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Hormonal Manipulation with Finasteride or Oral Contraception Does Not Influence Incidence of Renal Cell Carcinoma

Aashish Kabra¹, Jonathan Gelfond², and Michael A. Liss^{1,3}

¹Department of Urology, University of Texas Health Science Center San Antonio

²Department of Biostatistics, University of Texas Health Science Center San Antonio

³Department of Surgery, South Texas Veterans Healthcare System, San Antonio

Abstract

Objective—Androgens have been suspected to be involved in initiation of renal cell carcinoma due to a two-fold increased risk in men compared to women. To investigate the role of self-reported finasteride or oral contraceptive use in the PLCO in order to determine if androgen receptor reduces renal cancer development.

Methods—We query the Prostate, Lung, Colorectal, and Ovarian (PCLO) trial for predictor variables from the baseline questionnaire (BQM) and follow up questionnaires enquiring medication use, specifically the use of 5-alpha reductase inhibitors (5-ARI; dutasteride or finasteride) and oral contraceptive therapy (OCT). The primary outcome of this study was incidence of renal cancer. Statistical analysis included Student T test for continuous variables, chi-squared or Fisher's exact tests for dichotomous or categorical variables, and multivariable analysis using Cox proportional hazards models.

Results—Eight percent (n=6,117 / 73,694) of men in the PLCO trial reported use of Finasteride. 52 (10.6%) of the 492 men diagnosed with renal cancer had self-reported exposure to finasteride and was not significant in univariable analysis (52/6169; 0.84% vs. 440/66454; 0.67%, p=0.12) or multivariable main effects analysis (HR 1.12, 95% CI 0.83, 1.5, p=0.47). Approximately 54 percent of women (n=40,997/75,989) in the PLCO trial reported use of oral contraceptives via questionnaire. 136 (52.1%) of the 261 women diagnosed with renal cancer had self-reported exposure to OCT and was not significant in univariable analysis (136/40,997; 0.33% vs. 125/34992; 0.36%, p=0.36) or in multivariable main effects analysis (HR 1.03, 95% CI 0.97, 1.1, p=0.30).

Conclusions—Self reported use of finasteride or oral contraceptives is not associated with a reduced renal cancer incidence.

Keywords

Renal Cancer; Estrogen; Testosterone; Hormone; Prevention

Introduction

Renal cancer is estimated to have an incidence of 12.6 per 100,000 men in developed countries compared to only 3.4 per 100,000 women.(Torre, Bray et al. 2015) Therefore, androgens have been suspected to be involved in initiation of renal cell carcinoma (RCC). Male gender and obesity (body mass index >30) both have implications regarding the incidence of renal cancer with a nearly two-fold risk, respectively.(Sanfilippo, McTigue et al. 2014) Estrogen production from adipose tissue and the abundance of testosterone in men have led to investigations implicating the androgen receptor as a potential target.(Feldman and Motzer 2006) The androgen receptor can be influenced by the amount of testosterone and dihydrotestosterone (DHT) in circulation. Currently, studies have shown that higher AR expression found in RCC is associated with more aggressive cancer with advanced pathologic T stage and Fuhrman grade, possibly by inducing of HIF-2alpha/VEGF signaling.(Chang, Lee et al. 2014, He, Li et al. 2014) Finasteride or oral contraceptives may interact with the androgen receptor and thereby play a role in natural history of RCC. We investigate the role of self-reported finasteride or oral contraceptive use in the PLCO as it relates to the incidence of RCC in the Prostate, Lung, Colorectal, and Ovarian (PLCO) screening study.

Methods

Study Population

After internal review board (IRB) approval and data transfer agreement (CDAS project # 120), we obtained de-identified data from subjects enrolled in the Prostate, Lung, Colon, and Ovarian (PLCO) Cancer Screening Trial. The PLCO is a National Cancer Institute (NCI) sponsored randomized trial investigating the effects of screening on cancer outcomes in subjects aged 55 to 74 years from 1993 to 2001 and have followed them for 13 years.

Outcomes and risk factors

The primary outcome of this study was incidence of renal cancer defined by questionnaire and medical record confirmation in the context of the PLCO clinical trial. Predictor variables were obtained from the baseline questionnaire (BQM) and follow up questionnaires enquiring medication use, specifically the use of 5-alpha reductase inhibitors (5-ARI; dutasteride or finasteride) and oral contraceptive therapy (OCT). The World Health Organization (WHO) standard categorization of body mass index (BMI) was utilized. Hypertension was obtained via questionnaire.

