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# Decreased risk of bladder cancer in men treated with quinazoline-based α1-adrenoceptor antagonists

**Research Article**

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**Abbreviations:** benign prostatic hypertrophy, (BPH); Fas-associated death domain, (FADD); Kentucky Cancer Registry, (KCR); Surveillance, Epidemiology, and End Results, (SEER); transgenic adenocarcinoma of mouse prostate, (TRAMP); vascular endothelial growth factor, (VEGF); Veterans Administration, (VA)

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## Summary

**Previous studies documented that human bladder cancer cells are sensitive to the apoptotic effects of quinazoline-derived α1-adrenoreceptor antagonists and bladder tumors exhibit reduced tissue vascularity in response to terazosin. More recent evidence suggests that exposure to quinazoline α1-adrenorecptor antagonists leads to a significant reduction in prostate cancer incidence. This retrospective observational cohort study was conducted to determine whether male patients treated with quinazoline α1-adrenoceptor antagonists for either benign prostate hyperplasia (BPH) or hypertension have a decreased risk of developing bladder cancer. Review of the medical records of all male patients enrolled at the Lexington Veterans Administration (VA) Medical Center identified men exposed to quinazoline-based α1-adrenoceptor antagonists (Jan 1, 1998-Dec 31, 2002) for either hypertension and/or benign prostate obstructive symptoms. The whole group of 27,138 male patients was linked to the Markey Cancer Center's Kentucky Cancer Registry (KCR), part of the NCI's Surveillance, Epidemiology, and End Results (SEER) Program, to identify all incident bladder cancer cases diagnosed in this population. Measures of disease incidence, relative risk, and attributable risk were calculated to compare the risk of developing bladder cancer for α1-blocker-exposed versus unexposed men. A two-by-two contingency table of α1-antagonist exposure versus bladder cancer diagnoses was constructed and the relative risk was calculated. Our analysis revealed a cumulative bladder cancer incidence of 0.24% among the α1-blocker-exposed men compared to 0.42% in the unexposed group. Thus, there was a risk difference of -0.0018, which indicates that 1.8 fewer bladder cancer cases developed per 1000 exposed men. Alternatively stated, 556 men would need to be treated with quinazoline α1-blockers to prevent one case of bladder cancer. Exposure to quinazoline α1-blockers thus may have prevented 7 to 8 bladder cancer cases among the 4173 treated men during the study period .The data yield an unadjusted risk ratio of 0.57 (95% CI: 0.30, 1.08) and therefore, men treated with α1-adrenoreceptor antagonists have a 43% lower relative risk of developing bladder cancer than unexposed men (p=0.083). Our inability to determine person-years at risk of developing bladder cancer for each unexposed control patient, was a limitation for calculating an incidence ratio and rate difference. These results offer an initial indication that exposure to doxazosin and terazosin decreases the incidence of bladder cancer. This is the first epidemiological evidence that the anti-tumor action of quinazoline-based α1-antagonists may potentially translate into a protective effect from bladder cancer development.**

# I. Introduction

Carcinoma of the bladder is projected to be the fourth most common cancer in males and ninth in females in 2006 (Jemal et al, 2006). The incidence and mortality of transitional cell carcinoma of the bladder has increased in recent years with an estimated 61,420 new cases and 13,060 deaths in 2006 and 67,160 new cases and 13,750 deaths in 2007 (Jemal et al, 2006, 2007). Loss of apoptosis is causally linked in the development of bladder cancer (Reed, 1999) as illustrated by the observation that *in vitro* bladder cancer cells eventually become resistant to cytotoxic drugs (Kerret al, 1994); therefore, induction of apoptosis is an attractive therapeutic target. Uncontrolled angiogenesis also plays a role in bladder cancer development because without generating blood supply, bladder tumors are unable to grow over 2-3mm (Folkman, 1971; Streeter and Harris, 2002). Angiogenesis and microvessel density parallel disease progression as well as overall survival in bladder cancer, which supports targeting therapies that inhibit angiogenesis (Bochner et al, 1995). Quinazoline α1-adrenoreceptor antagonists have been shown to promote apoptosis and to inhibit angiogenesis (Garrison et al, 2007).

