

# RACIAL/ETHNIC DIFFERENCES IN UPPER-TRACT UROTHELIAL CANCER

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**Objectives:** Information on clinical characteristics, pattern of initial treatment and survival in patient with upper-tract urothelial carcinomas (UTUC) is scarce. Our study examined the racial/ethnic differences in patients diagnosed with incident UTUC.

**Design:** Observational study. The data analyses included: proportion and ANOVA for categorical and continuous variables, respectively; Kaplan-Meier method for calculating overall survival; and Cox-proportional hazards models for obtaining adjusted hazard-ratios.

**Setting:** Regions of the Surveillance, Epidemiology and End Results (SEER).

**Patients or Participants:** 16,702 incident UTUC patients identified from the SEER dataset 1988–2007 (14,192 White, 967 Hispanic, 718 African American and 825 Asian).

**Interventions:** None.

**Main Outcome Measures:** Race/ethnicity-specific distributions of demographics, tumor characteristics, patterns of initial treatment, and survival.

**Results:** African American and Hispanic patients were diagnosed at a younger age than Whites and Asians ( $P=.001$ ). Hispanics were more likely to be diagnosed with larger tumor size than Whites and Asians ( $P<.0001$ ). Asians were more likely to be diagnosed with advanced stage and higher tumor grade. Cox-regression revealed that Whites and Asians were significantly less likely to die after UTUC diagnosis than African Americans (HR=.78, 95% CI=.67–.91 and HR=.75, 95% CI=.61–.91, respectively; all  $P<.01$ ).

**Conclusions:** Our study found that Asians had worse tumor characteristics at the initial presentation than the other groups in this study, but that their risk of dying was lower. Further research is needed to include a larger number of Asian patients to examine subgroup differences and to confirm the paradoxical finding of higher survival with poor clinical characteristics. (*Ethn Dis.* 2012;22[3]:295–301)

**Key Words:** Race/ethnicity, Urothelial Cancer, Difference, SEER Program

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## INTRODUCTION

Over the last two decades, major advances in cancer screening, diagnosis and treatment have led to significant improvement in cancer survival. According to the US Centers for Disease Control's Office of Minority Health and Health Disparities, life expectancy and overall health have improved in recent years for most Americans.<sup>1</sup> Despite this improved survival, not all Americans are benefiting equally. Recent studies indicate that racial/ethnic disparities in cancer not only persist but are, in fact, worsening.<sup>2</sup> Racial/ethnic differences have been observed in every aspect of cancer, and in most cases minority populations such as African Americans and Hispanics have shown poorer outcomes than Whites.<sup>3,4</sup>

Current epidemiological information on upper-tract urothelial carcinomas (UTUC) involving the renal pelvis (RP) and ureter are scarce. The National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER, 1973–2005) data show that, over the past 3 decades, the incidence of UTUC has increased modestly from 1.88 to 2.06 cases per 100,000 person-years.<sup>5</sup> Researchers have pointed out analgesic abuse, especially phenacetin; smoking; occupational exposure to dye; and chronic infection as some risk factors of urothelial cancer.<sup>6,7</sup> Studies have shown that men, Whites and older people are more likely to suffer from UTUC.<sup>5</sup> This relatively rare malignancy accounts for

