World Journal of Urology (2019) 37:1127–1135
https://doi.org/10.1007/s00345-018-2504-3

ORIGINAL ARTICLE

The effect of androgen deprivation treatment on subsequent risk of bladder cancer diagnosis in male patients treated for prostate cancer

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Received: 4 May 2018 / Accepted: 21 September 2018 / Published online: 1 October 2018

Abstract

Introduction Bladder cancer (BCa) is three-to-four times more common in men than in women. To explain this gender gap, several theories have been proposed, including the impact of androgen hormones. The aim of this study was to investigate the differential impact of androgen deprivation therapy (ADT) on subsequent risk of developing BCa in men with prostate cancer (PCa).

Methods A total of 196,914 patients diagnosed with histologically confirmed localized PCa between 2000 and 2009 were identified in the SEER-Medicare insurance program-linked database. Competing-risk regression analyses were performed to assess the risk of developing BCa adjusting for the risk of all-cause mortality. Univariable and multivariable competing-risk regression analyses were performed to test the effect of ADT on BCa incidence for each PCa treatment modality.

Results Of the 196,914 individuals included in the study, 68,421 (34.7%) received ADT. Median (IQR) follow-up was 59 (29–95) months. Overall, a total of 2495 (1.3%) individuals developed BCa during follow-up. After stratification according to ADT, the 10-year cumulative incidence rate was 1.75% (95% CI 1.65–1.85). In the untreated group, the 10-year cumulative incidence rate was 1.99% (95% CI 1.83–2.15). In multivariable competing-risk regression, the use of ADT was not associated with BCa, after accounting for the risk of dying from any cause ($p = 0.1$).

Conclusion We failed to identify any impact of ADT on the risk of developing a subsequent BCa even after stratifying according to the type of treatment. Further studies are required to explain the gender gap in BCa incidence and outcomes.

Keywords Prostate cancer · Androgen deprivation treatment · Bladder cancer · ADT · Metastases · Survival

Introduction

The incidence of bladder cancer (BCa) is three-to-four times higher in men than in women. However, women are diagnosed with more advanced disease and have less favorable prognosis after treatment [1–3]. Several hypotheses have

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00345-018-2504-3) contains supplementary material, which is available to authorized users.

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been explored to explain this gender-difference. For instance, there are known differences in the exposure to BCa-specific carcinogens. In particular, tobacco exposure, the most common risk factor for BCa, is differentially distributed between genders [4]. The incidence of smoking is greater in men relative to women, which is further compounded by the fact that men who smoke also tend to consumer higher quantities of tobacco products [4]. Similarly, men have greater exposure to occupational carcinogens, such as 2-naphthylamine and 4,4′-methylenebis[2-chloroaniline] (MBOCA) [5]. Finally, differential exposure to inherent sex hormones may play a role in this gender gap.

The discovery of sex steroid receptors, especially androgen receptors (ARs), in the bladder wall [6–8] has initiated investigation into their potential role in BCa development and prognosis [9–13]. Several recent investigations assessed the role of hormonal pathways in the development of urothelial carcinoma [9, 14, 15]. Despite preclinical models showing conflicting results, the general concept that ARs might promote BCa development led to hypothesize that modulation of these receptors with the use of androgen deprivation therapy (ADT) could prevent BCa development or prognosis. In the preclinical setting, very promising results supported this hypothesis [10–13, 16]. However, data in the clinical setting are still limited, with very few studies evaluating the effect of ADT on BCa development, and all suffering from limitations and biases [17, 18]. To that end, we investigated the impact of ADT in patients affected by prostate cancer (PCa) on subsequent risk of developing BCa in a large population-based cohort adjusting for the competing-risk of dying from any cause.

