Published in final edited form as:

J Urol. 2007 November ; 178(5): 2176–2180.

EFFECT OF α 1-ADRENOCEPTOR ANTAGONIST EXPOSURE ON PROSTATE CANCER INCIDENCE: AN OBSERVATIONAL COHORT STUDY

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Abstract

PURPOSE—Quinazoline-based α 1-adrenoceptor antagonists (α 1-blockers), doxazosin and terazosin, suppress prostate tumor growth via induction of apoptosis and reduction of tissue vascularity. We hypothesize that by inducing apoptosis and targeting angiogenesis these drugs serve as chemopreventive agents of human prostate cancer. We therefore performed an exploratory observational cohort study to assess whether α 1-blocker exposure affects the incidence prostate cancer and overall survival experience.

MATERIALS AND METHODS—The medical records of all male patients enrolled at the Lexington Veterans Administration (VA) Medical Center were searched to identify men treated with quinazoline-based α 1-adrenoreceptor antagonists between Jan 1, 1998 and Dec 31, 2002 for either hypertension and/or benign prostate enlargement. Medical records were subsequently linked to 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 to identify all incident prostate cancer cases diagnosed. All newly diagnosed, prostate cancer cases unexposed to α 1-adrenoreceptor antagonists in the total male VA population during this time period also were identified from the KCR's database. Measures of disease incidence, relative risk, and attributable risk were calculated to compare the risk of developing prostate cancer for α 1-blocker-exposed versus unexposed men. Kaplan Meier curves and Cox regression models were used to compare the overall survival between α 1-blocker-exposed and unexposed prostate cancer cases.

RESULTS—Our analysis revealed a cumulative incidence of 1.65% among the α 1-blocker-exposed men compared to 2.41% in the unexposed group. These data yield an unadjusted risk ratio of 0.683

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Support: This work was supported by the James F. Hardyman Urology Research Funds, the Markey Cancer Center at the University of Kentucky and an NIH/NCI grant R01-CA10757-03 (NK).

(95% CI: 0.532, 0.876) and risk difference of -0.0076 , which indicates that 7.6 fewer prostate cancer cases developed per 1000 exposed men. Exposure to quinazoline $\alpha 1$ -blockers thus may have prevented 32 prostate cancer cases among the 4070 treated men during the study period. Men exposed to quinazoline-based $\alpha 1$ -adrenoceptor antagonists therefore, have a 1.46 times lower relative risk and 31.7% lower attributable risk of developing prostate cancer than unexposed men. There was no association between $\alpha 1$ -adrenoceptor antagonist -exposure and overall patient survival.

CONCLUSIONS—These data suggest that exposure to quinazoline-based $\alpha 1$ -adrenoceptor antagonists significantly decreases the incidence of prostate cancer. This is the first epidemiological evidence to suggest that the apoptotic and anti-angiogenic effects of these drugs may prevent the development of prostate cancer.

Keywords

Prostate Cancer; $\alpha 1$ -adrenoceptor antagonists; prevention

INTRODUCTION

Prostate cancer is the most common cancer in men ¹. It is projected that 234,460 new prostate cancer cases will be diagnosed and 27,350 men will die of prostate cancer in 2006 ^{1, 2}. While there are several effective treatment options for localized disease including prostatectomy, radiotherapy and androgen ablation, therapeutic modalities available for metastatic prostate cancer have limited efficacy as a consequence of tumor progression to androgen-independent state, loss of apoptotic controls, and enhanced angiogenesis ^{3, 4}. Primary chemopreventive strategies targeting the signaling pathways which regulate apoptosis and angiogenesis in androgen-dependent and androgen-independent prostate tumors, represent attractive approaches for reducing the incidence, and the morbidity and mortality associated with prostate cancer.