The quinazoline-based α1-adrenoreceptor antagonists, doxazosin and terazosin, are FDA-approved drugs characterized by a few, well-tolerated side effects, primarily dizziness, used clinically for the treatment of benign prostatic hypertrophy (BPH) and systemic hypertension. The α1-adrenoceptor antagonists exert their effect via directly targeting α1-adrenoceptors in smooth muscle cells in the prostate gland and bladder neck (Walden et al, 1997; McConnellet al, 2003), causing a decrease in smooth muscle tone to relieve bladder obstruction secondary to periurethral prostatic enlargement (Caine, 1990). Growing evidence from retrospective clinical studies demonstrates that in addition to causing smooth muscle relaxation and a decrease in vascular pressure, the quinazoline-based α1-adrenoceptor antagonists also can induce apoptosis and suppress angiogenesis in benign and malignant prostate tumors (Kyprianou et al, 1998; Chon, et al, 1999; Kyprianou, 2003). Pharmacologically-relevant levels of the two leading α1-adrenoceptor antagonists used in the US, doxazosin and terazosin, selectively induce apoptosis in benign and malignant prostate epithelial cells, as well as stromal smooth muscle cells, without affecting cell proliferation *in vitro* or in clinical tumor specimens (Chon et al, 1999). The apoptotic action of quinazolines engages an α1-adrenoceptor-independent mechanism, and affects both androgen-independent and androgen-dependent prostate cancer cells (Benning. and Kyprianou, 2002; Garrison and Kyprianou, 2004; Kyprianou and Benning., 2004). Apoptosis induction proceeds via two classic pathways, the extrinsic death-receptor pathway involving caspase 8 activation, and the intrinsic pathway involving mitochondrial cytochrome C and caspase 9 activation (Wolf and Green, 1999). We recently demonstrated that doxazosin (quinazoline-α1-adrenoceptor antagonist) activates the receptor-mediated pathway of apoptosis via Fas-associated death domain (FADD) and caspase-8 activation (Garrison and Kyprianou, 2006) in both prostate epithelial and endothelial cells by promoting TGF-β1 signaling via IκB induction (Garrison and Kyprianou, 2004), and by inhibiting protein kinase B/Akt activation to promote anoikis (Grossmann, 2002; Keledjian and Kyprianou, 2002; Shaw et al, 2004). The quinazolines suppress angiogenesis by targeting vascular endothelial growth factor (VEGF)- mediated endothelial tube formation (Panet al, 2003; Keledjian et al, 2005).

Tahmatzopoulos and colleagues recently reported that bladder tumors treated with terazosin had significantly decreased tissue vascularity and an increased apoptotic index as compared to untreated bladder tumors (Tahmatzopouloset al, 2005). Our previous studies established that human bladder cancer cells are susceptible to the apoptotic effect of the quinazolines *in vitro* (Kyprianou and Jacobs, 2000). Taken together this *in vitro* data, with our recent retrospective analysis indicating the quinazoline alpha1-adrenorecptor antagonists lowered the incidence of prostate cancer prompted the current epidemiological study.

In this observational cohort study, we investigated whether use of the quinazoline-based α1-adrenoceptor antagonists is associated with a decreased risk of bladder cancer. Our retrospective analysis suggests that men treated with this class of α1-adrrenoceptor antagonists have a reduced risk of developing bladder cancer, suggesting that the apoptotic and anti-angiogenic action of these drugs at the cellular level might be a potential mechanism contributing to the prevention of clinical disease.

