

Original Article: Clinical Investigation**Incidence and survival variations of upper tract urothelial cancer in Taiwan (2001–2010)**Ming-Yen Lin,^{1,2} Sheng-Wen Niu,^{3,4} Wei-Ming Li,^{5,6,7} Huei-Lan Lee,⁸ Li-Tzong Chen,^{9,10,11} Wen-Jeng Wu^{5,6,7} and Shang-Jyh Hwang^{1,2,4,12}

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Abbreviations & Acronyms

APC = annual percent change
CI = confidence interval
CR = crude rate
DM = diabetes mellitus
ESKD = end-stage kidney disease
ICD-O-FT = International Classification of Diseases for Oncology, Field Trial Edition
LISA = local indicators of spatial autocorrelation
NHI = National Health Insurance
SR = standardized rate
UTUC = urinary tract urothelial carcinoma

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Objectives: To assess temporal patterns and regional differences in the incidence rate, and factors associated with survival of urinary tract urothelial carcinoma.

Methods: The medical records of 8830 patients with new diagnoses of urinary tract urothelial carcinoma in the years 2001–2010 were retrieved from Taiwan National databases. Temporal trends, regional disparity and related survival factors were evaluated using the Cochran–Armitage trend test, local Moran's *I* statistic and log-rank test, respectively.

Results: The annual urinary tract urothelial carcinoma incidence rates (standardized by age) were steady at approximately 3.14–3.41 per 100 000 person-years. Notably, women had a significantly higher annual urinary tract urothelial carcinoma incidence than men in most of the years studied (range of female-to-male annual standardized rate ratio: 2.08–3.25), and diabetes prevalence in urinary tract urothelial carcinoma increased significantly from 12.3% to 23.4% per year over the 10 years. High urinary tract urothelial carcinoma incidence cluster areas other than the latest endemic area of “blackfoot disease” were newly identified by local Moran's *I* statistic ($P < 0.05$). Furthermore, older age, male sex, end-stage kidney disease and more advanced tumor grade were associated with lower 5-year overall survival probabilities in the 2001–2015 cohort.

Conclusions: The incidence and survival of urinary tract urothelial carcinoma over the decade 2001–2010 were different according to population and regional features. Various urinary tract urothelial carcinoma screening, prevention, treatment and care plans should be developed depending on age, sex, comorbidity and area of residence.

Key words: geographic variation, incidence, survival, trends, upper tract urothelial carcinoma.

Introduction

UTUC is a rare and under-recognized malignancy with an incidence range of 1.2–4.7 cases per 100 000 person-years globally.^{1–9} Although exposure to smoking, alcohol consumption, aromatic amines, arsenic, aristolochic acid and so on have been considered as factors highly associated with UTUC development,¹⁰ identifying individuals with a high risk of UTUC is usually challenging. Smoking and alcohol consumption are usually related to other cancers, and the other specific exposures are quite difficult to assess. Aristolochic acid¹¹ and arsenic¹² have been linked with the development of UTUC in specific Asian populations; however, the long-term causal effects in humans are difficult to establish. Therefore, understanding the changes in the trends and distribution of UTUC incidence and survival according to various

human characteristics is crucial to infer new actions in the prevention, screening and most favorable treatment. The present study examined the temporal and spatial differences in the incidence and factors associated with survival of UTUC in Taiwan from 2001 to 2010.

Methods

Study population

We carried out the present retrospective observational study using data from the Health Promotion Administration, NHI Administration and Executive Yuan, Taiwan. The Taiwanese government established the National Cancer Registry in 1979 to monitor the incidence and mortality rate of various cancers, with hospitals with ≥ 50 beds required to report essential information, such as data on the personal characteristics, diagnosis and treatment of patients with cancer, using a standard format. The Taiwan Cancer Registry Annual Report database contains $>98\%$ of cancer patients whose cancer site, diagnosis date, tumor grade and treatments have been applied for several epidemiological studies.¹³

