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Androgen deprivation therapy for treatment of localized prostate cancer and risk of second primary malignancies

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Abstract

Background—While androgen deprivation therapy (ADT) is a common treatment for prostate cancer, little is known regarding its long term health effects, particularly as it relates to the development of second primary malignancies. Therefore, the goal of this study was to assess the association between ADT use and second primary malignancies among men diagnosed with localized prostate cancer.

Methods—We assessed whether use of ADT (specifically, gonadotropin-releasing hormone agonists) was associated with the development of second primary malignancies in a retrospective cohort of 24,038 men ages >18 years who were diagnosed with localized prostate cancer between 1998 and 2007, and followed through 2009. We used proportional hazards regression to estimate the risk of developing a second primary cancer among men who were treated with ADT compared to men who were not.

Results—Men who were treated with ADT were not more likely to develop any second primary malignancy compared to those who were not treated with ADT after adjustment for age, race, date of diagnosis, utilization, clinical stage, Gleason score and radiation therapy (HR: 1.10, 95% CI: 0.98, 1.22). Radiation therapy, diabetes and obesity did not modify the association between ADT use and second primary cancer risk.

Conclusion—Our results suggest among men with localized prostate cancer, androgen deprivation therapy is not associated with an increased risk of second primary malignancies.

Impact—When evaluating the risks and benefits of using ADT as a treatment for localized prostate cancer, considering the risk of second primary malignancies may not be clinically important.

Keywords

androgen deprivation therapy; prostate cancer; second primary malignancy; adverse effects

Introduction

While androgen deprivation therapy (ADT) is a common treatment for prostate cancer, little is known regarding its long term health effects. However, the use of ADT remains a common, albeit controversial, treatment option for localized prostate cancer.(1) Previous studies have linked ADT use to increased risk of osteoporosis, fractures and cardiovascular outcomes.(2-4) Gillessen et al. found a positive association between long-term use of ADT

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and the development of colorectal cancer. (5) However, it remains unclear whether the use of ADT increases the risk of other second primary malignancies. Because ADT is associated with other known risk factors for cancer such as diabetes and obesity (2, 3, 6), its use may potentially influence second cancer development through these pathways. Also, it has been hypothesized that androgens may protect against carcinogenesis. (7, 8) It is plausible the suppression of androgen may then promote the progression of carcinogenesis. Therefore, the goal of this study was to assess the association between ADT use and second primary malignancies among a cohort of men diagnosed with localized prostate cancer.

Methods

A retrospective cohort of 24,038 men ages 18 years and older enrolled in Kaiser Permanente Southern California health plan who were diagnosed with localized prostate cancer between 1998 and 2007 were followed through 2009 for the development of second primary cancers as identified through the NCI-SEER affiliated cancer registry. Men diagnosed with a second primary cancer or who died from it within 6 months of prostate cancer diagnosis (N=173), had a history of chemotherapy treatment (n=29) or who underwent orchiectomy (N=82) were excluded. ADT use was defined as any use of a gonadotropin-releasing hormone (GnRH) agonist and was treated as a time-dependent exposure so that men could contribute person-time to the ADT group after treatment initiation and to the no ADT group either before ADT initiation, or if they never received ADT during follow-up. Proportional hazards regression was used to estimate the risk of a second primary cancer among men who were treated with ADT compared to men who were not after adjustment for age, race, date of prostate cancer diagnosis, utilization, prostate cancer clinical stage, Gleason score and radiation therapy. Censoring occurred at development of second cancer, death, health plan disenrollment or end of study, whichever occurred first. This study had 90% power to detect a difference in effect of 1.25 or greater (0.8 or smaller). All analyses were performed using SAS 9.3 (Cary, NC) with an alpha level of 0.05.

Results

Of the 24,038 men with localized prostate cancer, 1359 (5.7%) were diagnosed with a second primary cancer during follow-up. The most common site was colorectal (0.78%), followed by lung/bronchus (0.75%), bladder (0.55%) and kidney (0.32%). Men who were diagnosed with a second primary cancer were older, had lower income and education, and were more likely to have a history of type 2 diabetes and hypertension. (Table 1) Men who were treated with ADT were equally as likely to develop any second primary cancer (regardless of site) as men who were not treated with ADT after adjustment for age, race, date of prostate cancer diagnosis, utilization, clinical stage, Gleason score and radiation therapy (HR: 1.10, 95% CI: 0.98, 1.22). (Table 2) Radiation therapy, diabetes and obesity did not modify the association between ADT use and second primary cancer risk. (Data not shown)

Discussion

In this study of men with localized prostate cancer, ADT therapy was not associated with an increased risk of second primary malignancies. In contrast to a previous study (5), ADT use was also not associated with an increased risk of colorectal cancer. It is possible that the inclusion of younger men in this study may have resulted in a lower risk of secondary cancers overall, thus resulting in more conservative estimates of the risk of second primary cancers than reported previously.

