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Associations between interventions for urolithiasis and urinary tract cancer among patients in Taiwan

The effect of early intervention

Chien-Liang Lin, MD[a,c,d], Wen-Tsung Huang, MD[a], Wen-Chou Fan, MD[b], Yin-Hsun Feng, MD[a], Chia-Ho Lin, MD[b], Chian-Shiung Lin, MD[b], Chih-Cheng Lu, MD[b], Tse-Chou Cheng, MD[b], Chao-Jung Tsao, MD[a], Sheng-Hsiang Lin, PhD[d,e,*]

Abstract

The aim of this study was to investigate cancer risk in patients with a history of urolithiasis and to determine whether intervention for calculi attenuated the risk of subsequent urinary tract cancer (UTC).

Using data from the National Health Insurance Research Database in Taiwan, we performed a nationwide cohort study enrolling participants (n = 42,732) aged > 30 years who were diagnosed with urinary tract calculi between 2000 and 2009. Age- and gender-matched insured individuals (n = 213,660) found in the health service records over the same period were recruited as the control group. The Cox proportional hazards model and competing risks regression model were used to examine the relationship between urolithiasis and UTC, as well as whether early intervention for urolithiasis decreased the subsequent cancer risk relative to late intervention.

Participants with a previous diagnosis of urolithiasis (n = 695) had a 1.82-fold (95% CI: 1.66–1.99, $P < 0.001$) increased risk of developing UTC. Furthermore, the risk of UTC associated with urolithiasis was higher in women (adjusted HR: 2.43, 95% CI: 1.94–3.05) than in men (adjusted HR: 1.72, 95% CI: 1.55–1.90). When stratified by cancer site, the adjusted HR for bladder, renal pelvis/ureter, renal, and prostate cancers were 1.94 (95% CI: 1.62–2.33), 2.94 (95% CI: 2.24–3.87), 2.94 (95% CI: 2.29–3.77), and 1.45 (95% CI: 1.27–1.65), respectively. Patients who received interventions for urolithiasis within 3 months of detection had a decreased risk of subsequent UTC (adjusted HR: 0.53, 95% CI: 0.40–0.71, $P < 0.001$).

The present study demonstrated that urolithiasis increased the risk of subsequent UTC, especially upper UTC. Hence, it is recommended that physicians administer the appropriate interventions as early as possible upon diagnosis of urolithiasis.

Abbreviations: CI = confidence interval, CRR = competing risks regression, EC = Enrollee category, ESWL = Extracorporeal shock wave lithotripsy, HR = hazard ratio, ICD = International Classification of Disease, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute, SD = standard deviation, UTC = urinary tract cancer, UTI = urinary tract infection, UUT = upper urinary tract, LUT = lower urinary tract.

Keywords: Cohort study, intervention, urinary tract cancer, urolithiasis

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[a] Division of Hematology and Oncology, [b] Division of Urology, Chi-Mei Medical Center, Liouying Campus, [c] Min-Hwei Junior College of Health Care Management Department of Nursing, [d] Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, [e] Biostatistics Consulting Center, National Cheng Kung University Hospital, Tainan, Taiwan.

[*] Correspondence: Sheng-Hsiang Lin, Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan (e-mail: shlin922@mail.ncku.edu.tw).

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1. Introduction

Urolithiasis is a vital public health issue that has gradually increased in prevalence, with an incidence of 4% to 20% in economically developed countries worldwide.[1] The variable incidence and prevalence of urolithiasis in different countries depends on dietary habits,[2] chronic diseases,[3] socioeconomic status,[4,5] and even climate.[6] In Taiwan, 8.93% of the general population > 20 years of age has experienced at least 1 episode of urolithiasis.[7] Although treatment has advanced significantly, the annual health care cost of resolving urinary tract calculi amounts to $2.1 billion in the USA.[8] This disease can lead to several complications, such as disability in daily life, increased risk of urinary tract infection, renal insufficiency, and even urinary tract cancer (UTC).