Materials and methods

Data source and study population

The study relied on the SEER-Medicare insurance program-linked database [19]. The SEER registries cover approximately 28% of the US population with Medicare administrative data. The identification of the study cohort consisted of several steps. First, we identified patients diagnosed between 2000 and 2009 with histologically confirmed PCa [International Classification of Diseases (ICD) for Oncology site code 61.9, histologic code 8140] aged 65 years or older. Only patients with non-regional and non-metastatic disease at diagnosis were considered (N0, M0). Additional subjects with unknown race, socio-economic status, biopsy Gleason score and clinical T stage were excluded. This resulted in a cohort of 218,614 individuals, from which, we further identified 3863 records that contained a claim for BCa [International Classification of Diseases (ICD) for Oncology site code C67.0–C67.9, any histologic code]. After calculation of the time lag between PCa diagnosis and BCa diagnosis, we excluded from the study cohort all patients with a time lag less or equal to 6 months, with the assumption that these patients might have a concomitant PCa and BCa ($n = 931$). An arbitrary time cut-off had to be chosen to differentiate between patients who could have been diagnosed with BCa and PCa at the same time. The arbitrary cut-off of 6 months was chosen based on the choice to define PCa treatment as the treatment received within 6 months from diagnosis. Previous studies from the SEER-Medicare also use this 6-months cut-off [20]. Finally, we identified individuals treated with ADT as part of their primary cancer management strategy (within 6 months from PCa diagnosis) and excluded patients who received ADT after this set time ($n = 20{,}769$). This resulted in the final cohort of 196,914 individuals. Supplementary Figure 1 reports inclusion and exclusion criteria of the cohort.

Variable definition

Patient characteristics included age at diagnosis, gender, race (white, black, other), comorbid conditions, as well as marital status, socio-economic status and region of origin. Given the well-known importance of smoking on the risk of BCa, Medicare claims were used to perform stratification according to ever-smoker status. Baseline comorbid conditions were recorded in all 196,914 patients and were identified using unique ICD-9-CM diagnostic codes by the Medicare claims for the 12-month interval preceding PCa diagnosis. The CCI was derived from the Medicare claims using previously validated algorithms [21]. Moreover, standard PCa clinical features (biopsy Gleason score and clinical T stage) were defined for each patient.

