	5814	10.3	1772	19.4	18,443	17.5	1711	12.0	2575	14.4	5836	4.5
Age (years)																
66–69	14,822	14.8	4055	10.4	7,306	12.9	1785	19.6	18,400	17.4	1672	11.7	2271	12.7	19,659	15.0
70–74	24,442	24.4	7608	19.6	12,152	21.5	2272	24.9	27,514	26.1	2854	20.0	3768	21.1	34,938	26.7
75–79	25,424	25.4	9468	24.4	13,658	24.2	2228	24.4	26,749	25.4	3333	23.4	4382	24.5	35,010	26.8
80–84	19,987	20.0	8987	23.1	12,338	21.9	1633	17.9	19,770	18.7	3242	22.8	4075	22.8	24,414	18.7
85+	15,325	15.3	8755	22.5	10,979	19.5	1198	13.1	13,033	12.4	3140	22.0	3358	18.8	16,692	12.8
Race/ethnicity																
Unknown	217	0.2	72	0.2	124	0.2	27	0.3	286	0.3	28	0.2	37	0.2	225	0.2
White	83,930	83.9	36,117	92.9	48,841	86.5	7942	87.1	91,068	86.3	14,014	98.4	16,082	90.1	110,198	84.3
Black	5413	5.4	1198	3.1	3802	6.7	656	7.2	7599	7.2	58	0.4	540	3.0	12,790	9.8
API	4819	4.8	662	1.7	1618	2.9	192	2.1	3025	2.9	44	0.3	486	2.7	3060	2.3
Hispanic	2448	2.4	363	0.9	750	1.3	103	1.1	1120	1.1	52	0.4	306	1.7	2090	1.6
AIAN	368	0.4	46	0.1	102	0.2	25	0.3	208	0.2	–[a]	–[a]	26	0.1	300	0.2
Other	2805	2.8	415	1.1	1196	2.1	171	1.9	2160	2.0	–[a]	–[a]	377	2.1	2050	1.6
Obesity																
No	98,094	98.1	38,057	97.9	55,365	98.1	8898	97.6	103,373	98.0	13,907	97.7	17,482	97.9	128,801	98.5
Yes	1906	1.9	816	2.1	1068	1.9	218	2.4	2093	2.0	334	2.3	372	2.1	1912	1.5
Smoking																
No	97,312	97.3	37,276	95.9	54,858	97.2	8613	94.5	96,832	91.8	13,868	97.4	17,287	96.8	127,730	97.7
Yes	2688	2.7	1597	4.1	1575	2.8	503	5.5	8634	8.2	373	2.6	567	3.2	2983	2.3
Alcohol																
No	99,694	99.7	38,750	99.7	56,174	99.5	9011	98.8	104,680	99.3	14,200	99.7	17,814	99.8	130,288	99.7
Yes	306	0.3	123	0.3	259	0.5	105	1.2	786	0.7	41	0.3	40	0.2	425	0.3
Hypogonadism																
No	99423	99.4	38658	99.4	56229	99.6	9061	99.4	104874	99.4	14,137	99.3	17725	99.3	130,225	99.6
Yes	577	0.6	215	0.6	204	0.4	55	0.6	592	0.6	104	0.7	129	0.7	488	0.4
Chronic fatigue																
No	89,933	89.9	34,504	88.8	51,161	90.7	8099	88.8	93,848	89.0	12,541	88.1	15,733	88.1	120,136	91.9
Yes	10,067	10.1	4369	11.2	5272	9.3	1017	11.2	11,618	11.0	1700	11.9	2121	11.9	10,577	8.1
Erectile dysfunction																
No	96,822	96.8	37,728	97.1	55,047	97.5	8827	96.8	102,072	96.8	13,741	96.5	17,211	96.4	127,057	97.2
Yes	3178	3.2	1145	2.9	1386	2.5	289	3.2	3394	3.2	500	3.5	643	3.6	3656	2.8