The debate on whether urolithiasis induces subsequent malignant changes has continued without a consistent conclusion for the last 4 decades. An epidemiological study of 2982 bladder cancer patients revealed an increased relative risk (RR) of bladder cancer in those with a history of urinary tract infection (RR: 1.6, 95% CI: 1.4–1.8) or bladder stones (RR: 1.8, 95% CI: 1.1–2.8), but not kidney stones, indicating that local chronic inflammation induced by infection or bladder stones may result in malignancy.[9] Similarly, another case-control study using the National Health Insurance Research Database (NHIRD) in Taiwan that enrolled 2086 bladder cancer cases found that men and women with bladder calculi had a 3.45- and 3.05-fold increased risk of developing bladder cancer respectively.[10] Using the same database, a separate study reported an increased odds ratio (OR: 3.18, 95% CI: 2.75–3.68) for kidney cancer, including transitional cell carcinoma (TCC) and renal cell carcinoma (RCC), in people with previous urinary calculi.[11] The largest cohort study using a national hospital database to date was performed in Sweden and revealed that patients with antecedent urolithiasis had a higher risk of renal pelvis/ureter cancer and bladder cancer after a 25-year follow-up.[12] In contrast, a Copenhagen case-control study revealed no elevation of cancer risk in patients with stones, except in women with kidney stones (RR: 3.7, 95% CI: 1.2–12.1).[13] Additionally, an Italian study using participants with pathologically confirmed TCC of the bladder reported nonsignificant odds ratios in patients with whole urinary tract calculi.[14,15] The aforementioned studies report variable results owing to differences in case selection, calculi sites, and patient demographics, but there is sufficient evidence to demonstrate that the risk of UTC is increased not only by infection-induced irritation, but also by urolithiasis-induced irritation that leads to local inflammation in the urinary tract.

We hypothesized that participants diagnosed with urolithiasis may be at an increased risk of subsequent UTC and that early intervention for urolithiasis may be associated with a reduced risk of UTC. To the best of our knowledge, the efficacy of interventions for urolithiasis that alleviate pain and decrease urinary tract complications have been established by several studies, but any effect on subsequent malignancy has yet to be demonstrated.[16] Therefore, the aim of our study was to investigate not only the relationship between urolithiasis and UTC, but also whether interventions for the disease, including extracorporeal shock wave lithotripsy (ESWL) and surgical methods, could attenuate the risk of UTC.

2. Materials and methods

2.1. Database

We used data from the Longitudinal Health Insurance Database 2005 (LHID2005), which was acquired from the NHIRD and provided by the National Health Research Institute (NHRI) in Taiwan. The NHIRD covers the 22.60 million of Taiwan's 22.96 million residents who are enrolled in the National Health Insurance (NHI) program, which was launched on March 1, 1995. The LHID2005 consists of 1,000,000 beneficiaries from the 2005 registry and was constructed from the NHIRD by the NHRI using a systematic sampling method. As such, the LHID2005 is representative of all NHI enrollees, and there are no significant differences in age, gender, geographic distribution, or annual turnover rate between the LHID2005 and the original NHIRD. For each beneficiary, the LHID2005 records gender, birth date, residential area, medical terms for any catastrophic illnesses suffered, as well as expenditure and details of ambulatory care orders by visit, inpatient orders by admission, and prescriptions dispensed at contracted pharmacies. No more than 3 and 5 diagnoses were obtained from the prescriptions provided at ambulatory visits and on admission, respectively. These data were recorded from 1996 to the end of 2011, except for beneficiaries who had died or were not yet born.

During the construction of the LHID2005, the NHRI scrambled patient identification numbers to protect beneficiaries' privacy and adhere to regulations for the protection of personal electronic data. Hence, our study was granted exemption from full review by the Institutional Review Board of the Chi-Mei Medical Center (Application number: 10206-E04).

2.2. Study sample and design

We performed a population-based cohort study and enrolled only beneficiaries aged > 30 years, owing to the extremely low incidence of urolithiasis in persons under the age of 30 in Taiwan.[17] The definition of urolithiasis group were participants, selected from LHID2005 beneficiaries, who were diagnosed with urolithiasis twice (ICD-9-CM codes: 592.0, 592.1, 592.9, 594.0, 594.1, 594.2, 594.8, and 594.9) during outpatient department visits that were accompanied by an ultrasound of the urinary tract, urine analysis, and kidney, ureter, and bladder (KUB) radiography or who were diagnosed with once of urolithiasis at admission between January 1, 2000, and December 31, 2009.[18] The index date of these participants was defined as the first day of diagnosis of urinary tract stones. Participants known to have a malignant disease (ICD-9-CM code: 140–239) before the index date were excluded. To prevent misclassification, participants who were diagnosed with UTC within 1 year of the index date were also excluded.

Participants in the nonurolithiasis group were selected from LHID2005 beneficiaries without urolithiasis, using frequency matching at a case:control ratio of 1:5 within the following strata: age, gender, and index date. The index date of the nonurolithiasis group was defined as the beginning of each calendar month matching with each urolithiasis subject.