Outcomes and statistical analyses

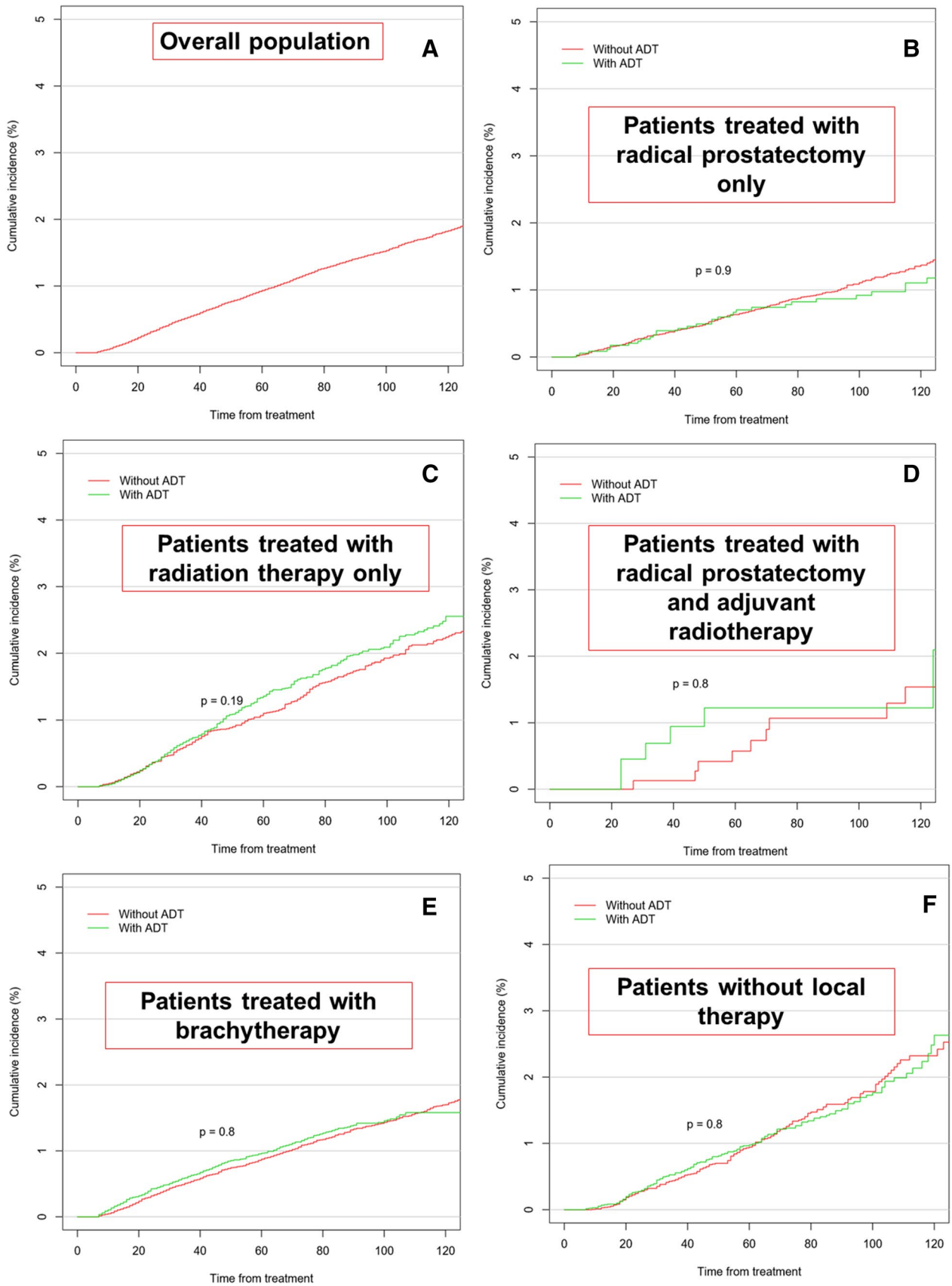
The primary objective of the present study consisted of investigating the effect of ADT on subsequent BCa incidence. To evaluate our hypothesis, our analyses consisted of several steps. First, we evaluated differences between individuals treated with ADT compared to their untreated counterparts. Descriptive statistics was performed focusing on frequencies and proportions. Median and interquartile ranges (IQRs) were reported for continuous variables. Chi-square and Mann–Whitney tests were used to compare the statistical significance in proportions and medians, respectively. Second, given the fact that PCa individuals receive ADT because of unfavorable PCa characteristics, which exposes these individuals to a higher risk of mortality, we relied on competing-risk regression analyses. Specifically, cumulative incidence plots were performed after adjusting for the risk of all-cause mortality. Finally, univariable and multivariable competing-risk regression analyses were performed to

Table 1 Descriptive characteristics of our study cohort, composed of 196,914 patients diagnosed with prostate cancer between 1989 and 2009