Incident rate and survival of UTUC

Patients newly diagnosed with UTUC in the years 2001–2010 were identified from the Taiwan National Cancer Registry Annual Report dataset using the ICD-O-FT codes 189.1 and 189.2 or the third edition of ICD-O codes C659 and C669. The UTUC diagnosis date was considered the index date in the present study. We collected patient characteristics namely age, sex, urbanization of residence and diagnosis year from the databases, categorizing the patients by age group (<45 , 45–54, 55–64, 65–74 and ≥ 75 years), sex (male and female), urbanization level (rural and urban) and diagnosis year (2001–2010). The definition of urbanization developed by Lui *et al.* was determined by assigning 1–7 ratings (1 for most rural; 7 for most urban) to townships based on the clusterings of their characteristics.¹⁴ We further calculated the average value of the township ratings within one county and classified the county as urban (ratings 1–3) or rural (ratings 4–7). The Taiwan population numbers in the middle of each year were obtained from the Directorate-General of Budget, Accounting and Statistics, Taiwan Executive Yuan. Deaths were ascertained from the National Death Registry database. Follow-up duration was calculated from the date of UTUC diagnosis to the date of death or the end of 2010.

Variation assessment

Sources of variation in disease rate generally include demographic factors (age and sex), time, and space. First, we evaluated demographic factors contributing to the differences in incidence rate by stratifying the patient's age and sex. Second, the annual incidence rate was standardized by the age distribution (<45 , 45–54, 55–64, 65–74 and ≥ 75 years) of the World Health Organization's 2000 standard population, and explored the temporal trend of UTUC by sex. Third, the geographic variations of incidence proportion were evaluated

by comparing proportions of 352 main townships, and because the township of the patient's residence cannot be obtained from the claim data, the township of the insurance registry was used instead. The approach has been proved to be a suitable application for patients with cancer.¹⁵ In addition, our previous works reported that DM and ESKD were the main factors associated with an excessive risk of bladder recurrence.¹⁶ We investigated the prevalence of diabetes and ESKD in an annual incident cohort to reflect changing trends of care burden in UTUC. Finally, some factors that might affect overall and cancer-specific survival, such as cohort period (2001–2003 and 2004–2005 years), age, sex, urbanization level of the living area (rural and urban), main comorbidity (hypertension, diabetes and ESKD) and tumor grade (low, intermediate, high, anaplastic, undermine), were assessed in survival analyses. Hypertension and diabetes were determined based on the ICD-9-Clinical Modification codes 401–405 and 250 appeared two or more times in ambulatory claims records or one or more times in inpatient claim records during the year before UTUC diagnosis. Patients who had undergone long-term dialysis before UTUC diagnosis were considered as having ESKD.

Statistical analysis

Age/sex-specific incident rates over the years 2001–2010 were calculated by dividing the aggregative number of incident cases in a specific age-sex category by the person-years of the mid-period population size for that category and multiplying the result by 100 000. Annual incidence rates were calculated by dividing the annual number of new UTUC cases diagnosed in a specific age-sex category by person-year of the mid-year population size for that category and multiplying the result by 100 000. The differences in age-standardized incidence rates between sex in each year were evaluated by the standardized rate ratio with 95% CIs, and tested by the Z-test. The annual percentage changes in the crude incident rate and standardized incident rate were estimated by a generalized linear model with a log-linear link and assuming Poisson distribution. The Cochran-Armitage trend test was carried out to access the shift of time trends in the incidence rates of UTUC and the prevalence rates of DM and ESKD across 10 years. To avoid overfluctuation of incidence rates in small areas, geographic incidence proportion was calculated by dividing the cumulative number of incident cases of each township during the years 2001–2010 by the person-years of the mid-period size of each township resident and multiplying the result by 100 000. We used Anselin's LISA analysis to access spatial autocorrelation and determine if UTUC incidence in the township is significantly similar or dissimilar from their neighbors. The LISA map through local Moran's *I* statistic suggests two classes of positive spatial clusters (high-high: townships with a high incidence surrounded by high incidences, low-low: townships with a low incidence surrounded by low incidences) and two classes of spatial outliers (high-low: townships with a high incidence surrounded by low incidences, low-high: townships with a low incidence surrounded by high incidences). The *P*-values of local Moran's *I* statistic were

obtained through the Monte Carlo procedure based on 9999 conditional randomizations.

Kaplan–Meier survival analysis was used to estimate the cumulative 5-year overall and cancer-specific survival probabilities in the 2001–2005 incidence cohort. The differences of survival probabilities between groups were evaluated by the log-rank test. In addition, multivariable analyses with a forced entry approach were also carried out by a Cox proportional hazards model. Statistical analyses were carried out using SAS 9.3 (SAS Institute, Cary, NC, USA), and graphs were made using Geoda 1.12 (GeoDa Press LLC, Chicago, IL, USA; geodacenter.github.io/download.html) and GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA).