Table 1. continued

	Cancer site-specific cases															
	Controls		**Bladder**		**Colorectal**		**Oesophageal**		**Lung & bronchus**		**Melanoma**		**NHL**		**Prostate**	
Total	**100,000**		**38,873**		**56,433**		**9116**		**105,466**		**14,241**		**17,854**		**130,713**	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Benign prostatic hyperplasia																
No	98,367	98.4	38,256	98.4	55,797	98.9	8948	98.2	103,306	98.0	13,973	98.1	17,483	97.9	129,606	99.2
Yes	1633	1.6	617	1.6	636	1.1	168	1.8	2160	2.0	268	1.9	371	2.1	1107	0.8
Rurality/urbanicity																
BigMetro	55,692	55.7	21,729	55.9	31,055	55.0	4874	53.5	55,390	52.5	7994	56.1	9954	55.8	74,500	57.0
Metro	26,236	26.2	10,395	26.7	14,644	25.9	2657	29.1	29,060	27.6	3913	27.5	4749	26.6	32,449	24.8
Urban	6881	6.9	2650	6.8	3867	6.9	627	6.9	7457	7.1	899	6.3	1156	6.5	8721	6.7
LessUrban	9120	9.1	3328	8.6	5570	9.9	762	8.4	10,885	10.3	1147	8.1	1618	9.1	12,288	9.4
Rural	2051	2.1	771	2.0	–[a]	–[a]	196	2.2	2659	2.5	–[a]	–[a]	–[a]	–[a]	2738	2.1
Missing	20	0.0	—	0.0	–[a]	–[a]	—	0.0	15	0.0	–[a]	–[a]	–[a]	–[a]	17	0.0
Income quintile																
1	19,048	19.0	6750	17.4	11,645	20.6	1893	20.8	22,167	21.0	1956	13.7	2965	16.6	27,404	21.0
2	18,919	18.9	7717	19.9	11,348	20.1	1740	19.1	21,671	20.5	2550	17.9	3390	19.0	25,449	19.5
3	19,439	19.4	7840	20.2	11,482	20.3	1792	19.7	21,256	20.2	2771	19.5	3536	19.8	25,470	19.5
4	19,557	19.6	8064	20.7	10,887	19.3	1723	18.9	20,345	19.3	3033	21.3	3705	20.8	25,062	19.2
5	21,230	21.2	7951	20.5	10,093	17.9	1790	19.6	18,370	17.4	3720	26.1	3992	22.4	25,116	19.2
Missing	1807	1.8	551	1.4	978	1.7	178	2.0	1657	1.6	211	1.5	266	1.5	2212	1.7
Charlson Comorbidity Index																
None	75,116	75.1	26,620	68.5	40,663	72.1	6552	71.9	70,058	66.4	10,271	72.1	12,813	71.8	100,209	76.7
Low	16,910	16.9	7896	20.3	10,301	18.3	1638	18.0	22,465	21.3	2635	18.5	3290	18.4	21,164	16.2
Moderate	5157	5.2	2668	6.9	3384	6.0	591	6.5	7988	7.6	840	5.9	1122	6.3	6115	4.7
High	2817	2.8	1689	4.3	2085	3.7	335	3.7	4955	4.7	495	3.5	629	3.5	3225	2.5
Hospital and outpatient visits																
Hospital (mean/SD)	0.20 (0.65)		0.25 (0.71)		0.22 (0.69)		0.23 (0.70)		0.24 (0.73)		0.24 (0.72)		0.23 (0.67)		0.20 (0.62)	
Outpatient (mean/SD)	1.87 (3.62)		2.18 (3.83)		1.80 (3.64)		2.04 (3.82)		2.07 (3.87)		2.07 (3.87)		2.23 (3.88)		1.77 (3.37)	

AIAN American Indian/Alaskan Native, *API* Asian and/or Pacific Islander, *NHL* non-Hodgkin lymphoma.
[a]Per the SEER-Medicare data use agreement, cell counts in this row are suppressed due to a cell having a case count of less than 11.

comorbidity index score of 3+ relative to men in the TT injection/implantation analysis. Those in the topical TT analytic subset also had higher proportions of men diagnosed with fatigue, BPH and smokers.

TT and site-specific cancer risks

Table 2 presents the associations between TT and cancer risks for each mode of administration. We identified 2351 cases and 646 controls whose Medicare Part B claims included HCPCS codes for outpatient injection/implantation TT between 1992 and 2015, and 106 cases and 45 controls whose Medicare Part D claims included NDCs for topical TT. Overall, we observed no significant relationship between injection/implantation TT and any of the seven cancers. Topical TT was inversely associated with colorectal cancer (OR and 95% CI: 0.19; 0.05–0.77); however, this association was not statistically significant following the Bonferroni correction.