	With ADT $n = 68,421$ (34.7%)	Without ADT $n = 128,493$ (65.3%)	Overall $n = 196,914$	p value
Age at PCa diagnosis, (years)				
Median	75	71	72	< 0.001
IQR	70–79	68–76	69–77	
Ethnicity, *n* (%)				
Caucasian	54,975 (80.3)	106,363 (82.8)	161,338 (81.9)	< 0.001
African American	7917 (11.6)	13,911 (10.8)	21,828 (11.1)	
Other	5529 (8.1)	8219 (6.4)	13,748 (7.0)	
Marital status				
Married	45,930 (67.1)	93,383 (72.7)	139,313(70.7)	< 0.001
Unmarried	14,326 (20.9)	24,531 (19.1)	38,857 (19.7)	
Unknown	8165 (11.9)	10,579 (8.2)	18,744 (9.5)	
Charlson comorbidity index, *n* (%)				
0	33,141 (48.4)	81,404 (63.4)	114,545(58.2)	< 0.001
1	20,020 (29.3)	28.366 (22.1)	48,386 (24.6)	
2	7739 (11.3)	9631 (7.5)	17,370 (8.8)	
≥ 3	7521 (11.0)	9092 (7.1)	16,613 (8.4)	
Ever-smoker				
No	45,873 (67.0)	92,480 (72.0)	138,353(70.3)	< 0.001
Yes	33,548 (33.0)	36,013 (28.0)	69,561 (29.7)	
Biopsy Gleason score, *n* (%)				
≤ 6	10,767 (15.7)	41,517 (32.3)	52,284 (26.6)	< 0.001
7	35,764 (52.3)	71,726 (55.8)	107,490(54.6)	
8–10	21,890 (32.0)	15,250 (11.9)	37,140 (18.9)	
Clinical T stage, *n* (%)				
T1	28,331 (41.4)	60,994 (47.5)	89,325 (45.4)	< 0.001
T1	36,719 (53.7)	60,459 (47.1)	97,178 (49.4)	
T3	2440 (3.6)	3407 (2.7)	5847 (3.0)	
T4	931 (1.4)	3633 (2.8)	4564 (2.3)	
Prostate cancer treatment, *n* (%)				
RP	3552 (5.2)	33,583 (26.1)	37,135 (18.9)	< 0.001
RT	22,084 (32.3)	18,813 (14.6)	40,897 (20.8)	
RP + RT	497 (0.7)	867 (0.7)	1364 (0.7)	
BT	13,858 (20.3)	18,720 (14.6)	32,578 (16.5)	
NLT	28,430 (41.6)	56,510 (44.0)	84,940 (43.1)	
Population density, *n* (%)				
Urban	56,691 (82.9)	109,777 (85.4)	166,468(84.5)	< 0.001
Rural	11,730 (17.1)	18,716 (14.6)	30,446 (15.5)	
US region, *n* (%)				
Midwest	9972 (14.6)	20,373 (15.9)	30,345 (15.4)	< 0.001
Northeast	17,075 (25.0)	17,688 (13.8)	34,763 (17.7)	
South	15,129 (22.1)	25,688 (20.0)	40,817 (20.7)	
West	26,245 (38.4)	64,744 (50.4)	90,989 (46.2)	
Socio-economic status, *n* (%)				
High	35,554 (52.00	61,455 (47.8)	97,009 (49.3)	< 0.001
Low	32,867 (48.0)	67,038 (52.2)	99,905 (50.7)	

Comorbidities are presented according to comorbid condition groupings of the Deyo adaptation of the Charlson comorbidity index

ADT androgen deprivation therapy, *PCa* prostate cancer, *RP* Radical prostatectomy, *RT* external beam radiation therapy, *BT* brachytherapy, *NLT* no local treatment


Overall population
A
Cumulative incidence (%)
Time from treatment
Without ADT
With ADT
B
Patients treated with radical prostatectomy only
p = 0.9
C
Patients treated with radiation therapy only
p = 0.19
D
Patients treated with radical prostatectomy and adjuvant radiotherapy
p = 0.8
E
Patients treated with brachytherapy
p = 0.8
F
Patients without local therapy
p = 0.8

◂**Fig. 1** Cumulative incidence in overall population (**a**) and stratifying according to androgen deprivation therapy in patients treated with radical prostatectomy (**b**), radiation therapy (**c**), radical prostatectomy and adjuvant external beam radiation therapy (**d**), brachytherapy (**e**) and non-local therapy (**f**)

formally test the effect of ADT on BCa incidence for each PCa treatment modality. All multivariable models were adjusted for age, race, PCa clinical tumor stage, PCa biopsy Gleason score, as well as marital, socio-economic status and ever-smoker status.