# II. Patients and Methods

## A. Patient Cohort construction

A retrospective observational study was performed on a cohort of male patients seen at the Lexington Veterans Affairs (VA) Hospital between January 1, 1998 and December 31, 2003. The total number of men seen at the VA during this 5-yr period (n = 27,138) was determined from the VA's electronic hospital registry, and the total number of bladder cancer cases diagnosed at the VA between 1998 and 2002 (n= 107) was obtained from the Markey Cancer Center's Kentucky Cancer Registry (KCR), a statewide population-based central cancer registry that is part of the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. Information about age at diagnosis, race (Caucasian or non-Caucasian), disease stage at diagnosis (I, II, III, IV, not applicable, and unknown), tumor grade (1, 2, 3, 4, unknown), and tumor histology (carcinoma NOS, small cell carcinoma, adenocarcinoma NOS, mucinous adenocarcinoma, infiltrating duct carcinoma; NOS, not otherwise specified) was obtained from the KCR. All men exposed to a quinazoline-based α1-adrenoceptor antagonist, doxazosin (1-8mg/day), prazosin (2-10mg/day), or terazosin (1-10mg/day) for either systemic hypertension or BPH between 1998 and 2002 (n = 4,173) were identified from the VA's electronic pharmacy records and linked to the KCR's database. The data identified all quinazoline α1-blocker-exposed bladder cancer cases diagnosed at the VA greater than 2 months after treatment (n = 10) and exposed patients without bladder cancer (n = 4,163). Bladder cancer cases diagnosed less than 2 months after initiating quinazoline α1-blocker treatment were assumed to have pre-existing cancer and, therefore, classified as unexposed bladder cancer cases. The number of unexposed patients with bladder cancer (n = 97) and without bladder cancer (n = 22,868) was calculated subsequently

by subtraction from the margin totals of a two-by-two contingency table (**Table 1**).

## III. Results

### A. Quinazoline-based α1-adrenoceptor antagonist exposure is associated with reduced bladder cancer incidence

A two-by-two contingency table of bladder cancer and non-cancer cases versus quinazoline α1-adenoceptor antagonist-treated and untreated men seen at the Lexington VA was constructed (**Table 1**). These data were used to calculate measures of disease incidence (cumulative incidence), relative risk, attributable risk (risk difference), and % attributable risk (% risk difference) and to determine whether significant differences exist between α1-blocker-exposed versus unexposed (control) men in developing bladder cancer using a $\chi^2$-test and 95% confidence intervals. As shown on **Table 1**, the α1-adrenoceptor antagonist-exposed group had a bladder cancer cumulative incidence of 0.24% compared to 0.42% in the unexposed group, which yields a risk difference of -0.0018 and an unadjusted relative risk of 0.57 (95% CI: 0.30, 1.08) for α1-adrenoceptor exposed versus unexposed men. This risk ratio indicates that men treated with α1-adrenoceptor antagonists have a 1.76 times lower risk (p = 0.083) and a relative risk reduction of 43.3% meaning that 43.3% of the bladder cancer incidence in the control group might have been prevented by giving the medication. Interpretation of the risk difference indicates that 1.8 fewer bladder cancer cases developed per 1000 treated men; i.e., 7 to 8 additional bladder cancer cases would have been expected among the 4173 treated men in the Lexington VA cohort during the study period, had they not been exposed to quinazoline-based α1-adrenoceptor antagonists. This can be "translated" into 556 men needed to be treated with quinazoline α1-blockers to prevent one case of bladder cancer.

## IV. Discussion

Carcinoma of the bladder is a heterogeneous disease that progresses from carcinoma *in situ* to metastatic disease. Treating advanced metastatic disease has few options other than chemotherapy and radiation with median survival of one year (Hussain and James, 2003). The concept that the quinazoline-based α1-adrenoreceptor antagonists may play a role in both preventing tumor initiation as well as mitigating progression to metastatic disease by targeting anoikis and angiogenesis is of potentially significant therapeutic value. Experimental studies have established the apoptotic and anti-angiogenic action of quinazoline-based α1-adrenoceptor antagonists (doxazosin and terazosin) against bladder cancer cells, benign and malignant prostatic epithelial cells, as well as endothelial cells via a mechanism independent of α1-adrenoceptor action (Kyprianou and Jacobs, 2000; Benning and Kyprianou, 2002; Keledjianet al, 2005; Garrison and Kyprianou, 2006). *In vitro*, the quinazolines trigger anoikis in prostate cancer cells, directly inhibit endothelial cell adhesion, migration, invasion, and induce apoptosis of vascular endothelial cells by potentially targeting VEGF signaling (Keledjian and Kyprianou, 2003; Pan et al, 2003; Keledjian et al, 2005). *In vivo*, administration of doxazosin prior to tumor initiation has been shown to reduce prostate tumor weight and suppress metastasis in the transgenic adenocarcinoma of mouse prostate (TRAMP) model (Chiang et al, 2005). Furthermore, bladder tumors treated with terazosin exhibited a significantly decreased tissue vascularity and increased apoptic index compared to untreated bladder tumors (Tahmatzopoulos et al, 2005). These observations establish a biologically plausible role for the quinazolines as chemotherapeutic and chemopreventive agents of bladder cancer. The well-established safety profile and wide-spread clinical use of these FDA-approved drugs supports their suitability and feasibility as long-term chemopreventive agents (Lepor et al, 1992; Chapple et al, 1994).