Results

After selecting the first cancer registry record of each person ($n = 810\ 168$) after 2000, a total of 8830 patients (4039 men and 4791 women) with new diagnoses of UTUC in the years 2001–2010 were identified. The crude incident rates in the female population increased from 3.47 in 2001 to 4.89 per 100 000 person-years in 2010, an average annual 4.28% increase, whereas those in the male population showed a similar trend with an average annual 4.14% increase from 2.86 in 2001 to 4.04 per 100 000 person-years in 2010 (Table 1). Notably, the average incidence rate across the observed years remained approximately 1.25-fold significantly higher in the female than in the male population, even after controlling age influences. The female population represented notably higher UTUC standardized incidence rates than the male population, particularly in the older age group (≥ 65 years; Fig. 1). Consistently stable standardized incidence rates of UTUC were found in the overall (3.14–3.64 per 100 000 person-years from 2001 to 2010, $P = 0.84$ by the Cochran–Armitage trend test), male (2.84–3.22, $P = 0.79$) and female population (3.45–3.58, $P = 0.91$) throughout the study period (Fig. 2). The annual prevalence of diabetes was nearly double, increasing

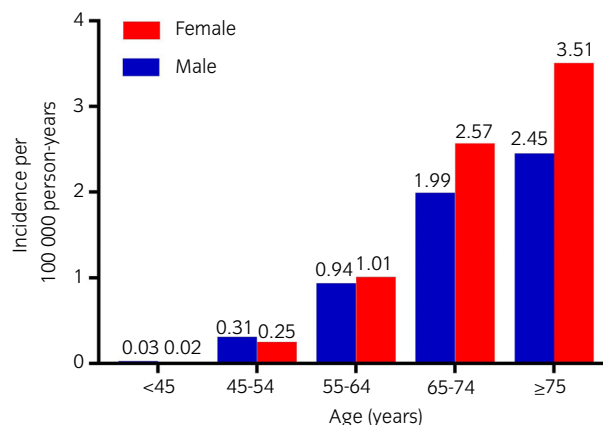


Fig. 1 Sex-specific incidence of UTUC by age in 2001–2010.

by 12.3% to 23.4% during the 10 years ($P < 0.001$ by the Cochran–Armitage trend test) (Fig. 3a), whereas the annual prevalence of ESKD showed a relatively stable trend between 2001 to 2010 (range 10.3–8.8%, $P = 0.22$) (Fig. 3b). Similar trends in the prevalence of diabetes and ESKD in UTUC were observed, even after stratifying by sex.

The median and interquartile range of the township-level 10-year cumulative UTUC incidence was 4.0 and 2.4–5.9 per 100 000 person-years, respectively. In spatial cluster analysis, the LISA results showed high-high clusters (hotspots) of UTUC incidence in the northern ($n = 2$), southwestern coast ($n = 13$), southwestern mountains ($n = 9$) and southern coast ($n = 2$) regions (Fig. 4; Table S1). After setting $P < 0.001$ as the significance level, these results were confirmed for the southwestern coast ($n = 13$) and southwestern mountainous ($n = 9$) regions (Table S2).

In the 2001–2005 cohort ($n = 3870$), 2349 patients died during the 5-year follow-up period, including 341 deaths

Table 1 Age-standardized incidence rate ratio of UTUC for sex (female-to-male) comparison

Calendar year	Female				Male				Standardized rate ratio (95% CI)	P-value
	Case	Person-years	CR†	SR†,‡	Case	Person-years	CR†	SR†,‡		
2001	379	10 924 270	3.47	2.84	327	11 416 850	2.86	3.45	2.56 (1.05–1.41)	0.005*
2002	383	10 999 642	3.48	2.68	318	11 463 530	2.77	3.40	3.09 (1.09–1.47)	0.001*
2003	416	11 062 427	3.76	3.14	382	11 500 236	3.32	3.54	1.70 (0.98–1.3)	0.05
2004	436	11 118 512	3.92	2.99	375	11 528 324	3.25	3.52	2.30 (1.02–1.35)	0.01*
2005	479	11 177 740	4.29	2.97	375	11 552 013	3.25	3.72	3.25 (1.09–1.43)	0.001*
2006	522	11 246 382	4.64	3.40	449	11 577 073	3.88	3.89	2.08 (1.01–1.3)	0.02*
2007	517	11 317 207	4.57	3.42	459	11 600 237	3.96	3.69	1.17 (0.95–1.22)	0.12
2008	553	11 380 137	4.86	3.09	425	11 617 559	3.66	3.77	3.04 (1.07–1.38)	0.001*
2009	543	11 446 859	4.74	3.20	459	11 631 543	3.95	3.55	1.62 (0.98–1.26)	0.05
2010	563	11 504 968	4.89	3.22	470	11 635 980	4.04	3.58	1.67 (0.98–1.26)	0.05
Estimated APC (95% CI)			4.28 (–6.11, 15.83)	1.69 (–10.06, 14.96)			4.14 (–7.26, 16.94)	0.68 (–10.12, 12.79)		