We followed up with all participants until death, development of UTC, or the end of 2011. We also further classified instances of UTC as upper urinary tract (UUT) cancer (kidney, ureter pelvis, and ureter) or lower urinary tract (LUT) cancer (bladder, prostate gland, and urethra). Due to inherent differences between the treatment and nontreatment groups, such as varying severity of initial clinical manifestations, we divided participants in the urolithiasis cohort who had undergone intervention into early and late treatment groups to assess the cancer-free probability of both groups and to avoid confounding by indication.[19] Early treatment was defined as treatment administered anytime within 3 months following the index date, whereas late treatment was

administered any time after that. Intervention strategies for urolithiasis that we were interested in include ESWL, percutaneous nephrolithotomy, nephro-pyelolithotomy, ureterolithotomy, staghorn stone nephro-pyelolithotomy, ureteroscopic lithotripsy, retroperitoneoscopic or laparoscopic pyelolithotomy, and cystourethroscopy with removal of the ureteral calculus.

2.3. Covariates

In the NHI database, the residential area is used as a proxy to represent beneficiaries' health care affluence. In Taiwan, the most abundant health care resources are found in the northern area, followed by the central, southern, eastern, and offshore areas. In this study, we also used enrollee category (EC) and monthly income to estimate individual socioeconomic status.[20] Based on their occupation and source of income, participants in our cohort were classified into 1 of 4 ECs as follows: EC1 consisted of civil servants who were regularly paid, EC2 consisted of employees of private enterprises or institutions, EC3 consisted of self-employed individuals, other employees, and members of the farmer's or fishermen's associations, and EC4 consisted of low-income families or unemployed pensioners. Using population density and the percentages of residents working in agriculture, we classified urbanization into 3 levels: urban, suburban, and rural.

Comorbidities were considered only if the condition occurred in an inpatient setting, or if they appeared in 2 or more ambulatory care claims coded 1 year before and after the index date. Some comorbid chronic diseases that are known to influence the risk of UTC, including diabetes mellitus, coronary heart disease, renal disease, tobacco consumption disorder, obesity, and alcohol abuse, were selected for analysis. Patients with tobacco consumption disorder were defined as those who had requested outpatient aid to quit smoking (ICD-9-CM code: 305.1). Furthermore, factors including urinary tract infection, hydronephrosis, interstitial cystitis, schistosomiasis, and ureteral stricture were also considered.

2.4. Validation

We validated the ICD-9-CM codes used to identify diagnoses of urolithiasis and UTC using the claims database of the admissions and outpatient department at Chi-Mei Medical Center, Liouying campus, an 870-bed regional teaching hospital in southern Taiwan. Records from 200 participants' fitting our eligibility criteria for the urolithiasis group were randomly selected for validation. We required 2 conditions for a positive diagnosis of urolithiasis: first, the report of sonography, intravenous pyelography, and computed tomography scan were described in sure terms by a radiologist; second, patients whose report presented ambiguous diagnosis for urolithiasis had accepted intervention for calculi eventually. Of the 200 participants, 15 patient records showed no evidence of stones. To validate diagnoses of UTC, we randomly selected 200 patients with the corresponding ICD-9-CM codes (recorded once at admission and twice in the outpatient department) for histological confirmation of UTC. Pathology reports could not be obtained for 9 patients. The positive predictive values (PPV) for a true positive diagnosis of urolithiasis and UTC were 92.5% (95% CI: 88.9%–96.2%) and 95.5% (95% CI: 92.6%–98.3%), respectively.

In addition, we randomly selected 200 patients from the claims database of Chi-Mei Medical Center, Liouying campus, who had initially accepted ESWL or surgical intervention for urolithiasis between January 1 and December 31 2009. These patients' registry dates, which were declared to the Bureau of National Health Insurance by the Applications Department of Chi-Mei Medical Center, Liouying campus, were then compared with the true date of intervention from the claims database. The registry dates of the selected participants all corresponded to the first true day of intervention, thus obtaining 100% PPV for intervention start dates.

2.5. Statistical analysis

The baseline demographics of the cohort, including differences between the urolithiasis and nonurolithiasis groups in terms of residential area, urbanization level, occupation, income level, and comorbidities, were compared using the chi-square test. Cox proportional hazards regression analysis was used to calculate the difference in the adjusted hazard ratios (HRs) and 95% CIs of the risk of developing UTC between these 2 groups. Confounders, including age, gender, residential area, EC, monthly income, urbanization level, diabetes mellitus, congestive heart disease, tobacco use, obesity, alcohol abuse, hydronephrosis, ureteral stricture, and urinary tract infection, were used to adjust the HR. The HRs that violated the assumption of proportional hazards were calculated using a stratified Cox regression model. Furthermore, we used competing risks regression models to adjust for the competing risk of death and compute a more precise HR for UTC. The crude HR, adjusted HR, and competing risks regression (CRR) were calculated to compare the risk of UTC, stratifying not only by age and gender, but also by classifying the specific sites of UTC (including renal, pelvis/ureter, bladder, prostate, urethral, and unspecified). Finally, we used Cox proportional hazards regression analysis to compare the risk of subsequent UTC of those in the urolithiasis group who accepted early intervention, to those who accepted late intervention. All statistical analyses were performed using SAS 9.3 software (SAS Institute Inc., Cary, NC) except CRR (performed in R, using the R 3.2.0 package "cmprsk").[21,22]