Statistical Analysis

PLCO database was queried for the primary outcome of renal cancer. Demographics were investigated, specifically focusing on medication predictor variables of 5-ARI and OCT medications controlling for previously identified risk factors of BMI and hypertension. Statistical analysis included testing for bivariate associations between renal cancer status and risk factors using the Student T test for continuous variables, chi-squared or Fisher's exact tests for dichotomous or categorical variables. The incidence of RCC was modeled using

Cox proportional hazards models, and all risk factors were considered within the same model adjusting for demographics and comorbidities.

Results

We obtained local IRB approval and request to the PLCO for data with data use agreement forms. We then investigated existing data regarding RCC incidence and the use of 5 alpha reductase inhibitor use in men and oral contraception in women and.

5 alpha reductase inhibitor in men and RCC incidence

Eight percent (n=6,117 / 73,694) of men in the PLCO trial reported use of Finasteride via questionnaire. Only 52 (10.6%) of the 492 men diagnosed with renal cancer had self-reported exposure to finasteride and was not significant in univariable analysis (52/6169; 0.84% vs. 440/66454; 0.67%, p=0.12). In multivariable main effects analysis, finasteride did not have an association with increased or decreased incidence of RCC in men (HR 1.12, 95% CI 0.83, 1.5, p=0.47) adjusted for smoking, age, study arm, education, body mass index, race/ethnicity, family history of renal cancer, and diabetes. Men who were exposed to finasteride also did not benefit from a delayed time in onset of renal cancer (Figure 1). About 1.5 percent of men were removed from the adjusted analysis because of missing covariates.

Oral contraceptive use in women and RCC incidence

Approximately 54 percent of women (n=40,997/75,989) in the PLCO trial reported use of oral contraceptives via questionnaire. 136 (52.1%) of the 261 women diagnosed with renal cancer had self-reported exposure to OCT and was not significant in univariable analysis (136/40,997; 0.33% vs. 125/34992; 0.36%, p=0.36). In multivariable main effects analysis, contraceptive use did not have an association with increased or decreased incidence of RCC in women (HR 1.03, 95% CI 0.97, 1.1, p=0.30) adjusted for smoking, age, study arm, education, body mass index, race/eth, family history of renal cancer, and diabetes. Women who used oral contraceptives did not benefit from a delayed time in onset of renal cancer (Figure 2). About 0.01 percent of women were removed from the adjusted analysis because of missing covariates.

Discussion

The increased incidence of RCC in men compared to women suggests a possible sex-linked risk factor. We queried the PLCO study to determine the effects of finasteride use on the incidence of RCC. Our analysis of the more than 79,000 men in the PLCO study showed that a self reported use of finasteride is not associated with a reduced RCC incidence. Additionally, oral contraceptive use was not associated with RCC incidence in women either. However, the concept of hormonal manipulation has been robust in animal models. A recent study by Tian et al. described a using finasteride to reduce microvessel density, VEGF protein expression in glomeruli, and VEGF mRNA expression in the renal cortex tissue in diabetic rats (all $P < 0.05$). (Tian, Zhao et al. 2015) Urologists use finasteride to reduce microvessel density in men with hematuria from enlarged prostates. Moreover, finasteride

has shown a reduction in prostate cancer formation in the prostate cancer prevention trial. Therefore, we sought to investigate if this could prevent renal masses by this mechanism though we have shown this not to be the case in our data set.

The effects of estrogen on renal tumors have stimulated interest in the role of female hormonal and reproductive factors in renal cancer development. Exogenous estrogens have been shown in animals to promote and induce renal cancer formation (Cavalieri, Kumar et al. 2001) and sex hormone receptor expression in both normal and malignant renal tissue suggests that endocrine regulation could directly influence renal cancer development. Moreover, estrogens also influence the catechol-estrogen pathway as well as produce related reactive-oxygen species production. These pathways have been well described in breast cancer and also have been linked to the AKT pathway, which plays a prominent role in renal cancer. (Fussell, Udasin et al. 2011) (Habib and Liang 2014) Our analysis did not suggest an association between oral contraceptives and RCC incidence but other studies have (insert reference). Anatomical changes to the renal during pregnancy might make nephrons more vulnerable to inflammation and oxidative stress. Lastly, hormonal disturbance has been associated with obesity and smoking (Cramer, Harlow et al. 1995), two major risk factors most consistently observed across renal cancer studies.

The link between androgen receptor and RCC incidence has been less clear in patients. Several studies showed loss of AR in renal cell carcinoma (RCC) in conjunction with increasing clinical stage and pathological grade (Langner, Ratschek et al. 2004, Zhu, Liang et al. 2014), but others found that higher AR expression correlated with worse outcomes. Limited functional studies with renal cell lines suggested tumor-promoting activity of AR (Ha, Lee et al. 2015). There may be significant clinical implications and development of treatment strategies after clear understanding of this relationship.