All statistical testing were two-sided with a level of significance set at $p < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 3.3.0; http://www.r-project.org/).

Results

Baseline characteristics

Of the 196,914 individuals included in the study, 68,421 (34.7%) received ADT. Median (IQR) follow-up was 59 (29–95) months. Overall, a total of 2495 (1.3%) individuals developed BCa during follow-up. As expected, baseline characteristics of ADT patients significantly differed from their counterparts on whom ADT was not given (Table 1). Specifically, ADT patients were older (75 vs. 71 years; $p < 0.001$) and more likely to belong to a high socio-economic status (52.0% vs. 47.8%; $p < 0.001$). Moreover, a lower proportion of individuals of Caucasian origin was observed among patients treated with ADT vs. non-ADT patients (80.3% vs. 82.8%; $p < 0.001$), as well as a lower proportion of married individuals (67.1% vs. 72.7%; $p < 0.001$). More individuals with CCI of 2 or CCI ≥ 3 were observed in the ADT group (11.3% and 11.0%, respectively) compared to patients in whom ADT was not given (7.5% and 7.1%, $p < 0.001$). Additionally, a higher proportion of smokers was identified among individuals treated with ADT vs. non-ADT patients (33.0% vs. 28.0%; $p < 0.001$).

Patients treated with ADT were more likely to show worse PCa features compared to their non-ADT counterparts, such as Gleason score 8–10 (32.0% vs. 11.9%, $p < 0.001$). Interestingly, we identified a lower rate of T4 tumors in the ADT cohort, compared to the non-ADT cohort (1.4% vs. 2.8%, $p < 0.001$), and a higher proportion of T2 tumors (53.7% vs. 47.1%, respectively, $p < 0.001$). Regarding clinical management of these patients, those receiving ADT were more likely to receive radiation therapy compared to patients who did not receive ADT (EBRT 32.3% vs. 14.6% and brachytherapy 20.3% vs. 14.6%, $p < 0.001$).

Unadjusted BCa estimates in the overall population and according to PCa treatment

Cumulative incidence-derived 10-year BCa-diagnosis rate in the overall population was 1.7% (95% CI 1.6–1.8%; $N = 2183$). After stratification according to ADT administration, the 10-year cumulative incidence rate was 1.75% (95% CI 1.65–1.85; $N = 830$). In the untreated group, the 10-year cumulative incidence rate was 1.99% (95% CI 1.83–2.15; $N = 1353$). After further stratification of the study cohort according to PCa primary treatment, we observed no difference in BCa incidence rates between patients treated with or without ADT. Comparison between incidence-derived 10-year BCa diagnosis rates in each group is provided in Fig. 1 and Table 2.

Adjusted BCa estimates

Table 3 shows uni- and multivariable competing-risk regression analyses predicting BCa. In multivariable competing-risk regression analyses, the use of ADT was not independently associated with BCa development, after accounting for the risk of dying from any cause ($p = 0.1$). Subanalyses were performed after stratification according to the primary treatment for PCa; in every group, we confirmed the lack of significant association between ADT administration and the risk of BCa development (Supplementary Table 1, 2, 3, and 4). For the group of patients treated with RP + RT, subanalyses were not performed because of the low number of events in this group ($n = 18$).