2.6. Sensitivity analysis

Given the unmeasured confounding factors, a sensitivity analysis was performed using the R package "obsSens" to assess the potential range of HRs associated with exposure to calculi. By adding a hypothetical unmeasured confounder, we could observe which results were confounded by this add-on factor with various prevalence in the urolithiasis and nonurolithiasis groups.

3. Results

From the beginning of the study in 2000 to its end in 2009, 42,732 participants were diagnosed with urolithiasis, including 27,956 men (65.4%) and 14,776 women (34.6%). The prevalence of urinary calculi was the highest in Taiwanese individuals aged 40 to 59 years (51.75%). Age and sex distribution was equal between the urolithiasis and nonurolithiasis groups. However, the incidence of comorbidities such as diabetes, coronary heart disease, renal disease, obesity, urinary tract infection, tobacco and alcohol abuse, hydronephrosis, interstitial cystitis, schistosomiasis, and ureteral stricture were significantly different between the urolithiasis group and the nonurolithiasis group (Table 1). No participants in our cohort were diagnosed with schistosomiasis because it is not endemic in Taiwan. The median follow-up times in the urolithiasis group and nonurolithiasis group were 7.23 (IQR: 4.97–9.49 years) and 8.00 years (IQR: 5.50–10.50 years), respectively.

Table 1

Demographic characteristics of participants in the urolithiasis and nonurolithiasis groups.

Category	Subcategory	Urolithiasis group (n = 42,732) No. (%)	Nonurolithiasis group (n = 213,660) No. (%)	*P*
Male		27,956 (65.42)	139,780 (65.42)	0.995
Age, y	30–39	8965 (20.98)	44,825 (20.98)	1
	40–49	11,961 (27.99)	59,805 (27.99)	
	50–59	10,152 (23.76)	50,760 (23.76)	
	60–69	6423 (15.03)	32,115 (15.03)	
	≥70	5231 (12.24)	26,155 (12.24)	
Living area*	North	19,667 (46.03)	100,221 (46.91)	<0.001
	Central	11,210 (26.23)	49,090 (22.98)	
	South	10,463 (24.49)	57,628 (26.97)	
	East and Offshore	1390 (3.25)	6715 (3.14)	
Enrollee category	1	3543 (8.29)	18,313 (8.57)	<0.001
	2	14,995 (35.09)	76,583 (35.84)	
	3	17,234 (40.33)	79,200 (37.07)	
	4	6960 (16.29)	39,564 (18.52)	
Monthly income	NT$ ≤15,840	13,971 (32.69)	76,155 (35.64)	<0.001
	NT$ 15,841–25,000	16,662 (38.99)	78,651 (36.81)	
	≥NT$ 25,001	12,099 (28.31)	58,854 (27.55)	
Urbanization Level†	1 (most urbanized)	17,110 (40.04)	88,414 (41.38)	<0.001
	2	12,790 (29.93)	63,256 (29.61)	
	3 (least urbanized)	12,830 (30.03)	61,984 (29.01)	
Comorbidity				
	Diabetes mellitus	4468 (10.46)	16,644 (7.79)	<0.001
	CHD	1161 (2.72)	4417 (2.07)	<0.001
	Renal disease	2573 (6.02)	5433 (2.54)	<0.001
	Tobacco consumption disorder	311 (0.73)	987 (0.46)	<0.001
	Obesity	274 (0.64)	656 (0.31)	<0.001
	Alcohol abuse	542 (1.27)	1713 (0.80)	<0.001
	Hydronephrosis	18 (0.04)	30 (0.01)	0.001
	Urinary stricture	775 (1.81)	75 (0.04)	<0.001
	Interstitial cystitis	109 (0.26)	0	<0.001
	Schistosomiasis	0	0	–
	UTI	8481 (19.85)	9985 (4.67)	<0.001

Significant differences between groups in living area, enrollee category, urbanization level, and all comorbidities, $P < 0.001$.