Subsequently, we examined relationships between TT and cancer risks by disease stage; associations by injection/implantation are presented in Table 3 and associations by topical TT are presented in Supplemental Table 3. *Bladder:* There were no apparent associations between TT by either form of administration for localised/regional or distant-stage bladder cancers. *Colorectal:* Topical TT was inversely associated with localised/regional colorectal cancer (OR and 95% CI: 0.18; 0.07–0.47), whereas both modes of TT administration were associated with distant-stage disease ($OR_{injection/implantation}$ and 95% CI: 0.75; 0.62–0.90); $OR_{topical}$ and 95% CI: 0.11; 0.05–0.24). Notably, associations between TT and colorectal cancer retained statistical significance following Bonferroni correction. *Oesophageal:* Topical TT exposure was associated with a lower risk of oesophageal cancer (OR and 95% CI: 0.34; 0.14–0.87). *Lung & bronchus:* We observed non-significant inverse associations between TT and lung and bronchus cancers ($OR_{injection/implantation}$ and 95% CI: 0.86; 0.73–1.00); $OR_{topical}$ and 95% CI: 0.62; 0.35–1.09). *Melanoma:* Localised/regional melanoma risk was elevated, albeit statistically non-significantly, with injection/implantation TT exposure, and was significantly elevated by topical TT exposure (OR and 95% CI: 2.41, 1.01–5.78). Injection/implantation TT exposure was also associated with a higher risk of distant-stage melanoma (OR and 95% CI: 1.70, 1.37–2.11); this association retained statistical significance following Bonferroni correction. *Prostate:* Both modes of TT exposure were associated with inverse risks of distant-stage prostate cancer, though not statistically significant for topical TT forms ($OR_{injection/implantation}$ and 95% CI: 0.72; 0.60–0.86); $OR_{topical}$ and 95% CI: 0.50; 0.24–1.03). The association between TT by injection/implantation and distant-stage prostate cancer remained statistically significant following Bonferroni correction. Of note, stage information was unavailable for patients diagnosed with NHL.

We found no evidence of effect modification for cancer risks by the presence of hypogonadism for either mode of TT administration (Supplemental Table 2).

We observed consistent inverse associations between TT by injection/implantation for distal time exposures and risks of distant-stage colorectal and prostate cancers (Table 4). Notably, TT exposure was associated with an increased risk of distant-stage melanoma for all four time points in our time-windows analysis, particularly for exposure within 12–24 months of case/control selection (OR and 95% CI: 2.54, 1.64, 3.95). The small sample size precluded our ability to examine time- and stage-specific estimates for topical TT exposure.

DISCUSSION

In this study, we examined associations between ever-use of TT and seven cancer risks among men in the SEER-Medicare linked database. Irrespective of the mode of administration, TT was inversely associated with distant-stage prostate and colorectal cancers; by contrast, injection/implantation TT use was associated

Table 2. Testosterone therapy (TT) and cancer risks among men in the SEER-Medicare database, 1992–2015.

	Injection/Implantation (1992–2015)						Topical (2008–2015)					
	TT		TT				TT		TT			
	Exposed		Unexposed				Exposed		Unexposed			
	n	(%)	*n*	(%)	Adjusted OR (95% CI)	*P* value	*n*	(%)	*n*	(%)	Adjusted OR (95% CI)	*P* value
	Total						Total					
Controls	646	(0.77)	83,423	(99.23)	(REF)	(REF)	45	(0.59)	7628	(99.41)	(REF)	(REF)
Cases	2351	(0.73)	318,123	(99.27)			106	(0.39)	27,386	(99.61)		
Bladder	266	(0.78)	34,016	(99.22)	1.01 (0.62, 1.64)	0.965	17	(0.57)	2975	(99.43)	1.14 (0.31, 4.15)	0.841
Colorectal	320	(0.65)	48,642	(99.35)	0.89 (0.55, 1.43)	0.617	_[a]	_[a]	_[a]	_[a]	0.19 (0.05, 0.77)	0.020
Oesophagus	52	(0.65)	7935	(99.35)	0.90 (0.53, 1.53)	0.704	_[a]	_[a]	_[a]	_[a]	0.71 (0.17, 3.00)	0.645
Lung & bronchus	622	(0.68)	91,408	(99.32)	0.94 (0.60, 1.47)	0.774	51	(0.43)	11,906	(99.57)	0.69 (0.22, 2.14)	0.516
Melanoma	128	(1.01)	12,514	(98.99)	1.28 (0.77, 2.12)	0.337	_[a]	_[a]	_[a]	_[a]	1.87 (0.50, 7.01)	0.354
NHL	157	(0.99)	15,731	(99.01)	1.27 (0.77, 2.09)	0.352	_[a]	_[a]	_[a]	_[a]	0.84 (0.21, 3.41)	0.805
Prostate cancer	806	(0.74)	107,877	(99.26)	0.97 (0.63, 1.50)	0.897	_[a]	_[a]	_[a]	_[a]	0.50 (0.13, 1.93)	0.314