It is evidence that there is a relationship between RCC and the hormonal pathway. Further studies will be needed to elucidate the actual relationship and mechanisms involved in order to be able to employ possible preventive or therapeutic targets. However clinical trials for this concept would be difficult due to the large sample size needed and small population of men developing renal cancer.

Limitations of the study include the exclusion of young adults and children as the PCLO trial entry age was limited to 55 to 74. Children and young adults are not necessarily at risk for these cancers; however, renal cell cancer has been not to affect both genders in the third and fourth decades of life and may alter our findings if included. Additionally, the use of finasteride or OCT are based on questionnaire data that could lead to recall bias and the inability to perform dose related response analysis due to small numbers.

In conclusions, despite recent excitement surrounding the androgen receptor as a target for the prevention of RCC, our analysis of the PLCO study showed that a self reported use of finasteride or oral contraceptives is not associated with a reduced renal cancer incidence. However, further studies will be needed to elucidate the actual relationship and mechanisms involved in order to be able to employ possible preventive or therapeutic targets in the future.

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Incidence by Finasteride

Figure 1. Finasteride and Renal Cancer Incidence

Covariate adjusted survival curve noting the incidence of renal cancer in men who did and did not indicate they had taken finasteride via a standardized Prostate, Lung, Colorectal, and Ovarian questionnaire.

Figure 2. Oral Contraception and Renal Cancer Incidence

Covariate adjusted survival curve noting the incidence of renal cancer in women who did and did not indicate they had taken oral contraception via a standardized Prostate, Lung, Colorectal, and Ovarian questionnaire.

Table 1

Demographics and comorbidities by Renal Cancer Status

Variable	No Renal Cancer	Renal Cancer	P-value
Age, mean (median; IQR)	62.6 (62; 58–67)	63.3 (63; 59.2–67)	< 0.001
Gender, no. (%)			< 0.001
Female	75728 (50.8)	261 (34.6)	
Male	73201 (49.2)	493 (65.4)	
Body Mass Index, mean (median; IQR)	27.3 (26.6; 24–29.8)	28.6 (27.9; 25.1–31.2)	< 0.001
Race, no. (%)			0.09
White, Non-Hispanic	131640 (88.4)	681 (90.3)	
Black, Non-Hispanic	7659 (5.1)	35 (4.6)	
Hispanic	2795 (1.9)	17 (2.3)	
Other	6835 (4.6)	21 (2.8)	
Family History of Renal Cancer, no. (%)	2183 (1.5)	12 (1.6)	0.89
5 Alpha Reductase Exposure, no. (%)	6117 (8.5)	52 (10.6)	0.12
Oral Contraception Exposure, no. (%)	40997 (54.2)	136 (52.1)	0.53
Diabetes, no. (%)	11424 (7.7)	73 (9.7)	0.05
Myocardial Infarction, no. (%)	13411 (9.1)	95 (12.7)	0.001
Hypertension, no. (%)	50526 (34.1)	326 (43.5)	< 0.001
Stroke, no. (%)	3605 (2.4)	22 (2.9)	0.44

Table 2

Cox proportional hazards model for Renal Cancer in men.

Variable	HR	CI95	Pvalue
Age	1.03	[1.01, 1.05]	0.001
Screening Arm	1.20	[1, 1.44]	0.05
Body Mass Index	1.05	[1.02, 1.07]	<0.0001
Education level	0.99	[0.94, 1.05]	0.73
Hypertension	1.23	[1.02, 1.49]	0.03
Smoking (pack decades)	1.04	[1.01, 1.07]	0.01
5 alpha reductase exposure	1.12	[0.83, 1.5]	0.47
Black, Non-Hispanic vs. White	0.70	[0.41, 1.2]	0.2
Hispanic vs. White	0.99	[0.51, 1.91]	0.96
Other vs. White	0.76	[0.46, 1.23]	0.26
Family history of Renal Cancer	1.01	[0.45, 2.25]	0.99

Table 3

Cox proportional hazards model for Renal Cancer in women.

Variable	HR	CI95	Pvalue
Age	1.03	[1, 1.05]	0.03
Screening Arm	1.01	[0.79, 1.29]	0.95
Oral Contraceptive	1.03	[0.97, 1.1]	0.3
Body mass index	1.04	[1.02, 1.06]	<0.0001
Education	0.89	[0.82, 0.97]	0.01
Hypertension	1.52	[1.17, 1.96]	0.002
Smoker (pack decades)	1.07	[1.03, 1.12]	0.002
Black, Non-Hispanic vs. White	1.21	[0.76, 1.93]	0.43
Hispanic vs. White	1.49	[0.66, 3.36]	0.34
Other vs. White	0.43	[0.16, 1.15]	0.09
Family history of Renal Cancer	1.28	[0.57, 2.87]	0.56