The estimated APC with 95% CIs was assessed by a generalized linear model with a log-linear link and assuming Poisson distribution. *Statistical significance that was tested by Z-test ($P < 0.05$). †Unit of incident rate: per 100 000 person-years. ‡Annual incidence rate was standardized by the age distribution (<45, 45–54, 55–64, 65–74, ≥ 75 years) of World Health Organization's 2000 standard population.

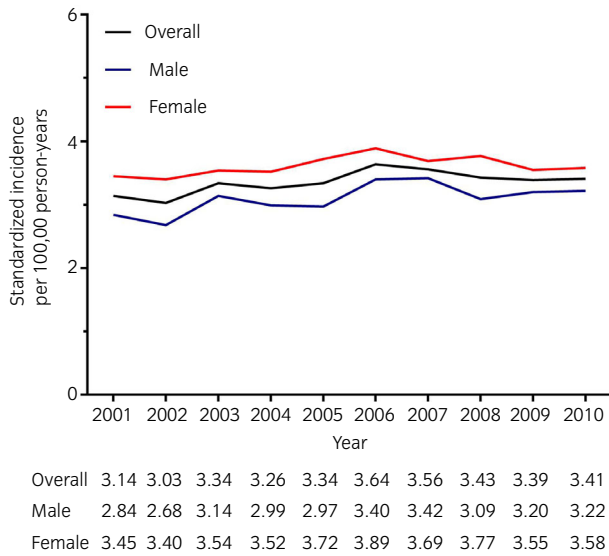


Fig. 2 Trends in age-standardized incidence rates for UTUC in 2001–2010. The annual incidence rate was standardized to the World Health Organization's 2000 standard population.

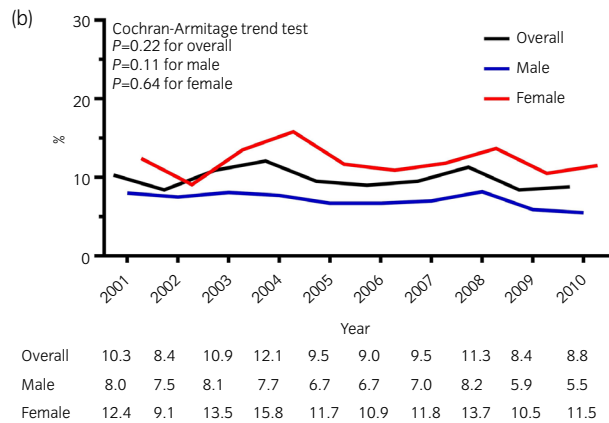
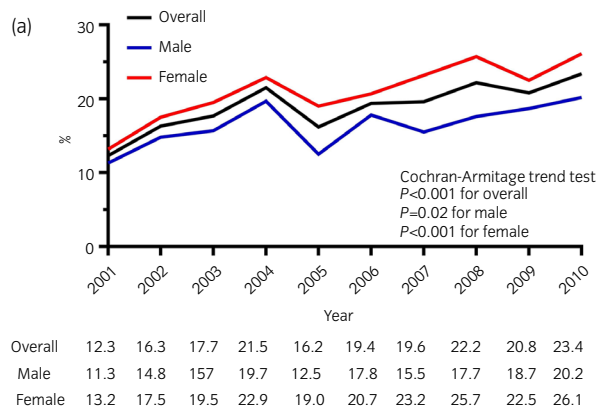


Fig. 3 Prevalence trend of the main comorbidity in patients with UTUC in 2001–2010. (a) DM and (b) ESKD.

caused by UTUC (Table 2). The cumulative overall survival probability was 48.0%, and older male patients living in a rural area with main comorbidities and more advanced tumor