CHD = coronary heart disease, UTI = urinary tract infection.

* There are 8 missing values for the living area.

† There are 8 missing values for the urbanization level.

Of the 42,732 participants with urinary tract calculi, 1.63% (553 men and 142 women; 695 total) were subsequently diagnosed with urinary tract neoplasm, with a mean of 4.61 years (SD: 2.59 years) from the index date. The incidence density rate of cancer in the urolithiasis and nonurolithiasis groups was 2.3 and 1.19 per 1000 person-years respectively, with the rate increasing by age (Supplementary Table 1, http://links.lww.com/MD/B452). The Cox regression model was calculated with confounders to obtain an adjusted HR of 1.82, with a 95% CI of 1.66 to 1.99. When stratified by the gender, the adjusted HRs in men and women were 1.72 (95% CI: 1.55–1.90) and 2.43 (95% CI: 1.94–3.05), respectively (Table 2). Using the CRR model, the adjusted HRs for men and women were 1.71 (95% CI: 1.54–1.89) and 2.42 (95% CI: 1.92–3.05), respectively. In the

Table 2

Multivariable-adjusted Cox regression models and multivariable-adjusted competing risks regression models hazard ratios for urinary tract cancer among the study participants during the follow-up years.

	Total		Male		Female	
Urinary tract cancer	Urolithiasis group n (%)	Nonurolithiasis group n (%)	Urolithiasis group n (%)	Nonurolithiasis group n (%)	Urolithiasis group n (%)	Nonurolithiasis group n (%)
Yes	695 (1.63)	1957 (0.92)	553 (1.98)	1708 (1.22)	142 (0.96)	249 (0.34)
No	42,037 (98.37)	211,703 (99.08)	27,403 (98.06)	138,069 (98.78)	14,634 (99.04)	73,634 (99.66)
Crude HR (95% CI)	1.97 (1.81–2.15)*	1	1.80 (1.63–1.98)*	1	3.16 (2.57–3.88)*	1
Cox model (95% CI)	1.82 (1.66–1.99)*,†	1	1.72 (1.55–1.90)*,†	1	2.43 (1.94–3.05)*	1
CRR model (95% CI)	1.81 (1.65–1.98)*,†	1	1.71 (1.54–1.89)*,†	1	2.42 (1.92–3.05)*	1

Adjustments were made for age, gender, geographic location, enrollee category, income, urbanization level, and comorbidities.

CI = confidence interval, CRR = Fine and Gray competing risks regression, HR = hazard ratio.

* $P < 0.001$.

† Using a stratified Cox regression model.

Table 3

Multivariable-adjusted Cox regression models and multivariable-adjusted competing risks regression models hazard ratio for urinary tract cancer among the study participants, stratified by gender and age.