10% of all renal tumors and 5%–7% of all urothelial malignancies.<sup>8</sup>

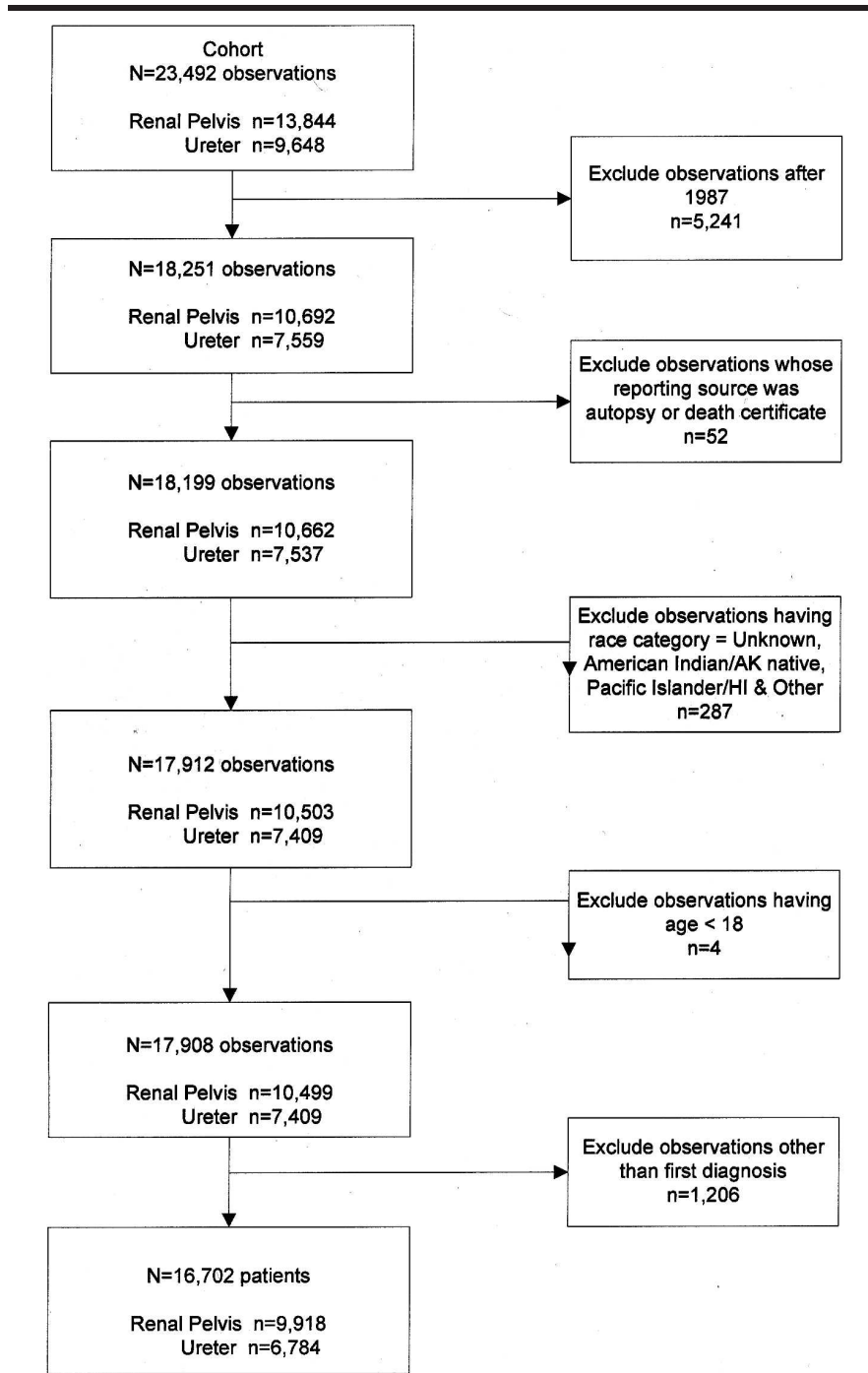
With the advancement of awareness and technology, an increasing number of UTUC cases are now diagnosed at the in-situ stage<sup>9</sup> but 30% to 40% of patients are still diagnosed with lymph-node metastasis, a stage where racial/ethnic differences are usually seen to be more pronounced.<sup>10,11</sup> One UTUC study reports that Whites are less likely to be diagnosed with nodal metastasis than others ( $P=.04$ ).<sup>12</sup> Another study revealed that White patients had significantly longer survival than African Americans ( $P<.01$ ), but no such differences were observed for Hispanics ( $P=.07$ ).<sup>5</sup> Researchers have also reported that Hispanics are similar to African Americans in terms of sociodemographic characteristics but are similar to Whites in terms of clinical presentation and survival for genitourinary cancer.<sup>13</sup> To our knowledge, the limited previous work on the epidemiology of UTUC has mainly focused on African Americans and Whites, and thus omitted Hispanic and Asian populations, which are rapidly increasing in the United States and represent 13% and 5% of the US population, respectively.<sup>14</sup>

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**Fig 1.** Flowchart showing results of the selection process during identification of participants from the Surveillance, Epidemiology and End Results database, 1988–2007, for this study

Since UTUC is a rare cancer, use of a large dataset is necessary to study the disease. We used the NCI-SEER dataset to provide a comprehensive view of racial/ethnic differences in demograph-

ics, tumor characteristics, pattern of the initial treatment, and survival for incident UTUC patients. Although racial/ethnic differences have been examined for some urothelial cancers, including

bladder and kidney,<sup>15–17</sup> little published data examine the disease course of UTUC in various racial/ethnic groups. Recognizing these limitations, we conducted this study to understand the racial/ethnic disparities in UTUC, treating Hispanics and Asians as separate groups in the analyses.