The quinazoline $\alpha 1$ -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 $\alpha 1$ -adrenoreceptor antagonists exert their effect via a traditional mechanism that directly targets $\alpha 1$ -adrenoceptors of smooth muscle cells in the prostate gland and bladder neck ^{5, 6}, causing a decrease in smooth muscle tone and relieving bladder obstruction secondary to periurethral prostatic enlargement ⁷. Growing evidence from retrospective clinical studies, however, demonstrates that in addition to causing smooth muscle relaxation and a decrease in vascular pressure, the quinazoline-based $\alpha 1$ -adrenoceptor antagonists also can induce apoptosis and suppress angiogenesis in benign and malignant prostate tumors ^{8–10}. Pharmacologically-relevant levels of the two leading $\alpha 1$ -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 ⁸. The unique apoptotic action of the quinazolines proceeds via a mechanism that is independent of $\alpha 1$ -adrenoceptors, and affects both androgen-independent and androgen-dependent prostate cancer cells ^{3, 11, 12}.

Apoptosis induction proceeds via two distinct pathways, the extrinsic death-receptor pathway involving caspase 8 activation, and the intrinsic pathway involving mitochondrial cytochrome C and caspase 9 activation ^{13–16}. We recently demonstrated that the quinazoline-based $\alpha 1$ -adrenoceptor antagonist, doxazosin, activates the receptor-mediated pathway of apoptosis via Fas-associated death domain (FADD) and caspase-8 activation ¹⁷. Earlier evidence indicated that the quinazolines exert their apoptotic effect on both prostate epithelial and endothelial cells by promoting TGF- $\beta 1$ signaling via I κ B induction ³, and by inhibiting protein kinase B/Akt

activation to promote anoikis^{18–20}. Additional studies from this laboratory, as well as by other investigators, have documented the ability of the quinazolines to suppress tissue angiogenesis by targeting vascular endothelial growth factor (VEGF)^{21, 22}.

In this exploratory observational cohort study, we investigated whether the quinazoline-based α 1-adrenoceptor antagonists have a potential role as chemopreventive compounds of prostate cancer. Our retrospective analysis suggests that men treated with this class of α 1-adrenoceptor antagonists for either BPH or hypertension have a reduced risk of developing prostate cancer, suggesting that the apoptotic and anti-angiogenic action of these drugs at the cellular level may prevent clinical disease. This study provides the first epidemiological evidence that the quinazoline-based α 1-adrenoceptor antagonists, doxazosin and terazosin, may provide a substantial public health benefit by reducing the incidence of prostate cancer cases by 31.7%. The well-tolerated side effects of the quinazolines may enable their immediate use as chemopreventive agents of prostate cancer.

PATIENTS AND METHODS

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 prostate cancer cases diagnosed at the VA between 1998 and 2002 ($n = 623$) 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 for all 623 prostate cancer cases. All men who initiated treatment with one of the quinazoline-based α 1-adrenoceptor antagonists, doxazosin (1–8mg/day), prazosin (2–10mg/day), or terazosin (1–10mg/day) for either systemic hypertension or BPH between 1998 and 2002 ($n = 4,198$) were identified from the VA's electronic pharmacy records, and linked to the KCR's data base to identify all quinazoline α 1-blocker-exposed prostate cancer cases diagnosed at the VA greater than 2 months after treatment initiation ($n = 67$) and exposed patients without prostate cancer ($n = 4,003$). The assumption was made that prostate cancer cases diagnosed less than 2 months after initiating quinazoline α 1-blocker treatment ($n = 119$) already had cancer and, therefore, classified these patients as unexposed prostate cancer cases. The number of unexposed patients with prostate cancer ($n = 556$) and without prostate cancer ($n = 22,512$) subsequently were calculated by subtraction from the margin totals of a two-by-two contingency table (Table I).

Statistical Analyses

A secondary objective was to determine the relationship between quinazoline α 1-adrenoceptor antagonist exposure and overall survival among incident prostate cancer cases. A two-by-two contingency table of prostate cancer and non-cancer cases versus quinazoline α 1-adrenoceptor antagonist-treated and untreated men seen at the Lexington VA was constructed (Table I). These data were used to calculate measures of disease incidence (cumulative incidence), relative risk (risk ratio), attributable risk (risk difference), and % attributable risk (% risk difference) and to determine whether significant differences exist between α 1-blocker-exposed versus unexposed (control) men in developing prostate cancer using a χ^2 -test and 95% confidence intervals.