	Total		Male		Female	
	Urolithiasis group n (%)	Nonurolithiasis group n (%)	Urolithiasis group n (%)	Nonurolithiasis group n (%)	Urolithiasis group n (%)	Nonurolithiasis group n (%)
30–39 years old						
Urinary tract cancer	31 (0.35)	62 (0.14)	23 (0.35)	52 (0.16)	8 (0.33)	10 (0.08)
Crude HR (95% CI)	2.72 (1.77–4.19)*	1	2.40 (1.47–3.92)*	1	4.41 (1.74–11.22)*	1
Cox model (95% CI)	2.31 (1.47–3.64)*,‡	1	2.07 (1.24–3.46)*	1	3.40 (1.21–9.58)†	1
CRR model (95%CI)	2.39 (2.40–3.85)*,‡	1	2.11 (1.28–3.46)*	1	3.19 (1.04–9.84)	1
40–49 years old						
Urinary tract cancer	72 (0.6)	183 (0.31)	57 (0.69)	145 (0.35)	15 (0.41)	38 (0.21)
Crude HR (95% CI)	2.16 (1.64–2.84)*	1	2.18 (1.60–2.96)*	1	2.10 (1.16–3.82)†	1
Cox model (95% CI)	1.72 (1.29–2.30)*	1	1.73 (1.25–2.39)*	1	1.61 (0.83–3.12)	1
CRR model (95%CI)	1.79 (1.34–2.49)*	1	1.86 (1.36–2.56)*	1	1.76 (0.85–3.62)	1
50–59 years old						
Urinary tract cancer	153 (1.51)	427 (0.84)	125 (2.02)	365 (1.18)	28 (0.70)	62 (0.31)
Crude HR (95% CI)	2.04 (1.69–2.45)*	1	1.96 (1.60–2.40)*	1	2.53 (1.62–3.96)*	1
Cox model (95% CI)	1.66 (1.37–2.03)*	1	1.68 (1.35–2.08)*	1	1.58 (0.97–2.57)†	1
CRR model (95%CI)	1.72 (1.42–2.12)*	1	1.83 (1.49–2.26)*	1	1.79 (1.12–2.85)†	1
60–69 years old						
Urinary tract cancer	222 (3.46)	582 (1.81)	180 (4.79)	510 (2.72)	42 (1.57)	72 (0.54)
Crude HR (95% CI)	2.15 (1.84–2.51)*	1	1.99 (1.68–2.36)*	1	3.34 (2.28–4.90)*	1
Cox model (95% CI)	2.00 (1.70–2.35)*,‡	1	1.92 (1.61–2.29)*	1	2.64 (1.74–3.99)*	1
CRR model (95%CI)	2.04 (1.73–2.41)*,‡	1	1.97 (1.66–2.34)*,	1	2.99 (1.97–4.53)*	1
Above 70 years old						
Urinary tract cancer	217 (4.15)	703 (2.69)	168 (5.25)	636 (3.98)	49 (2.41)	67 (0.66)
Crude HR (95% CI)	1.74 (1.49–2.03)*	1	1.50 (1.26–1.77)*	1	4.08 (2.82–5.90)*	1
Cox model (95% CI)	1.59 (1.35–1.86)*,‡	1	1.40 (1.17–1.67)*	1	3.32 (2.15–4.82)*	1
CRR model (95%CI)	1.67 (1.44–1.95)*,‡	1	1.46 (1.23–1.74)*	1	3.42 (2.35–4.98)*	1
Trend for age group						
Cox model	2.18 (2.10–2.26)*	1	2.28 (2.19–2.38)*	1	1.69 (1.54–1.86)*	1
CRR model	2.04 (1.98–2.11)*	1	2.27 (2.18–2.36)*	1	1.67 (2.12–3.30)*	1

Adjustments were made for age, gender, geographic location, enrollee category, income, urbanization level, and comorbidities.
HR, hazard ratio; CI, confidence interval; CRR, Fine and Gray competing risks regression
* $P < 0.001$.
† $P < 0.05$.
‡ Using a stratified Cox regression model.

urolithiasis group, we further found that men had a 2.72-fold (95% CI: 2.25–3.30) greater risk of UTC than women, whereas in the nonurolithiasis group, men had a 4.28-fold (95% CI: 3.74–4.91) greater risk than women (Supplementary Table 2, http://links.lww.com/MD/B452).

When stratifying by age in 10-year intervals, all age categories in the urolithiasis group had a higher risk of UTC than those in the nonurolithiasis group, with 30- to 39-year-olds having the highest risk levels, followed by 60- to 69-year-olds (Table 3). After further stratification by the gender, the risks were still higher in the urolithiasis group than in the nonurolithiasis group, except for HRs calculated using the CRR model for women aged 40 to 49.

Urolithiasis and nonurolithiasis cohorts were characterized according to the specific site of UTC (Table 4). The highest HRs returned by the CRR model were those of ureter/renal pelvis cancer (HR: 3.08, 95% CI: 2.35–4.04) and renal cancer (HR: 3.00, 95% CI: 2.34–3.84), whereas the HRs associated with bladder and prostate cancer were 2.05 (95% CI: 1.72–2.46) and 1.53 (95% CI: 1.34–1.73) respectively. Further classification of UTC to UUT and LUT cancers resulted in hazard ratios of malignancy of 2.85 (95% CI: 2.36–3.46) and 1.60 (95% CI: 1.44–1.78) respectively, using the CRR model (Supplementary Table 3, http://links.lww.com/MD/B452).

Of the 42,732 participants with urolithiasis, 12,694 had undergone intervention for calculi during the follow-up period up to the end of 2011. As described earlier, we further divided this treatment cohort into early intervention (n = 9084) and late-intervention (n = 3610) groups to compare their cancer-free survival. As expected, those treated early had significantly longer cancer-free survival than those with late treatment (adjusted HR: 0.53, 95% CI: 0.40–0.71, $P < 0.001$) (Fig. 1). When segregated by cancer sites, we found that early intervention was associated with longer survival in patients with bladder cancer (adjusted HR: 0.37, 95% CI: 0.25–0.57), renal cancer (adjusted HR: 0.54, 95% CI: 0.30–0.97), renal pelvic/ureter cancer (adjusted HR: 0.42, 95% CI: 0.23–0.74), and unspecific site of UTC (adjusted HR: 0.60, 95% CI: 0.43–0.85), but not in patients with prostate cancer (Supplementary Figure 1, http://links.lww.com/MD/B452).