## METHODS

We analyzed NCI-SEER data (1988–2007), which recorded demographic and clinical data for the incident cancer cases of 12 states and represent about 10% of the US population.<sup>18</sup> We limited our analysis to 1988–2007 data, as information on lymph-node dissection (LND) was absent before 1988. Using the 1988–2007 data, we identified 18,251 new cases of UTUC, using the International Classification of Disease for Oncology codes for RP (ICD-O-3 C65.9) and ureter cancer (ICD-O-3 C66.9).<sup>19</sup> Our exclusion criteria included: 1) patient not identifiable as White, Hispanic, African American or Asian; 2) aged <18 years; 3) UTUC as non-primary cancer; and 4) diagnosed during autopsy. All these exclusion criteria resulted in a sample size of 16,702 cases in this study (see the flow diagram as Figure 1).

Information gathered for each patient included race/ethnicity, age at diagnosis, and sex. Tumor-related characteristics included tumor location, tumor size, cancer stage and grade. Cancer stage was recorded as in situ, local, regional, or distant, based on the SEER 2000 summary staging system.<sup>20</sup> Tumor grade was labeled as grade I, II, III, or IV and later collapsed into 2 categories as low grade (grades I and II) or high grade (grades III and IV). Information on lymph nodes included whether lymph nodes were dissected/removed; and, if removed, total number of nodes removed and number of positive nodes found. Positive lymph-node density was calculated as the

**Table 1. Sociodemographic characteristics (N=16,702) by race/ethnicity, % unless otherwise specified**

Characteristics	White	Hispanic	African American	Asian	Difference by group
	n (%)	n (%)	n (%)	n (%)	
	<b>14,192 (85.0)</b>	<b>967 (5.8)</b>	<b>718 (4.3)</b>	<b>825 (4.9)</b>	
Mean age at diagnosis (SD)	71.8 (11.2)	69.1 (12.6)	67.9 (12.3)	71.6 (10.6)	W,A>H,AA <sup>a</sup>
Sex: male	60.4	59.7	56.5	58.8	NS
female	39.6	40.3	43.6	41.2	
Location: renal pelvis	58.8	66.7	64.5	57.0	H,AA>W,A <sup>a</sup>
ureter	41.2	33.3	35.5	43.0	
Tumor size in cm, mean (SD)	3.63 (2.80)	4.40 (3.55)	3.94 (2.24)	3.83 (2.73)	H>W,A <sup>a</sup>
missing	57.0	58.3	62.7	54.2	
Stage: in situ	24.8	19.6	20.9	16.4	W>H,A <sup>a</sup>
localized	24.5	25.8	24.1	22.6	NS
regional	36.7	37.2	34.0	45.5	A>W,H,AA <sup>a</sup>
distant	8.9	12.2	12.5	11.5	H,AA,A>W <sup>b</sup>
un-staged	5.1	5.2	8.5	4.0	
Tumor Grade: low	38.8	37.8	34.7	30.2	
high	46.7	46.6	43.6	56.7	A>W,AA,H <sup>a</sup>
undetermined	14.5	15.6	21.7	13.1	
LND: no	81.5	81.5	80.8	75.0	
yes	17.4	17.0	17.3	24.5	A>W,H,AA <sup>a</sup>
missing	1.1	1.5	1.9	0.5	
Mean # of nodes removed <sup>d</sup> (SD)	4.6 (6.2)	5.8 (8.8)	5.4 (6.7)	6.4 (9.2)	A>W <sup>b</sup>
Positive nodes found <sup>d</sup>	32.1	35.8	29.6	36.0	NS
Mean # of positive nodes <sup>d</sup> (SD)	2.4 (3.2)	2.9 (3.2)	3.0 (1.9)	2.2 (2.9)	NS
Treatment received: surgery	83.4	81.4	74.9	81.9	W>AA,A <sup>c</sup>
radiotherapy	1.6	2.3	2.4	1.5	NS
both	3.4	3.3	4.2	5.9	A>W <sup>a</sup>
missing	11.6	13.0	18.5	10.7	

<sup>a</sup> P<.0001.

<sup>b</sup> P<.001.

<sup>c</sup> P<.01.