To determine whether significant differences exist between α 1-blocker-exposed versus unexposed prostate cancer cases and overall survival (OS), we performed Kaplan-Meier and Cox proportional hazard regression analyses on 608 of the 623 prostate cancer cases diagnosed at the Lexington VA during the study period. The full case series was reduced to 608 prostate cancers due to missing values for either age at diagnosis, race, disease stage, or tumor grade to accommodate Kaplan-Meier plots, univariate and multivariate Cox regression models with equal input numbers for each covariate. Overall survival was defined as the date of diagnosis until the date of death from any cause. Since covariates that differ significantly between the exposed groups may be potential confounders or effect modifiers of the association between the exposure and OS, descriptive statistics for age at diagnosis (dichotomized as $\leq$ or $>$ 68 years of age), race, disease stage, tumor grade, and tumor histology versus exposure group were examined to identify any significant differences with respect to these covariates by Pearson's χ^2 -test. Log rank tests for Kaplan-Meier survival analysis and Wald χ^2 -tests for univariate and multivariate Cox proportional hazard models were used to test for differences between groups stratified by age at diagnosis ($\leq$ versus $>$ 68 years or on a continuous scale), race (Caucasian versus non-Caucasian), disease stage (I & II versus III & IV), tumor grade (I & II versus III & IV), and/or exposure (quinazoline-based α 1-adrenoceptor antagonists exposure versus unexposed). Multivariate Cox proportional hazard regression modeling also was used to test for interactions between covariates. Hazard ratios and 95% confidence intervals were calculated from each Cox regression model to estimate the magnitude of covariate effects. All statistical analyses were performed using SAS version 9.1.3 (Statistical Analysis Software Institute, Cary, NC).

RESULTS

Quinazoline-based α 1-Adrenoceptor Antagonist Exposure Is Associated with Reduced Prostate Cancer Incidence

Our observational cohort study revealed that among 4070 men treated with quinazoline-based α 1-adrenoceptor antagonists at the Lexington VA Medical Center (between January 1998–December 2002), 67 men developed prostate cancer, two months or longer after treatment initiation (Table I). In contrast, 556 incident prostate cancer cases were diagnosed among 23,068 unexposed men during this study period. As shown on Table I, the α 1-adrenoceptor antagonist-exposed group, therefore, had a prostate cancer cumulative incidence of 1.65% compared to 2.41% in the unexposed group, which yields an unadjusted risk ratio of 0.683 (95% CI: 0.532, 0.876) and risk difference of -0.0076 for α 1-antagonist-exposed versus unexposed men. This risk ratio indicates that men treated with α 1-adrenoreceptor antagonists have a 1.46 times lower relative risk and 31.7% lower attributable risk of developing prostate cancer than unexposed men ($p > 0.005$). Interpretation of the risk difference indicates that 7.6 fewer prostate cancer cases developed per 1000 treated men, i.e. 32 additional prostate cancer cases would have been expected among the 4070 treated men in the Lexington VA cohort, had they not been exposed to quinazoline-based α 1-adrenoceptor antagonists.

Association of Age, Race, Stage, and Tumor Grade with Overall Survival following Exposure to Quinazoline-based α 1-adrenoceptor Antagonists

Comparison of the prostate cancer cases of 67 quinazoline-based α 1-adrenoceptor antagonist-exposed and 556 unexposed men diagnosed at the Lexington VA Medical Center during the study period revealed a significant difference between the exposed and unexposed cases with respect to age at diagnosis ($p = 0.0006$), but not race ($p = 0.6752$), disease stage ($p = 0.9098$), tumor grade ($p = 0.2795$), or tumor histology ($p = 0.9877$); this indicates that age might be a potential confounder/effect modifier of the association between α 1-blocker exposure and overall survival (Table II). The exposed cases were older than the unexposed cases (median age 72 vs 68 years). As summarized on Table II, while there is an association between age at diagnosis

and reduced overall survival, race, stage, or tumor grade are not associated with quinazoline exposure.