Sensitivity analysis was performed to compute the trend of the adjusted HR for UTC, which was altered by the change in confounder prevalence in the urolithiasis and nonurolithiasis cohorts (Supplementary Figure 2, http://links.lww.com/MD/B452). For instance, when the unmeasured confounders were added for the nonurolithiasis group (prevalence = 1.0) but not for the urolithiasis group (prevalence = 0), the HR was 4.58, indicating a strong relationship with UTC. In contrast, when the unmeasured confounders were not added for the participants

Table 4

Multivariable-adjusted Cox regression models and multivariable-adjusted competing risks regression models hazard ratio for specific site of urinary tract cancer among the study participants.

	Total		Male		Female	
	Urolithiasis group n (%)	Nonurolithiasis group n (%)	Urolithiasis group n (%)	Nonurolithiasis group (%)	Urolithiasis group n (%)	Nonurolithiasis group (%)
Bladder cancer						
Yes	187 (0.44)	446 (0.21)	123 (0.44)	338 (0.24)	64 (0.43)	108 (0.15)
No	42,545 (99.56)	213,214 (99.79)	27,833 (99.56)	139,439 (99.76)	14,712 (99.57)	73,775 (99.85)
Crude HR (95% CI)	2.32 (1.95–2.75)*	1	2.02 (1.64–2.48)*	1	3.26 (2.39–4.44)*	1
Cox model (95% CI)	1.94 (1.62–2.33)*,†	1	1.77 (1.43–2.20)*,†	1	3.38 (1.70–3.34)*	1
CRR model (95%CI)	2.05 (1.72–2.46)*,†	1	1.89 (1.52–2.33)*,†	1	2.79 (2.00–3.90)*	1
Ureter cancer and renal pelvis cancer						
Yes	97 (0.23)	146 (0.07)	56 (0.20)	71 (0.05)	41 (0.28)	75 (0.1)
No	426,35 (99.77)	213,514 (99.93)	27,900 (99.80)	139,706 (99.95)	14,735 (99.72)	73,808 (99.9)
Crude HR (95% CI)	3.64 (2.81–4.70)*	1	4.28 (3.01–6.07)*	1	3.02 (2.06–4.42)*	1
Cox model (95% CI)	2.94 (2.24–3.87)*,†	1	3.57 (2.47–5.16)*	1	2.35 (1.55–3.55)*	1
CRR model (95%CI)	3.08 (2.35–4.04)*,†	1	3.90 (2.73–5.58)*	1	2.52 (1.68–3.77)*	1
Renal cancer						
Yes	108 (0.25)	185 (0.09)	62 (0.22)	119 (0.09)	46 (0.31)	66 (0.09)
No	42,624 (99.75)	213,475 (99.91)	27,894 (99.78)	139,658 (99.91)	14,730 (99.69)	73,817 (99.91)
Crude HR (95% CI)	3.24 (2.56–4.11)*	1	2.84 (2.09–3.87)*	1	3.96 (2.72–5.77)*	1
Cox model (95% CI)	2.94 (2.29–3.77)*	1	2.67 (1.94–3.66)*	1	2.50 (2.33–5.25)*	1
CRR model (95%CI)	3.00 (2.34–3.84)*	1	2.65 (1.93–3.64)*	1	3.72 (2.50–5.53)*	1
Prostate cancer‡						
Yes	312 (0.73)	1187 (0.56)	312 (1.11)	1187 (0.85)	0	0
No	42,420 (99.75)	212,473 (99.44)	27,894 (98.89)	139,658 (99.15)	14,776	73,883
Crude HR (95% CI)	–	–	1.46 (1.28–1.65)*	1	–	–
Cox model (95% CI)	–	–	1.45 (1.27–1.65)*,†	1	–	–
CRR model (95%CI)	–	–	1.53 (1.34–1.73)*,†	1	–	–
Urethral cancer						
Yes	1 (0.00)	7 (0.01)	1 (0.00)	7 (0.01)	1 (0.01)	0
No	42,731 (100)	213.653 (100)	32,721 (100)	139,770 (99.99)	14,775 (99.99)	73,883
Crude HR (95% CI)	0.76 (0.09–6.15)	1	–	–	–	–
Cox model (95% CI)	0.47 (0.05–4.15)	1	–	–	–	–
CRR model (95%CI)	0.58 (0.09–3.81)	1	–	–	–	–
Unspecific site						
Yes	37 (0.09)	56 (0.03)	21 (0.08)	34 (0.02)	16 (0.11)	22 (0.03)
No	42,695 (99.91)	213,604 (99.97)	27,935 (99.92)	139,743 (99.98)	14,760 (99.89)	73,861 (99.97)
Crude HR (95% CI)	3.62 (2.40–5.49)*	1	3.40 (1.97–5.86)*	1	3.96 (2.08–7.55)*	1
Cox model (95% CI)	2.93 (1.89–4.56)*	1	3.18 (1.81–5.60)*	1	2.53 (1.25–5.14)*	1
CRR model (95%CI)	3.02 (1.96–4.64)*	1	3.26 (1.93–5.50)*	1	2.60 (1.24–5.48)*	1