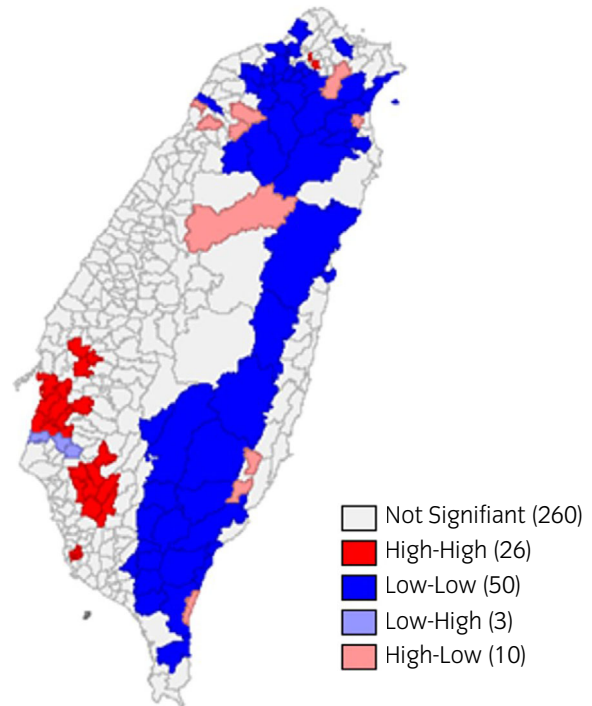


Fig. 4 Univariate local indicators of spatial association cluster maps for Taiwan UTUC incidence, 2001–2010. High-high represents that a township with high UTUC incidence is surrounded by neighbors with high UTUC incidence; low-low represents that a township with low UTUC incidence is surrounded by neighbors with low UTUC incidence; low-high represents that a township with low UTUC incidence is surrounded by neighbors with high UTUC incidence; and high-low represents that a township with high UTUC incidence is surrounded by neighbors with low UTUC incidence. The remaining 19 townships had no neighboring townships.

grades were associated with lower overall survival probability. In the multivariable analysis, older age, male sex, ESKD and more advanced tumor grade were significantly associated with higher mortality risk (Table 3). However, nearly 80% of the patients did not experience death caused by UTUC. Older age, hypertension and advanced tumor grade were factors associated with lower cancer-specific survival. Finally, age was the only factor associated with cancer-specific mortality in the multivariable analysis (Table 3).

Discussion

Although some risk factors for UTUC have been recognized, early detection of susceptible populations remains a challenge. To the best of our knowledge, this is one of the few studies that attempted to clarify UTUC epidemiological features in Asia, showing that women in Taiwan are more susceptible to UTUC, and diabetes prevalence in patients with UTUC has increased considerably. In addition, the study identified hotspot areas and factors associated with the 5-year overall and cancer-specific survival probabilities.

The present study showed that the stable annual age-standardized incidence of UTUC was similar to those reported in Asian countries^{5,9} and the USA,³ but different from other European countries^{6,7} and another report from

Table 2 Five-year survival probabilities in patients newly diagnosed with UTUC in the 2001–2005 cohort

	Case number	Overall			Cancer-specific		
		No. deaths	Survival probability	P-value	No. deaths	Survival probability	P-value
Overall	3870	2349	48.0	–	341	79.5	–
Age at diagnosis (years)				<0.001			<0.001
0–44	162	45	77.8		6	95.1	
45–54	441	155	73.7		18	94.4	
55–64	836	411	64.6		49	90.1	
65–74	1365	876	53.0		120	80.8	
≥75	1066	862	33.9		148	58.2	
Sex				0.002			0.37
Male	1777	1114	51.0		158	81.1	
Female	2093	1235	55.9		183	82.8	
Urbanization level				<0.001			0.05
Rural	1250	820	49.5		114	79.4	
Urban	2620	1529	55.6		227	83.2	
Cohort period (years)				0.01			0.15
2001–2003	2205	1391	54.0		199	81.1	
2004–2005	1665	958	53.2		142	83.3	
Comorbidity							
Hypertension				<0.001			0.01
No	2332	1325	56.0		201	83.6	
Yes	1538	1024	50.1		140	79.2	
DM				<0.001			0.13
No	3216	1899	54.9		285	82.6	
Yes	654	450	47.7		56	78.9	
ESKD				0.007			0.66
No	3472	2077	54.0		316	81.9	
Yes	398	272	50.8		25	83.4	
Tumor grade				<0.001			<0.001
Low	170	77	72.4		15	86.1	
Intermediate	837	427	67.0		46	89.9	
High	857	543	50.1		76	80.5	
Anaplastic	565	332	53.1		54	81.5	
Undermine	1441	970	46.0		150	76.8	

The cumulative 5-year survival probability was estimated using Kaplan–Meier survival analysis, and the difference between subgroups tested using the log-rank test.