Kaplan-Meier curves, shown on Figure 1, reveal that exposure to quinazoline-based $\alpha 1$ -adrenoceptor antagonists ($p=0.3731$) is not associated with overall survival, while age at diagnosis ($p<0.0001$), race ($p=0.0581$), disease stage ($p=0.0841$), and tumor grade ($p<0.0001$) are associated with the overall patient survival. The following observations are derived from this analysis: a) older men died at 33 mos after diagnosis compared to 67 mos for younger men; b) non-Caucasian men died 26 mos after diagnosis vs. 49 mos for Caucasian men; c) men with advanced stage disease died 23 mos after diagnosis vs. 49 mos for early stage disease, and d) men with high grade tumors died 23 mos after diagnosis vs. 51 mos for low-grade tumors. Univariate Cox proportional hazard regression models confirm that exposure to quinazoline-based $\alpha 1$ -adrenoceptor antagonists ($p=0.3733$) had no impact on overall survival, while age at diagnosis ($p<0.0001$), race (borderline significance, $p=0.0613$), disease stage (borderline significance, $p=0.0868$), and tumor grade ($p<0.0001$) were associated with overall survival. Multivariate Cox regression modeling further demonstrated that when mutually adjusted for each other, age at diagnosis ($p<0.0001$), race ($p=0.0388$), and tumor grade ($p=0.0004$), but not exposure to quinazoline-based $\alpha 1$ -adrenoceptor antagonists ($p=0.8495$) are independent prognostic factors of overall survival.

DISCUSSION

Treatment of androgen-independent metastatic prostate cancer remains a major therapeutic challenge, which could potentially be circumvented with an effective primary chemoprevention strategy. In this regard, a new role is emerging for quinazoline-based $\alpha 1$ -adrenoceptor antagonists in both preventing tumor initiation as well as mitigating progression to metastatic disease by targeting anoikis and angiogenesis. Experimental studies have established the apoptotic and anti-angiogenic action of quinazoline-based $\alpha 1$ -adrenoceptor antagonists (doxazosin and terazosin) against benign and malignant prostatic epithelial cells, as well as endothelial cells via a mechanism independent of $\alpha 1$ -adrenoceptor action^{11, 17, 21}. *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^{20–22}. *In vivo*, administration of doxazosin prior to tumor initiation has been shown to reduce prostate tumor weight and suppress metastasis in the TRAMP (transgenic adenocarcinoma of mouse prostate) model²³. Taken together, these observations establish a biologically plausible role for the quinazolines as possible chemotherapeutic, as well as chemopreventive agents of prostate cancer. The well-established safety profile (primarily dizziness) and wide-spread clinical use of these FDA-approved drugs renders them readily feasible and attractive long-term chemopreventive agents^{24, 25}.

The present study determined the relationship between exposure to quinazoline $\alpha 1$ -adrenoceptor antagonists and prostate cancer incidence. This retrospective analysis provides the first epidemiologic evidence of a significant chemopreventive effect for quinazoline $\alpha 1$ -adrenoceptor antagonists on human prostate cancer. Other chemopreventive agents, such as selective estrogen receptor modulators, vitamin E and selenium, and anti-inflammatory agents, have yet to produce clinically significant results²⁶. Here we report that men exposed to quinazoline $\alpha 1$ -adrenoceptor antagonists have a cumulative prostate cancer incidence of 1.65% compared to 2.41% for unexposed men, which yields an unadjusted risk ratio of 0.683 (95% CI: 0.532, 0.876) and risk difference of -0.0076 . Significantly enough, there were 32 fewer prostate cancer cases developed among the 4070 $\alpha 1$ -blocker-exposed men (7.6 per 1000). Thus men exposed to $\alpha 1$ -adrenoceptor antagonists, have a 1.46 times lower relative risk and 31.7% lower attributable risk of developing prostate cancer than non- $\alpha 1$ -antagonists treated patients.