Discussion

Bladder cancer is roughly 3–4 times more frequently diagnosed in men than in women [1]. Different hypotheses have been proposed to explain this difference with sex hormone exposure which was suggested to play an important role in BCa carcinogenesis. Preclinical in vivo and in vitro studies suggested that BCa might be an androgen-sensitive tumor. For example, several authors demonstrated that AR knockout or castrated rats do not develop BCa, while testosterone administration promotes BCa development in rats [10–13]. However, a more complex interaction between testosterone and estrogens might be involved, as the latter also plays a significant role in BCa progression [12, 16]. For example, a previous epidemiological study observed an increased risk of BCa development in postmenopausal women [22]. That being said, the presence of ARs in BCa is not necessarily associated with adverse disease features, as more advanced BCa stages were found to be inversely associated with AR expression [14, 16, 23]. However, even in this case, conflicting results are reported in the literature. For example,

Table 2 Bladder cancer incidence rates at 10 years after stratification according to the primary treatment for prostate cancer

	10-year cumulative incidence (95% CI)			*p* value
	With ADT	Without ADT	Overall	
Prostate cancer treatment				
RP	1.1% (0.7–1.5)	1.3% (1.2–1.6)	1.3% (1.2–1.5)	0.9
RT	2.6% (2.2–2.9)	2.3% (2.0–2.6)	2.4% (2.2–2.6)	0.2
RP + RT	1.2% (0.2–2.3)	1.5% (0.5–2.6)	1.5% (0.7–2.3)	0.8
BT	2.6% (2.0–3.3)	2.3% (1.9–2.7)	2.4% (2.1–2.8)	0.8
NLT	1.6% (1.4–1.8)	1.7% (1.6–1.8)	1.7% (1.6–1.8)	0.8

ADT androgen deprivation therapy, *RP* Radical prostatectomy, *RT* radiation therapy, *BT* external beam brachytherapy, *NLT* no local treatment

Mashhadi et al. [24] demonstrated that AR expression was associated with higher grade and higher stage tumors. Conversely, Mir et al. [25] did not to observe a statistically significant decrease in AR expression in higher BCa pathological stages. In consequence, the role of hormonal modulation in BCa is still controversial, and, while ARs might have a role in BCa, the nature of this role is debated. It could also have a multiphasic relationship with BCa, promoting carcinogenesis and inhibiting tumor progression and metastases.

For this reason, we hypothesized that administration of ADT would not correlate with differences in BCa incidence in patients with PCa. Interestingly, the present study showed that administration of ADT was apparently associated with worse BCa incidence rates in the overall population. However, the difference in 10-year cumulative incidence rates did not reach statistical significance. Moreover, it should be considered that a difference of 0.24% would translated in a number needed to harm of 417 and will have no clinical relevance. Additionally, we showed that no difference in BCa rates was observed after stratification according to PCa treatment, and this observation was confirmed in the competing-risk regression analyses.

Taken together, our results reject a possible role for ADT in BCa carcinogenesis and do not support the use of ADT for chemoprevention of BCa. Nonetheless, we believe that more studies are needed to better assess the real benefit of ADT, as this treatment would probably affect only a select cohort of patients in whom BCa does express ARs. The majority of the retrospective analyses performed in the literature, including ours, do not formally assess this variable, as determination of BCa-AR presence in tumoral tissue is not part of everyday clinical practice.

Izumi et al. [17] showed a possible role for ADT in chemoprevention of recurrent BCa. Specifically, when treated with ADT, subject with AR-positive BCa demonstrated reduced recurrence rates relative to control group. Despite the striking results that suggest that ARs play a role in BCa recurrence, they concluded that this difference was due to the fact that all the patients included in their analyses were treated with ADT. While it is true that some authors suggested that the expression of ARs in untreated patients does not correlate with different oncologic outcomes in BCa, Izumi et al. failed to formally demonstrate that ADT exerted an effect in AR-positive BCa but not in AR-negative BCa.