The present study provides initial epidemiologic evidence of a potential chemopreventive effect for quinazoline α1-adrenoreceptor antagonists on human bladder cancer. Men exposed to quinazoline α1-adrenoreceptor antagonists had a cumulative bladder cancer incidence of 0.24% compared to 0.42% for unexposed men, yielding an unadjusted relative risk of 0.57 (95% CI: 0.30, 1.08).

**Table 1**. Two-by-two contingency table constructed using data the from VA population illustrating incidence of cancer in treated versus untreated men.

| Treatment group | Positive for Bladder Cancer | Negative for Bladder Cancer | Total | Cumulative incidence |
|---|---|---|---|---|
| A1-alpha Blocker-exposed | 10 | 4163 | 4172 | 0.0024 |
| Unexposed | 97 | 22868 | 22965 | 0.0042 |
| Total | 107 | 27031 | 27138 | |

| | |
|---|---|
| $\chi^2$ p value | 0.083 |
| Rirk Ration (95% Cl) | 0.567 (0.299, 1.077) |
| Risk Difference | -0.0018 |
| % Risk Difference | -43.3 |

Our inability to determine person-years at risk of developing bladder cancer for each unexposed control patient prevented the calculation of an incidence ratio and rate difference, and might be considered as an obvious limitation of this retrospective study. In addition, two sources of misclassification bias might have impacted the data; first, patients in the unexposed group may have been prescribed quinazoline α1-blockers outside the VA system that might interfere with the impact of the defined period of exposure (2 mos) to the drug in the study. Such a misclassification would result in underestimating the protective effect of the α1-adrenoceptor-antagonist treatment. Second, patients in either the exposed or unexposed groups may have received a diagnosis of bladder cancer outside the VA. However, this type of misclassification should have had a minimal effect on the relative attributable risks observed here, assuming equal bladder cancer misclassification rates in both groups of patients. In addition, we were unable to collect information about potential confounders or effect modifiers such as age, race and ethnicity, smoking history, alcohol consumption, and body mass index; co-morbidity of BPH, hypertension, obesity, and other diseases; and the use of other medications for the unexposed control group. As such, we were not able to assess confounding or effect modification by these variables on bladder cancer incidence.

The possible protective effect by α1-adrenoceptor antagonists on bladder cancer incidence (43% decrease), calls for nested case-control cohort studies to confirm that quinazoline-based α1-blockers are preventive agents of bladder cancer, prior to considering implementation of a randomized chemoprevention trial. Such studies should minimize misclassification bias, adjust for confounding factors, and assess effect modification by relevant covariates and longer drug-exposure. Ongoing retrospective studies at our center focus on investigating whether non-quinazoline α1-adrenoceptor antagonists (such as the sulfonamide, tamsulosin) can confer protection as well. The additional actions of these drugs including the ability of doxazosin to hinder chemotaxis in human monocytes (Kintscher et al, 2001), inhibit cell cycle progression in human coronary artery smooth muscle cells (Kintscher et al, 2000), and reduce cellular proliferation and migration of vascular smooth muscle cells (Hu et al, 1998), should be "factored-in" when designing multi-center chemoprevention trials. Considering the cancer cell types sensitive to the apoptotic effect of quinazolines *in vitro* (Kyprianou and Jacobs, 2000), the potential chemopreventive action of α1-adrenoreceptor antagonists in other human malignancies calls for investigation.

In summary, our findings offer some indication that treatment of men with quinazoline-based α1-adrenoceptor antagonists for BPH and/or hypertension could have a substantial additional public health benefit by reducing the incidence of bladder cancer by 43%. The translational link between inhibition of angiogenesis and induction of bladder tumor cell anoikis by quinazoline α1-adrenoreceptor antagonists, provides a biological basis for the development of effective chemoprevention strategies for bladder cancer. Nested case-control, cohort, and randomized trials are required to confirm or reject the preventive effect of this class of quinazolines on bladder cancer incidence.

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