Interestingly, exposure to quinazoline-based α 1-adrenoceptor antagonists had no significant effect on the overall survival of prostate cancer patients. These findings support a role for quinazoline-based α 1-adrenoceptor antagonists as chemopreventive agents for prostate cancer, that could have a substantial public health impact. Several epidemiological criteria support our inference that the quinazolines serve as chemopreventive agents for prostate cancer including, biological plausibility, correct exposure-disease temporality, and a strong statistically significant exposure-disease association (HR=0.683, 95% CI; 0.532, 0.876). These observations were made possible because of the large size of the VA cohort (n = 27,138), which gave sufficient power to discern statistically significant differences in cancer incidence and, hence, estimate cancer risk between the exposed and unexposed groups of men. Finally, the entire male population seen at the VA during the time period was included in the cancer incidence analysis, eliminating case-control selection bias as a concern.

We recognize the exploratory nature of this cohort study and the potential limitations. First, our inability to determine person-years at risk of developing prostate cancer for each unexposed control patient prevented us from calculating an incidence rate ratio and rate difference. In addition, two sources of misclassification bias might have impacted the data: a) patients in the unexposed group may have been prescribed quinazoline α 1-blockers outside the VA system; and b) patients in the exposed/ unexposed groups may have received a diagnosis of prostate cancer outside the VA. One could argue however that this type of misclassification should have had a minimal effect on the relative/attributable risks observed in this retrospective study, assuming equal prostate cancer misclassification rates in the exposed and unexposed groups.

The protective effect by α 1-adrenoceptor antagonists on prostate cancer incidence (31.7% decrease in prostate cancer cases), calls for nested case-control cohort studies to confirm that quinazoline-based α 1-blockers are preventive agents of prostate cancer, prior to considering implementation of a randomized chemoprevention trial. Such studies should minimize misclassification bias, adjust for confounding or assess effect modification by relevant covariates and longer drug-exposure. Ongoing retrospective studies at our center focus on investigating whether non-quinazoline α 1-adrenoceptor antagonists (such as the sulfonamide, tamsulosin) can confer protection toward developing prostate cancer. Since doxazosin also hinders chemotaxis in human monocytes²⁷, inhibits cell cycle progression in human coronary artery smooth muscle cells²⁸, and reduces cellular proliferation and migration of vascular smooth muscle cells²⁹, the potential long-term adverse effects of these FDA-approved drugs on these cell populations (in different tissues and organs) should be evaluated before designing a multi-center chemoprevention trial for prostate cancer. Moreover the potential chemopreventive action of α 1-adrenoceptor antagonists in other human malignancies also merits pursuit, considering that human breast and bladder cancer cells exhibit apoptotic sensitivity to quinazolines *in vitro*¹². Lessons learned from the finasteride arm of the Prostate Cancer Prevention Trial revealed that men treated with finasteride had a lower prostate cancer incidence, but were more likely to have high-grade tumors³⁰. Here, we report that men exposed to quinazoline α 1-adrenoceptor antagonists have a lower incidence of prostate cancer, but there was no effect on the overall survival.

CONCLUSIONS

In summary, this is the first evidence to suggest that exposure to quinazoline-based α 1-adrenoceptor antagonists may protect men from developing prostate cancer. Thus treatment of men with quinazoline-based α 1-adrenoceptor antagonists for BPH and/or hypertension could have a substantial additional public health benefit by reducing the incidence of prostate cancer. Our data document a translational link between inhibition of angiogenesis and induction of prostate tumor cell anoikis by quinazoline α 1-adrenoceptor antagonists, and the development of an effective chemoprevention strategy for prostate cancer. Nested case-control, cohort, and

randomized prevention trials are required to confirm the chemopreventive effect of this class of α 1-adrenoceptor antagonists on prostate cancer.

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Abbreviations

BPH	benign prostatic hyperplasia
ECM	extracellular matrix, VEGF, vascular endothelial growth factor
VA	Veterans Affairs
TRAMP	Transgenic Adenocarcinoma of Mouse Prostate

Figure 1.

Kaplan-Meier curves for overall survival among prostate cancer patients unexposed to quinazoline $\alpha 1$ -adrenoreceptor antagonists versus unexposed (A), who were $\leq$ versus > 68 years of age at diagnosis (B), of Caucasian or non-Caucasian origin (C), had stage I & II or stage III & IV disease at diagnosis (D), and had grade I & II versus grade III & IV tumors at diagnosis (E) are shown.