[a]Per the SEER-Medicare data use agreement, cell counts in this row are suppressed due to a cell having a case count of less than 11.
Adjusted for: age (66–69, 70–74, 75–79, 80–84, 85+), year of cancer diagnosis/control selection, obesity, smoking, alcohol, hypogonadism, fatigue, erectile dysfunction, benign prostatic hyperplasia, Charlson Comorbidity Index, the average number of hospital visits per year, the average number of outpatient visits per year, rurality/urbanicity and median income by zip code.

Table 3. Testosterone therapy (TT) and cancer risks among men in the SEER-Medicare database by stage, 1992–2015.

	Injection/implantation (1992–2015)									
	Localised/regional						Distant			
	TT exposed		TT unexposed		Adjusted OR (95% CI)	*P* value	TT exposed		TT unexposed		Adjusted OR (95% CI)	*P* value
	n	%	*n*	%			*n*	%	*n*	%		
Controls	646	0.8	83,423	99.2			646	0.8	83,423	99.2		
Controls (prostate)[a]	640	0.8	78,885	99.2			640	0.8	78,885	99.2		
Bladder	248	0.8	31,216	99.2	1.03 (0.73, 1.47)	0.850	11	0.7	1584	99.3	0.98 (0.79, 1.21)	0.822
Colorectal	250	0.7	33,953	99.3	0.97 (0.68, 1.38)	0.873	62	0.5	11,633	99.5	0.75 (0.62, 0.90)	0.002[b]
Oesophagus	28	0.7	4101	99.3	0.96 (0.65, 1.42)	0.830	20	0.8	2644	99.3	1.06 (0.85, 1.33)	0.585
Lung and bronchus	274	0.8	35,021	99.2	1.08 (0.76, 1.52)	0.683	306	0.6	49,828	99.4	0.86 (0.73, 1.00)	0.050
Melanoma	108	1.0	10,787	99.0	1.27 (0.87, 1.83)	0.213	14	1.2	1131	98.8	1.70 (1.37, 2.11)	0.000[b]
Non-Hodgkin's lymphoma	—	—	—	—	—	—	—	—	—	—	—	—
Prostate Cancer	686	0.9	75,447	99.1	1.09 (0.79, 1.49)	0.597	50	0.5	9,875	99.5	0.72 (0.60, 0.86)	0.000[b]

[a]Staging data was only available for prostate cancer cases in 1994 and later.
[b]Significant following Bonferroni correction.
Adjusted for: age (66–69, 70–74, 75–79, 80–84, 85+), year of cancer diagnosis/control selection, obesity, smoking, alcohol, hypogonadism, fatigue, erectile dysfunction, benign prostatic hyperplasia, Charlson Comorbidity Index, average number of hospital visits per year, the average number of outpatient visits per year, rurality/urbanicity, and median income by zip code.

with a substantially increased risk of distant-stage melanoma, whereas topical TT was linked to a statistically non-significant increased risk of localised/regional melanoma. To our knowledge, this is the first study to examine TT and multi-site cancer risks among men.

While there is little evidence to suggest that endogenous testosterone is linked to prostate cancer development, the hormone is considered a possible contributor to prostate cancer progression. In the present study, we tested the hypothesis that exogenous testosterone use might be linked to tumour progression events that would be evidenced by positive associations in our case–control analysis. To the contrary, we observed null associations for 'ever-use' of TT and overall prostate risk and inverse risks for distant-stage disease. The extant epidemiologic literature reports a mix of inverse [13, 16–18] and null [15] associations. Remarkably, however, inverse associations between ever-use of TT and distant-stage prostate cancer have been consistently reported in all prior studies [15, 16, 18]. Thus, distant-stage prostate cancer may represent a distinct etiopathogenic subset of the disease, when compared with local/regional prostate cancers.