<sup>d</sup> If LND=yes.

W, White; H, Hispanic; AA, African Americans; A, Asians; LND, lymph-node dissection; NS, non-significant.

number of positive lymph nodes divided by total number of excised lymph nodes. We also gathered information about the type of treatment they received.

We tested differences in patient and disease characteristics by using ANOVA for continuous variables and a Chi-square test for categorical variables. Using the Kaplan-Meier product-limit method, we calculated separate analyses for overall survival stratified by race/ethnicity. The log-rank test was used to compare survival functions. Factors that were significant at the P<.2 level were included in the multivariate regression model. However, a tumor-location var-

iable was forced into the model to examine its effect. The Cox proportional hazard model was used to calculate the hazard ratio (HR). Interaction of race with some other covariates was also examined, using the Cox model. All statistical analyses were performed using SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

## RESULTS

Of the 16,702 UTUC patients, 14,192 were White (85%), 967 were Hispanic (5.8%), 718 were African Americans (4.3%) and 825 were Asians

(4.9%) (Table 1). Hispanics were diagnosed at a younger age (69.1 yrs) but with larger tumor size (4.4 cm) than their White and Asian counterparts (all P<.0001). Furthermore, Asian patients were less likely to be diagnosed with in-situ stage (P<.0001). Data also showed that lymph nodes were removed more often from Asian patients than other ethnic groups, and, on average, more lymph nodes were removed (6.4) from Asian patients (all P<.0001). We did not observe any racial/ethnic differences in positive lymph-node density.

Our data show that African American and Hispanic patients have significantly lower median survival than their

**Table 2. Race/ethnicity specific hazard ratios**

Characteristics	White	Hispanic	African American	Asian
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age at diagnosis, years	1.05 (1.04–1.05) <sup>b</sup>	1.05 (1.03–1.06) <sup>b</sup>	1.03 (1.02–1.05) <sup>b</sup>	1.05 (1.03–1.07) <sup>b</sup>
Sex: female, ref=male	.89 (.83–.95) <sup>b</sup>	1.15 (.88–1.49)	.62 (.45–.87) <sup>b</sup>	.91 (.69–1.20)
Location: ureter, ref=renal pelvis	.93 (.86–1.00)	1.02 (.74–1.42)	.84 (.56–1.27)	1.21 (.91–1.63)
Tumor size, cm	1.03 (1.02–1.04) <sup>b</sup>	1.02 (1.00–1.04)	1.08 (1.00–1.15) <sup>b</sup>	1.10 (1.05–1.15) <sup>b</sup>
Stage in situ	reference	reference	reference	reference
localized	1.26 (1.11–1.43) <sup>b</sup>	1.23 (.76–1.99)	1.10 (.63–1.92)	.86 (.48–1.53)
regional	2.00 (1.78–2.25) <sup>b</sup>	1.75 (1.10–2.77) <sup>b</sup>	1.85 (1.13–3.03) <sup>b</sup>	1.74 (1.05–2.88) <sup>b</sup>
distant	6.26 (5.42–7.23) <sup>b</sup>	8.26 (4.84–14.8) <sup>b</sup>	6.89 (3.66–12.9) <sup>b</sup>	4.98 (2.70–9.19) <sup>b</sup>
Grade low grade	reference	reference	reference	reference
high grade	1.18 (1.10–1.28) <sup>b</sup>	1.00 (.76–1.33)	1.46 (1.05–2.04) <sup>b</sup>	1.32 (.97–1.80)
Node removed: LND, ref=no LND	.88 (.79–.98) <sup>b</sup>	.85 (.56–1.31)	1.02 (.65–1.59)	1.07 (.71–1.59)
Node positive <sup>a</sup> , ref=neg. nodes	1.90 (1.64–2.20) <sup>b</sup>	2.16 (1.22–3.83) <sup>b</sup>	1.40 (.75–2.64)	1.45 (.89–2.36)
Treatment surgery	reference	reference	reference	reference
radiation	1.93 (1.51–2.47) <sup>b</sup>	2.86 (1.36–5.99) <sup>b</sup>	2.52 (.84–7.58)	4.68 (1.80–12.2) <sup>b</sup>
both	1.25 (1.08–1.46) <sup>b</sup>	1.10 (.62–1.97)	2.31 (1.24–4.31) <sup>b</sup>	1.60 (.98–2.59)

<sup>a</sup> If LND=yes.