Figure 2.

A plot of hazard ratios versus age at diagnosis is shown for patients with stage III & IV disease compared to patients with stage I & II disease. Hazard ratios were calculated from multivariate Cox regression model that included age at diagnosis, race, disease stage, tumor grade, and an interaction term for stage x age.

Table I

Measures of disease frequency and disease association between the α 1-alpha blocker-exposed and unexposed groups of men.

Treatment Group	Positive for Prost at e Cancer	Negative f or Prost at e Cancer	Tot al	Cumulative Incidence
α 1-alpha Blocker-exposed	67	400 3	407 0	0.0 165
Unexposed	55 6	2 2512	2 3068	0.0 241
Total	62 3	2 6515	2 7138	

χ^2 p value > 0.005

Risk Ratio (95% CI) 0.683 (0.53 2, 0.876)

Risk Difference -0.0 076

% Risk Difference-31.7

Table II

Descriptive statistics of age, race, stage, grade, and histology compared with exposure to α 1-adrenoreceptor antagonists for men with prostate cancer.

Covariate	Full Case Series (N=623)		χ^2 p-value	Reduced Case Series(N=608)**		χ^2 p-value
	Exposed	Unexposed		Exposed	Unexposed	
Age (Years)			0.0006			0.0005
≤ 68 (49.6, 50.5) *	20 (29.8)	289 (52.0)		20 (30.3)	287 (52.9)	
> 68 (50.4, 49.5) *	47 (70.1)	267 (48.0)		46 (69.7)	255 (47.0)	
Median (Range)	68 (50–89)	72 (46–99)		68 (50–89)	72 (46–99)	
Race			0.6752			0.6560
White (89.6, 89.3) *	61 (91.0)	497 (89.4)		60 (90.9)	483 (89.1)	
Other (10.4, 10.7) *	6 (9.0)	59 (10.6)		6 (9.1)	59 (11.0)	
Stage			0.9098			0.7458
1 (0.32, 0.33) *	0 (0)	2 (0.36)		0 (0)	2 (0.37)	
2 (83.9, 85.7) *	59 (88.1)	464 (83.4)		59 (89.4)	462 (85.2)	
3 (9.1, 9.4) *	4 (6.0)	53 (9.5)		4 (6.1)	53 (9.8)	
4 (5.3, 4.6) *	3 (4.5)	30 (5.4)		3 (4.5)	25 (4.6)	
Not Applicable (0.16) *	0 (0)	1 (0.18)				
Unknown (0.96) *	1 (1.5)	6 (1.1)				
Grade			0.2795			0.1514
1 (3.8, 3.9) *	3 (4.5)	21 (3.8)		3 (4.5)	21 (3.9)	
2 (72.2, 73.4) *	41 (61.2)	409 (73.6)		41 (62.1)	405 (74.7)	
3 (22.5, 22.5) *	22 (32.8)	118 (21.2)		22 (33.3)	115 (21.2)	
4 (0.16, 0.16) *	0 (0)	1 (0.18)		0 (0)	1 (0.18)	
Unknown (1.28) *	1 (1.5)	7 (1.3)				
Histology			0.9877			0.9469
Carcinoma, NOS (0.16, 0.16) *	0 (0)	1 (0.18)		0 (0)	1 (0.18)	
Small cell carcinoma (0.16, 0.16) *	0 (0)	1 (0.18)		0 (0)	1 (0.18)	
Adenocarcinoma, NOS (99.2, 99.5) *	67 (100)	551 (99.1)		66 (100)	539 (99.4)	
Mucinous adenocarcinoma (0.16, 0.16) *	0 (0)	1 (0.18)		0 (0)	1 (0.18)	
Infiltrating duct carcinoma (0.16) *	0 (0)	1 (0.18)				
Carcinosarcoma, NOS (0.16) *	0 (0)	1 (0.18)				

* (Row percent for complete case series, row percent for reduced case series.)

** Reduced case series was used for Kaplan-Meier and Cox regression analysis of overall survival.