While this study is one of the first to evaluate the risk of developing any type of second primary malignancy after ADT treatment, there are potential limitations to consider. Due to the complexities of determining injectable drug dosing in our data, ADT dose and duration were not available. Therefore, whether ADT dose influences second primary cancer development could not be assessed. Confounding by factors not measured in this study, such as the use of screening for secondary cancers, might have influenced the results. However, the use of screening is not thought to differ by ADT use, thus limiting the effect of this bias. Finally, because this study included only men with localized prostate cancer, generalizing these findings to men with advanced disease is limited.

Conclusions

In conclusion, ADT treatment for localized prostate cancer was not associated with an increased risk of second primary cancers. When evaluating the risks and benefits of using ADT as a treatment for localized prostate cancer, considering the risk of secondary cancers may not be clinically important.

Acknowledgments

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Table 1
Demographic and Medical Characteristics by Second Primary Cancer Status (N=24,038)

	Any second primary cancer N=1359	No second primary cancer N=22,679	p-value ^a
Demographics	N(%)	N(%)	
Age at baseline			
40-50	18 (1.3%)	1092 (4.8%)	<0.0001
50-60	190 (14%)	5551 (24.5%)	
60-70	532 (39.1%)	9139 (40.3%)	
70-80	506 (37.2%)	5498 (24.2%)	
80+	113 (8.3%)	1388 (6.1%)	
Race/ethnicity			
White	943 (69.4%)	13882 (61.2%)	<0.0001
Black	249 (18.3%)	3927 (17.3%)	
Asian/PI	49 (3.6%)	1307 (5.8%)	
Hispanic	112 (8.2%)	2969 (13.1%)	
Other/Unknown	6 (0.4%)	594 (2.6%)	
Household median income			
0%-25%	166 (30.5%)	3602 (26.5%)	0.0201
25%-50%	148 (27.2%)	3390 (24.9%)	
50%-75%	126 (23.2%)	3358 (24.7%)	
75%-100%	104 (19.1%)	3239 (23.8%)	
Education (years)			
Median (q1,q3)	38.6 (24.6, 55.0)	40.8 (26.2, 57.3)	0.0196
Medical History			
BMI^b			
Underweight (<18.5) Normal (18.5-24.9)	8 (0.8%) 250 (25.2%) 448 (45.1%)	75 (0.4%) 4124 (22%) 8733 (46.6%) 5814 (31%)	0.0218
Overweight (25-29.9) Obese (30 or greater)	288 (29%)		
History of Type 2 Diabetes			
No	900 (66.2%)	16714 (73.7%)	<0.0001
Yes	459 (33.8%)	5965 (26.3%)	
History of Hypertension			
No	143 (10.5%)	4500 (19.8%)	<0.0001
Yes	1216 (89.5%)	18179 (80.2%)	
Charlson Index			
0 1-2 3+	548 (62.6%) 289 (33%) 39 (4.5%)	12373 (68.4%) 4848 (26.8%) 856 (4.7%)	0.0003
Utilization (No. of visits)			
Median (q1, q3)	19.0 (10.0, 31.0)	15.0 (8.0, 26.0)	<0.0001
Prostate cancer characteristics			

	Any second primary cancer N=1359	No second primary cancer N=22,679	p-value ^a
Stage at diagnosis			
I	14 (1%)	87 (0.4%)	0.0016
II	1345 (99%)	22591 (99.6%)	
Radiation therapy			
No	1010 (74.3%)	18122 (79.9%)	<0.0001
Yes	349 (25.7%)	4557 (20.1%)	
Gleason score			
7	1153 (84.8%)	19866 (87.6%)	0.0029
> 7	206 (15.2%)	2813 (12.4%)	

^a Missing numbers were excluded in the estimation of P-values (2-sided).

^b BMI= body mass index

Table 2
Crude and Adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CI) of the associations between ADT use and second primary cancers among 24,038 men with localized prostate cancer

	# of Cases	Crude HR 95% CI	Adjusted HR 95% CI ^b
Any 2nd Primary Cancer			
No ADT	719	1.0 (ref)	1.0 (ref)
ADT ^a	640	0.94 (0.79, 1.12)	0.96 (0.79, 1.17)
Colorectal			
No ADT	113	1.0 (ref)	1.0 (ref)
ADT	74	0.77 (0.44, 1.35)	0.91 (0.47, 1.74)
Lung			
No ADT	78	1.0 (ref)	1.0 (ref)
ADT	100	1.27 (0.84, 1.91)	1.21 (0.71, 2.06)
Bladder			
No ADT	61	1.0 (ref)	1.0 (ref)
ADT	71	0.67 (0.38, 1.18)	0.53 (0.26, 1.06)
Kidney			
No ADT	49	1.0 (ref)	1.0 (ref)
ADT	27	1.92 (0.76, 4.82)	2.16 (0.51, 9.23)
Other			
No ADT	418	1.0 (ref)	1.0 (ref)
ADT	368	0.86 (0.68, 1.08)	0.92 (0.71, 1.20)

^a ADT defined as use of GnRH agonist only.

^b Adjusted for age, race, year of prostate cancer diagnosis, utilization (healthcare visits), stage, Gleason score, and radiation therapy.