<sup>b</sup> P<.05.

Notes: Factors that were significant in bivariate model at P<.2 level were included in the model for all 4 racial/ethnic groups. ‘Tumor location’ variable was forced into the model to examine its effect. LND, lymph-node dissection.

White and Asian counterparts (3.50, 4.25, 4.42, 4.83 years, respectively; P<.02). Table 2 shows that White and African American women were at lower risk of dying than their male counterparts (P<.05). Larger tumor size increased the risk of dying in all racial groups except Hispanics. High-grade tumor appeared to be significantly associated with higher risk of dying in Whites and African Americans only. However, LND increased survival only in White patients.

To further understand the relationship between race/ethnicity and survival, we performed Cox proportional hazard regression predicting survival (Table 3). It revealed that Whites and Asians were significantly less likely to die after UTUC diagnosis than African Americans (HR=.78, 95% CI=.67–.91 and HR=.75, 95% CI=.61–.91, respectively; all P<.001). We also observed a monotonic increase in HR with increasing stage. We also examined interaction effects of race by tumor size, stage and

grade on the survival rate; but neither of these effects was significant (all P>.05).

## DISCUSSION

To our knowledge, this is the first large-scale UTUC study to include Hispanics and Asians as separate groups in the analysis. Data from this study show that racial/ethnic differences do exist in terms of demographic and

clinical characteristics, the initial treatment and survival.

Results from our study showed that African American and Hispanic patients are diagnosed at a significantly younger age than Whites and Asians and support the findings of Karami et al, who showed that African Americans had earlier onset than Whites for the 12 most frequently occurring cancers.<sup>21</sup> Though the reason for this racial disparity is yet to be determined, some investigators claim that this disparity may be due to socioeconomic status, diet, nutrition, lifestyle, environmental stress, occupation and intrinsic biological and genetic differences.<sup>22,23</sup> However, it is well known that cancers arising at younger ages are usually more aggressive, found at a more advanced stage, and frequently result in unfavorable outcome compared with cancers that develop in older age.<sup>24</sup> The age at which cancer is diagnosed is also crucial for capitalizing on the maximum benefits of screening recommendations,

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*Data from this study show that racial/ethnic differences do exist in terms of demographic and clinical characteristics, the initial treatment and survival.*

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**Table 3. Overall hazard ratio by sample characteristics**

Characteristics	Hazard ratio (95% CI)
Race: African American	reference
Asian	.75 (.61-.91) <sup>b</sup>
White	.78 (.67-.91) <sup>b</sup>
Hispanic	.84 (.69-1.02)
Age at diagnosis, years	1.05 (1.04-1.05) <sup>b</sup>
Sex: female, ref=male	.89 (.83-.95) <sup>b</sup>
Location: ureter, ref=renal pelvis	.94 (.87-1.01)
Tumor size, cm	1.03 (1.02-1.04) <sup>b</sup>
Stage in situ	reference
localized	1.22 (1.09-1.37) <sup>b</sup>
regional	1.95 (1.76-2.17) <sup>b</sup>
distant	6.33 (5.55-7.22) <sup>b</sup>
Grade low	reference
high	1.19 (1.11-1.28) <sup>b</sup>
Node removed: LND, ref=no LND	.89 (.80-.98) <sup>b</sup>
Node positive <sup>a</sup> , ref= neg. nodes	1.87 (1.64-2.14) <sup>b</sup>
Treatment surgery	reference
radiation	2.29 (1.84-2.85) <sup>b</sup>
both	1.31 (1.14-1.50) <sup>b</sup>

<sup>a</sup> If LND=yes.  
<sup>b</sup> P<.05.  
LND, lymph-node dissection.

prevention programs, and outlining treatment strategies. Given the findings of significantly higher age of diagnosis in Asians than Hispanics and African Americans, our study adds new information to the existing body of literature.