In another study performed by Shiota et al. [18], ADT was significantly associated with lower rates of BCa diagnosis in a cohort of 1334 Japanese men. This report was the first-known study that demonstrates an effect of ADT on BCa incidence. This study, however, was limited by the disease characteristics of its cohort. 36.5% of the patients that Shiota and colleagues [18] included in the ADT group had nodal metastases, and almost half of the entire ADT group (48.9%) was metastatic. Conversely, almost none of the patients treated with RT and none of the patients treated with RP harbored nodal or distant metastases. As such, the ADT group would have had a truncated survival relative to those who did not receive ADT introducing survivorship bias. In consequence, it is possible that the 100% BCa-free survival rate that Shiota et al. reported in their study is at least partially due to the fact that these patients died shortly after the inclusion in the study. In our analyses, we tried to circumvent this limitation by excluding patients with nodal or distant metastases and by the use of a competing-risk model that accounted for the risk of mortality during the follow-up. Other authors reported conflicting results on this topic, Sathianathen et al. [26], in a secondary analysis on patients enrolled in the medical therapy for prostatic symptoms (MTOPS) study failed to observe any association between decreased dihydrotestosterone levels and BCa diagnosis. On the contrary, Morales et al. [27] found that patients treated with finasteride were at lower risk of harboring a diagnosis of BCa during the follow-up period.

Therefore, while in vivo and in vitro studies suggested a rationale for ADT use in the management of BCa risk, conflicting results prevent from drawing a definitive conclusion with no robust data to currently support a clear association in the clinical setting. That being said, the use of ADT has been proven to influence susceptibility to chemotherapy agents [14] and, thus, might be useful in metastatic patients, but the safety of this approach needs to be validated in other studies. A phase I prospective trial has been initiated to investigate enzalutamide in combination with cisplatin and gemcitabine (https://clinicaltrials.gov/ct2/show/NCT02300610). Given the high heterogeneity and the conflicting results reported in the literature, it is likely that a definitive answer might be given only in a prospective randomized trial.

Our study is not devoid of limitations. First, our findings were developed using administrative data, namely SEER-Medicare. In consequence, the inclusion of a select cohort

Table 3 Univariable and multivariable competing-risk regression analyses predicting bladder cancer incidence in patients diagnosed with prostate cancer between 1988 and 2009

	Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Androgen deprivation therapy				
No	Ref.	–	Ref.	–
Yes	1.08 (0.99–1.17)	0.08	0.93 (0.85–1.02)	0.1
PCa primary treatment				
RP	Ref.	–	Ref.	–
RT	1.60 (1.42–1.81)	< 0.001	1.69 (1.48–1.93)	< 0.001
RP + RT	1.11 (0.69–1.78)	0.7	1.07 (0.67–1.72)	0.8
BT	1.37 (1.19–1.59)	< 0.001	1.43 (1.23–1.66)	< 0.001
NLT	1.22 (1.09–1.37)	< 0.001	1.37 (1.21–1.55)	< 0.001
Age at PCa diagnosis	1.01 (1.01–1.01)	< 0.01	1.01 (1.01–1.02)	< 0.01
Ethnicity				
Caucasian	Ref.	–	Ref.	–
African American	0.50 (0.43–0.60)	< 0.001	0.54 (0.46–0.65)	< 0.001
Other	0.47 (0.38–0.58)	< 0.001	0.50 (0.40–0.62)	< 0.001
Ever-smoker				
No	Ref.	–	Ref.	–
Yes	1.85 (1.71–2.00)	< 0.001	1.94 (1.78–2.10)	< 0.001
Marital status				
Married	Ref.	–	Ref.	–
Unmarried	0.77 (0.70–0.86)	< 0.001	0.78 (0.70–0.87)	< 0.001
Unknown	0.79 (0.67–0.92)	< 0.01	0.77 (0.65–0.91)	< 0.01
Charlson comorbidity index				
0	Ref.	–	Ref.	–
1	1.02 (0.92–1.12)	0.7	0.93 (0.85–1.03)	0.2
2	0.94 (0.81–1.10)	0.5	0.84 (0.71–0.98)	0.02
≥ 3	0.94 (0.80–1.11)	0.4	0.85 (0.72–1.01)	0.06
PCa biopsy Gleason score				
≤ 6	Ref.	–	Ref.	–
7	1.16 (1.04–1.29)	< 0.01	1.15 (1.03–1.28)	0.01
8–10	1.15 (1.01–1.31)	0.03	1.14 (1.00–1.31)	0.05
PCa clinical T stage				
T1	Ref.	–	Ref.	–
T2	1.05 (0.97–1.14)	0.2	1.04 (0.96–1.14)	0.3
T3	1.14 (0.93–1.40)	0.2	1.19 (0.96–1.47)	0.1
T4	1.11 (0.91–1.36)	0.3	1.22 (0.99–1.50)	0.06
Population density				
Rural	Ref.	–	Ref.	–
Urban	0.98 (0.88–1.09)	0.7	0.97 (0.86–1.08)	0.6
US region				
Midwest	Ref.	–	Ref.	–
Northeast	1.09 (0.96–1.24)	0.2	1.10 (0.96–1.26)	0.2
South	0.77 (0.67–0.88)	< 0.001	0.78 (0.68–0.90)	< 0.001
West	0.92 (0.83–1.02)	0.1	1.00 (0.9–1.12)	0.9
Socio-economic status				
Low	Ref.	–	Ref.	–
High	0.84 (0.78–0.91)	< 0.001	0.97 (0.89–1.05)	0.48