In the US, men experience an approximate 15% higher cancer incidence and an approximate 30% higher cancer-related mortality, compared with women. While these observations are partially explained by differential exposure to established risk factors like smoking, alcohol, screening behaviour, and social support, several prevailing hypotheses point to differences in the balance of endogenous hormone exposures that may account for the higher cancer burden in men. However, little evidence is available for exogenous hormone use in relation to risks of cancers which are predominant in, or exclusive to, men. The results from our study demonstrate inverse associations for distant-stage colorectal cancer irrespective of the formulation of TT. Tissue-based studies also suggest differential androgen receptor activity between normal and malignant colorectal tissues [29, 30]. It follows that exogenous hormone exposure may be linked to molecular signalling events that reduce colorectal cancer development. While such therapies are unlikely to be prescribed for the primary prevention of colorectal cancer, these findings support evidence for hormonal mechanisms linked to colorectal carcinogenesis.

One of the most striking findings from our study was the positive association between ever-use of TT by injection/implantation and distant-stage melanoma. A recent study of TT prescribing patterns in the US showed that TT users were more likely to have higher SES and reside in the southern and western states, and thus would be exposed to higher levels of ultraviolet radiation [31]. Thus, regional differences are likely to play a key role in understanding the relationship between TT and melanoma. Nevertheless, observational and experimental studies have hypothesised that endogenous androgen levels could play a role in melanoma progression, thereby offering modest biological plausibility for exogenous androgen exposure as having a possible link to the disease [32, 33]. A prospective study of more than 180,000 men in the UK biobank demonstrated that higher endogenous testosterone levels were linked to an increased risk of melanoma [34]. Our finding of a potential link between *exogenous* testosterone and melanoma risk provides an interesting parallel to the UK Biobank study, thereby adding credence to the observed association. However, our statistical models do not include adjustments for well-established risk factors for melanoma, including ultraviolet radiation exposure or the presence of moles. Accordingly, the observed association could be due to unmeasured confounding.

We also report statistically non-significant inverse associations between ever-use of TT and lung and bronchus, and oesophageal cancers in this study. While these observations may point to important details surrounding the aetiology of these cancer sites,

Table 4. Time-windows of injection/implantation testosterone therapy exposure and cancer risks in the SEER-Medicare database, 1992–2015.

Months prior to selection/ diagnosis	Bladder		Colorectal		Oesophageal		Lung		Melanoma		Prostate	
	Case exposure odds	Adjusted OR (95% CI)	Case exposure odds	Adjusted OR (95% CI)	Case exposure odds	Adjusted OR (95% CI)	Case exposure odds	Adjusted OR (95% CI)	Case exposure odds	Adjusted OR (95% CI)	Case exposure odds	Adjusted OR (95% CI)
	Overall		Overall		Overall		Overall		Overall		Overall	
0–12	79/38,395	1.11 (0.49, 2.54)	89/55,844	0.87 (0.39, 1.98)	–[a]	0.82 (0.33, 2.05)	205/104,120	1.05 (0.49, 2.23)	31/14,048	1.14 (0.48, 2.72)	183/109,114	0.88 (0.38, 2.03)
12–24	64/38,395	1.11 (0.43, 2.89)	80/55,844	0.99 (0.39, 2.52)	–[a]	0.43 (0.15, 1.27)	160/104,120	1.02 (0.43, 2.45)	33/14,048	1.48 (0.55, 3.99)	170/109,114	0.90 (0.37, 2.19)
24–36	67/38,395	1.19 (0.48, 2.94)	54/55,844	0.68 (0.27, 1.71)	–[a]	1.33 (0.49, 3.59)	122/104,120	0.82 (0.35, 1.93)	25/14,048	1.18 (0.45, 3.09)	164/109,114	0.87 (0.38, 1.97)
36+	135/38,395	0.94 (0.48, 1.82)	186/55,844	0.94 (0.49, 1.79)	–[a]	0.95 (0.46, 1.94)	340/104,120	0.97 (0.52, 1.78)	70/14,048	1.27 (0.64, 2.52)	462/109,114	1.05 (0.58, 1.90)
	Local/regional		Local/regional		Local/regional		Local/regional		Local/regional		Local/regional	
0–12	72/35,230	1.09 (0.64, 1.86)	62/39,128	0.85 (0.50, 1.45)	–[a]	0.45 (0.25, 0.84)	79/40,122	1.03 (0.61, 1.75)	26/12,115	1.09 (0.62, 1.94)	145/83,947	0.89 (0.51, 1.55)
12–24	58/35,230	1.10 (0.57, 2.13)	60/39,128	1.03 (0.54, 1.99)	–[a]	0.57 (0.27, 1.22)	71/40,122	1.18 (0.61, 2.27)	26/12,115	1.36 (0.67, 2.76)	135/83,947	0.92 (0.50, 1.72)
24–36	61/35,230	1.19 (0.62, 2.31)	43/39,128	0.75 (0.38, 1.48)	–[a]	1.56 (0.74, 3.29)	55/40,122	0.98 (0.50, 1.92)	21/12,115	1.19 (0.58, 2.43)	140/83,947	0.96 (0.53, 1.73)
36+	129/35,230	1.00 (0.61, 1.61)	147/39,128	1.06 (0.66, 1.70)	–[a]	0.91 (0.53, 1.55)	148/40,122	1.11 (0.69, 1.79)	61/12,115	1.31 (0.79, 2.17)	411/83,947	1.22 (0.80, 1.87)
	Distant		Distant		Distant		Distant		Distant		Distant	
0–12	–[a]	0.63 (0.41, 0.95)	23/13,255	0.97 (0.69, 1.35)	–[a]	1.46 (0.94, 2.27)	116/56,428	1.12 (0.84, 1.48)	–[a]	1.78 (1.17, 2.72)	13/10,703	0.75 (0.51, 1.11)
12–24	–[a]	1.48 (0.96, 2.27)	17/13,255	0.89 (0.62, 1.27)	–[a]	0.42 (0.26, 0.68)	80/56,428	0.92 (0.68, 1.25)	–[a]	2.54 (1.64, 3.95)	–[a]	0.59 (0.41, 0.86)
24–36	–[a]	2.01 (1.31, 3.06)	–[a]	0.50 (0.35, 0.71)	–[a]	1.46 (0.94, 2.29)	61/56,428	0.75 (0.56, 1.02)	–[a]	1.72 (1.11, 2.65)	–[a]	0.54 (0.38, 0.77)
36+	–[a]	0.32 (0.24, 0.42)	36/13,255	0.79 (0.63, 1.00)	–[a]	1.26 (0.95, 1.66)	165/56,428	0.88 (0.72, 1.08)	–[a]	1.34 (1.02, 1.77)	33/10,703	0.82 (0.65, 1.04)