Taiwan.¹⁷ Besides comparability due to different definitions of UTUC,¹⁷ the most recent study highlights that the wide range of imaging applications used for UTUC diagnosis might bring substantial increases in the incidence and diagnosis at different TNM stages.⁶ It is worth examining how imaging usage trends affect the current trend in UTUC occurrences and prognosis, particularly in Asian countries.

In contrast to data from other countries, the incidence of UTUC was considerably higher in women, particularly among the older population, suggesting that risk factors other than smoking play a significant role in UTUC development in Taiwan. The male incidence is higher in younger age groups, but reversed in older age groups, implying that the effects of sex-specific etiologies on UTUC incidence are heterogeneous by age. This could be attributed to the likelihood of being exposed to carcinogens and the latency period of certain sex-specific etiologies, hence, the evaluation of UTUC carcinogens exposure by sex and how they affect the latency periods are warranted.

Although the mechanisms underlying the susceptibility of women to UTUC remain undetermined, clinical

observations^{18–20} and the present findings strongly support that a particular carcinogen for UTUC, aristolochic acid, is a key factor causing these special epidemiological features. A recent hospital-based study further showed that >90% of patients with UTUC present with aristolactam-DNA adducts, and at least 30% of them have specific mutations (A > T) in TP53, further supporting aristolochic acid as a major cause of UTUC in Taiwan.²¹ Women might be more likely to be exposed to slimming regimens or Chinese medicines potentially containing aristolochic acid, and have a longer life expectancy for UTUC development than men. As a result, women in Taiwan are more vulnerable to UTUC. However, further research on this inference is required.

Geographic variation identification is a useful tool in generating new hypotheses for the relationship of specific exposures and diseases, but it has been less applied to study rare cancers with uncertain etiology. The southwestern coast region of Taiwan, a “blackfoot disease” endemic area, has a clustered high incidence of UTUC. Blackfoot disease is a type of peripheral vascular disease caused by long-term drinking of artesian well water containing a high concentration of arsenic. Arsenic

Table 3 Hazard ratios of 5-year overall and cancer-specific mortality in patients newly diagnosed with UTUC in the 2001–2005 cohort

	Overall		Cancer-specific	
	Adjusted hazard ratio (95% CI)	P-value	Adjusted hazard ratio (95% CI)	P-value
Age at diagnosis (years)				
0–44	1.00 [Reference]		1.00 [Reference]	
45–54	1.32 (0.90–1.93)	0.16	1.19 (0.43–3.25)	0.74
55–64	2.13 (1.49–3.06)	<0.001	2.00 (0.78–5.10)	0.15
65–74	3.04 (2.14–4.34)	<0.001	3.76 (1.51–9.38)	0.004
≥75	4.93 (3.46–7.04)	<0.001	9.28 (3.73–23.10)	<0.001
Sex				
Female	1.00 [Reference]		1.00 [Reference]	
Male	1.24 (1.12–1.36)	<0.001	1.25 (0.97–1.61)	0.08
Urbanization level				
Rural	1.00 [Reference]		1.00 [Reference]	
Urban	1.08 (0.98–1.19)	0.14	1.19 (0.92–1.56)	0.19
Cohort period (years)				
2001–2003	1.00 [Reference]		1.00 [Reference]	
2004–2005	1.12 (1.00–1.25)	0.05	0.70 (0.52–0.94)	0.02
Comorbidity				
Hypertension				
No	1.00 [Reference]		1.00 [Reference]	
Yes	1.06 (0.96–1.17)	0.26	1.22 (0.93–1.59)	0.15
Diabetes				
No	1.00 [Reference]		1.00 [Reference]	
Yes	1.13 (1.00–1.28)	0.04	0.83 (0.58–1.20)	0.33
ESKD				
No	1.00 [Reference]		1.00 [Reference]	
Yes	1.57 (1.36–1.82)	<0.001	1.25 (0.73–2.14)	0.42
Tumor grade				
Low	1.00 [Reference]		1.00 [Reference]	
Intermediate	1.09 (0.85–1.39)	0.50	0.70 (0.39–1.26)	0.24
High	1.62 (1.27–2.06)	<0.001	1.37 (0.79–2.39)	0.27
Anaplastic	1.53 (1.19–1.97)	0.001	1.49 (0.83–2.69)	0.18
Undermine	1.31 (1.02–1.69)	0.03	1.61 (0.90–2.88)	0.11