HR hazard ratio, *CI* confidence interval, *Ref.* reference, *RP* radical prostatectomy, *RT* external beam radiation therapy, *BT* brachytherapy, *NLT* no local treatment, *PCa* prostate cancer

composed of Medicare beneficiaries aged 65 years or older might limit validity of long-term observations. Moreover, patients with N+/M+ were excluded from our series and the reported differences exist between ADT and control group regarding comorbidities and cancer grade might represent a selection bias. Second, lack of information regarding the dose and duration of ADT prevented us from adjusting our analyses for these potential confounders. Third, ADT is a generic term that comprises several different drugs with different molecular targets and mechanisms. While some of those drugs are direct AR antagonists (flutamide, bicalutamide, degarelix), others act as gonadotropin-releasing hormone (LHRH) analogues and therefore interact with LHRH receptors rather than ARs directly. While ADT as a generic term is accepted for PCa, the equipollence of these different drugs in BCa is not warranted. Moreover, no data regarding other concomitant medications (such as 5ARIs) were available in our cohort and might have influenced our findings. Fourth, tumor heterogeneity with different expressions of AR has been reported in previous studies and a chemoprevention with ADT might result effective in a select group of patients. Fifth, no data regarding the tumor stage were available and as consequence, the possible impact of ADT on aggressiveness or recurrence of BCa was not measured. Last but not least, the retrospective nature of the study and the limited follow-up (median 59 months) should be considered. Sixth, no data regarding histological type were available for this cohort [28]. This parameter might have an impact on differences in BCa diagnoses between male and female patients. Seventh, radiation therapy might be involved in several complications in urological patients [29]. In this regard, the findings confirm that RT might be a risk factor for a second primary BCa during the follow-up. However, we were not able to account for changes in radiation therapy schemes and these findings might not be applied to contemporary patients.

Conclusions

In summary, the currently available literature debates about a possible role of ADT for prevention of BCa development. While preclinical studies show conflicting results, clinical studies suffer from various limitations. The current study finds no direct relation between ADT and subsequent risk of developing BCa. More knowledge is needed to draw definitive conclusions whether BCa patients may benefit from ADT. Until then, the use of ADT outside guideline recommendations for PCa treatment should not be encouraged.

Author contributions MM: data collection, statistical analysis, manuscript writing; EZ: data collection, statistical analysis, manuscript writing; PK: project development, manuscript writing; AM: project development, manuscript writing; GG: data collection; NF: data collection; FM: data collection; AB: data collection; SFS: project development, manuscript writing.

Compliance with ethical standards

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

Ethical standards All participants gave their informed consent to use their data for this retrospective study involving human participants.

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