[a]Per the SEER-Medicare data use agreement, cell counts in this row are suppressed due to a cell having a case count of less than 11; cell counts are also suppressed where data presentation could be used to derive sample size for cells having a case count of less than 11.

our observations were somewhat inconsistent when evaluating effect estimates between the two modes of TT administration. We also observed a null association for TT and NHL.

The SEER-Medicare-linked database provides high-quality longitudinal, population-based data on treatment patterns and cancer outcomes among US men and women aged 65 years and older. Nevertheless, a primary limitation of the SEER-Medicare resource is that we only capture information on an older subset of the population. Thus, findings may only be generalisable to men aged 65 years and older, though men aged 40–64 years of age are those most likely to receive a prescription for TT [35]. Further, given the nature of Medicare, the data are left-truncated to age 65, meaning that we are unable to capture treatment patterns prior to the enrolment date. An additional limitation is the poor capture efficiency of potential confounding factors such as smoking and BMI. Even though the confounding structures of TT and cancer risks are poorly understood, the capture efficiency is unlikely to differ greatly by group, thus having minimal effects on the validity of the results. This study was also limited by the small numbers of TT users among cases and controls—particularly for topical use—and the inability to comprehensively assess long-term use of TT or to examine dosing intensity which is important in observational studies of drug effects on cancer [36]. Given this, we cannot rule out that the associations seen in this study may have resulted from confounding. Further, the estimates reported in our study may be subject to confounding by indication, given our poor capture efficiency for diagnoses of hypogonadism.

Observations from our study support previously published findings of the relationship between ever-use of TT and inverse risk of distant prostate cancer. We also report novel associations for an inverse risk of distant colorectal cancer and an increased risk of distant melanoma. The findings from this study suggest that ever-use of TT is not linked to increased risks of prostate or colorectal cancer. However, ever-use of injection/implantation TT may be associated with an increased risk of melanoma.

DATA AVAILABILITY

SEER-Medicare data are not publicly available. Data requests are managed and approved by Information Management Services, Inc.

CODE AVAILABILITY

The SEER-Medicare data and statistical code used to generate the results herein are not publicly available. Request for data and statistical code are managed and approved by Information Management Services, Inc.

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AUTHOR CONTRIBUTIONS

Conception and design: ENB, CKZ and MBC. Data analysis and interpretation: all authors. Manuscript writing: all authors. Final approval of manuscript: all authors.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

NIH OHSRP determined that this research activity was exempt from IRB review per 45 CFR 46.

CONSENT TO PUBLISH

Not applicable.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Eboneé N. Butler.