The results were obtained by multivariable Cox proportional hazards model.

exposure can also induce several human cancers, including skin, bladder, kidney, liver, prostate and lung cancer. A previous study found that with the installation of a municipal water supply from 1979 to 2003, the incidence of blackfoot disease slowly declined, but the area still had a high relative risk of bladder cancer compared with lung cancer, highlighting the need for the long-term tracking of the incidence of urinary cancers in this endemic area.²²

The other three novel hotspot areas of UTUC located outside the arsenic pollution area contribute additional possibilities such as soil, sources of tap water or other common exposures in explaining the unusually high incidence of UTUC within one area. A recent study strengthened this possibility by spreading crop soils and gardens that contain aristolochic acid I from Balkan endemic to non-endemic areas.²¹ Although the causes of UTUC are complex and diverse, it is suggested that urologists should select appropriate examinations for the differential diagnosis of urinary system diseases in older patients with overt hematuria based on their sex and residence history.

The overall 5-year overall survival probability in Taiwan is comparable with those reported in Western countries and

Japan,^{3,22,23} and is better than those reported in Australia.⁵ Tumor stage and age have been considered as key determinants in explaining the difference of UTUC outcomes within one country.^{24,25} Although patients with UTUC in Taiwan and China were significantly younger, typically female, and had a lower tumor stage than those in Japan and the USA, previous studies found similar prognoses between these countries, suggesting that international UTUC treatments and care are of comparable quality.^{23,26} In contrast to the findings of the present systematic review, men had a poorer overall survival rate, possibly because women with UTUC in Taiwan are healthier compared with those in other countries due to unique causes.²⁷ More international research exploring the influences of sex-specific etiologies and mechanisms on UTUC prognosis is required.

Although our previous study showed that chronic conditions accompanying UTUC substantially affected UTUC prognosis, the trends of chronic conditions in patients with UTUC have not yet been noted.¹⁶ In comparison with the trend of the proportion of ESKD, obviously the increasing trend of the proportion of DM reminds caregivers to focus not only on surgery-related complications, but also to incorporate the concept of extra cancer risk control in improving UTUC prognosis. The reasons for the persistently differing DM proportions between sexes in UTUC, which have gradually become larger in recent years, are unknown, but could partly be explained by the trends that elderly women have a higher prevalence of DM and tend to live longer than men; therefore, there is more opportunity to record greater morbidity within the observation period. Again, more research on the changes in morbidity trends is required.

Some limitations of the present study should be noted. First, our data source has inherent limitations, lacking detailed patient habits, tumor and sequential treatment data; therefore, it was not possible to describe these factors influencing UTUC incidence and survival in greater detail. Second, the causes and mechanisms of UTUC incidence and survival are complex, and the present results might not fully reflect individual variations or trends. Third, the updated data for the latest decade were unavailable, so the results might not completely represent the current situation. Finally, the special UTUC features in Taiwan might not be generalizable to other countries, hence, further cross-national studies to clarify etiologies or mechanisms causing these discrepancies between Taiwan and other countries are required. In the years 2001–2010, the annual incidence of UTUC was stably high in Taiwan. Female sex, older age and specific areas of residence were consistently related to higher UTUC incidence rates, whereas male sex, ESKD and more advanced tumor grade were associated with a lower 5-year overall survival, but not with cancer-specific survival. The present findings suggest that different UTUC screening, prevention, treatment and care plans should be developed based on these essential epidemiological features.

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Conflict of interest

None declared.

Approval of the research protocol

This study was approved by the institutional review board of Kaohsiung Medical University Hospital (KMUHIRB-20130089).

Informed consent

The requirement for informed consent was waived by the institutional review board of Kaohsiung Medical University Hospital, because all data were anonymized. All study procedures were carried out following the Declaration of Helsinki principle.

Registry and the Registration No. of the study/trial

Not applicable.

Animal studies

Not applicable.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Table S1. Townships in high-high clustering of upper tract urothelial cancer incidence rate by $P < 0.05$.

Table S2. Townships in high-high clustering of upper tract urothelial cancer incidence rate by $P < 0.001$.