We also noted significantly larger tumor size in Hispanics. Findings from prostate- and breast-cancer studies show that African Americans in general present with overall greater tumor size than Whites.<sup>25,26</sup> Our study extends this finding to Hispanics too. Larger tumor size may be attributed to this group’s lower access to advanced-quality imaging (eg, computed tomography, magnetic resonance imaging). Researchers have reported that tumor size is directly related to prognosis and, in general, larger tumors are associated with poorer survival.<sup>27</sup> This observation was supported by the findings of our study, in which larger tumor size was found to be associated with higher HR across all racial/ethnic groups. Our data support the need for early UTUC diagnosis, especially among Hispanics,

as these patients might have poor access and affordability to expensive cancer care and be more likely than other groups to go untreated.<sup>28</sup>

Though Asians were diagnosed more frequently with advanced-stage (regional and distant) and higher tumor grade (grades III and IV), paradoxically, they showed significantly higher median survival than others. This finding corroborates a US Centers for Disease Control report, in which Asian/Pacific Islanders fared better than others in terms of cancer survival.<sup>29</sup> However, survival variation could be influenced by many factors, such as comorbid conditions, cultural behaviors, and patient preferences.<sup>3,30</sup> Presentation of Asian patients with higher survival may reflect their better access to high-quality health care. It may be related to their higher annual income than other US groups, as well as their higher concentration in big cities, where advanced treatments are usually available from academic centers.<sup>31,32</sup> It also indicates that an appropriate, culture-specific, tailored

intervention is needed to increase cancer awareness for Asian communities to detect UTUC at an early stage.

Our study shows that, compared with other racial/ethnic groups, LND was done more often in Asians than in other ethnic groups; in addition, more lymph nodes were removed from them. This disparity could be attributed to more advanced-stage diagnosis (regional and distant) among Asian patients; LND is done to stage the disease more accurately, as the risk of lymph-node metastasis increases with advancing stage. However, in our study, LND improved survival only in Whites, which is in line with the findings of some previous bladder-, breast-, and colon-cancer studies.<sup>15,33,34</sup> Improved survival in LND and in node-negative cases among Whites may be due to the removal of more undetected micrometastases cases. But we were unable to determine how balanced these LND were (whether to undergo LND or number of nodes removed) by race/ethnicity, as they seem to be largely at the surgeon’s discretion. Our study also observed that, in only one third of cases, surgeons were removing lymph nodes from UTUC patients, which has also been reported by others.<sup>35</sup> In addition, absence of a definite standardized protocol/template for removing lymph nodes in UTUC patients and the introduction of endoscopic surgery have probably resulted in surgeons’ removing fewer lymph nodes these days.

Surgery, the gold-standard treatment, was undergone more often by Whites than African Americans and Asians. Radiotherapy plus surgery is usually offered mainly to patients with extensive disease, and our study showed that Asian patients received this more often than Whites. However, given the historic commitments of the medical establishment to principles of fairness, equity and distributive justice, the bias related to interpersonal perceptions, judgment, decision-making and behavior cannot be ruled out. In addition,



better survival in Asian patients could be attributed to more aggressive therapy, better response to therapy, or better compliance. Thus, the paradoxical finding of higher survival in Asians warrants further study.

Cox regression, after adjusting other covariates, revealed that African Americans were at higher risk of dying from UTUC than Whites and Asians. This finding matches observations from other cancer studies in which African Americans have consistently showed lower survival rates than Whites.<sup>36</sup> In our study Hispanics failed to show any significant differences in survival in comparison with Whites. This finding corroborates a study by Latini et al that reported Hispanics resemble Whites in terms of prostate-cancer presentation and survival.<sup>13</sup> Further studies are needed in other settings to confirm these findings.

Our study is not without limitations; SEER reports the findings of institutional pathology and not those of central histological review. The SEER database precludes a more detailed analysis of additional variables; thus, we could not include comorbid conditions, chemotherapy and type of surgery performed in our analysis. In addition, recent data indicate that sessile architecture, tumor necrosis, and lymphovascular invasion are also associated with UTUC survival.<sup>37</sup> While SEER data may not perfectly reflect national patterns, the SEER database is still the gold standard for cancer registries. Last but not least, Asian people included in our study do not (presumably) include homogeneous groups from Asia.

The results of our research indicate that demographics, disease characteristics, and survival disparities persist between races/ethnicities in UTUC. Our findings strongly suggest that data derived from other minority groups may not be equally applicable to Asians. Further research is needed to include larger numbers of Asian patients with different subgroups and more variables

to confirm the paradoxical findings of poor clinical characteristics with better survival. While there is no established screening test for UTUC, our findings call for more routine ureteroscopy, abdominal cross-sectional imaging or bladder-cancer surveillance (cystoscopy) regimens for all suspicious symptoms. Taken together, these interventions might contribute stage migration towards more in-situ stage lesions and improve survival, which, in turn, could reduce racial/ethnic differences.

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