Adjustments were made for age, gender, geographic location, enrollee category, income, urbanization level, and comorbidities.

CI = confidence interval, CRR = Fine and Gray competing risks regression, HR = hazard ratio.

* $P < 0.001$.

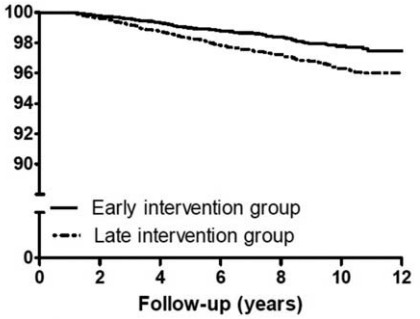
† Using a stratified Cox regression model.

‡ We only presented crude HR, Cox model, and CRR model of prostate cancer in men.

in the nonurolithiasis group (prevalence = 0) but were added for the participants in the urolithiasis group (prevalence = 1.0), the HR was < 1. Most of the HRs in different situations were > 1.0.

4. Discussion

We performed this population-based nationwide study to examine the association between urinary calculi and UTC because previous studies reported conflicting results. Our data revealed that participants with previous urolithiasis had a 1.82-fold higher risk of subsequent UTCs, particularly bladder, ureter/pelvis, prostate, and renal cancers, compared to participants without a history of urinary tract calculi. In our cohort, the peak incidence of urolithiasis occurred in 40- to 49-year-old participants, with a male-to-female ratio of 1.89. These figures are comparable with that of the general global population,[23] although a previous study has reported a higher incidence of upper urinary tract calculi in Taiwan.[18] To the best of our knowledge, this current study is the first to demonstrate that early treatment for urolithiasis could attenuate the risk of subsequent malignant formation. A prospective trial to evaluate the timing of intervention for calculi, which would affect cancer risk, could not be conducted because of ethical restrictions. As expected, patients who accepted intervention for urolithiasis within 3 months of the date of diagnosis had longer cancer-free survival than those who began treatment 3 months or longer post-diagnosis (Fig. 1). A similar study in Taiwan previously demonstrated that participants with a history of urolithiasis had an increased risk of all cancers, including prostate, bladder, and kidney cancers.[24] Using the same database, we further integrated death as a competing risk into the regression models to investigate the relationship between urolithiasis and UTC with greater accuracy. The largest study designed to illustrate the relationship between urinary calculi and cancer was a cohort study in Sweden that was



Number at risk							
Early intervention	9084	9000	6646	4389	2255	1182	3
Late intervention	3610	3590	3439	3115	2531	1398	1

Figure 1. Urinary tract cancer-free rate of early and late-intervention groups (adjusted hazard ratio: 0.53; 95% CI: 0.40–0.71, $P < 0.0001$).

limited to hospitalized patients with a diagnosis of urolithiasis since 1965; the follow-up period for this study lasted up to 25 years.[12] Participants in the Swedish study with renal pelvis/ureter cancer and bladder cancer had significantly higher standardized incidence ratios associated with previous urolithiasis, whereas those with renal cell cancer did not. In addition, women with urinary tract calculi had a higher risk of subsequent epithelial cell carcinogenesis compared to men, which is consistent with our present results. When we compared participants with UTC between the urolithiasis and nonurolithiasis groups and stratified the results by gender, we found that women had a greater risk of developing subsequent UTC, indicating that the influence of urolithiasis on subsequent UTC was more prominent in women. This may be caused by the fact that a shortened urethra in females is associated with an increased risk of infection by certain pathogens, which can induce struvite (infection-related) stone formation.[25,26] Nevertheless, when we directly compared men and women with UTC, regardless of whether or not they had a history of urolithiasis, we found that men had a higher risk of developing UTC. This implied that men were exposed to more risk factors for UTC formation than women were.

Kantor et al[9] reported that the risk of bladder cancer increased concomitantly with the frequency of urinary tract infection (UTI) and the presentation of bladder stones, which implied that a greater degree of irritation enhances the odds of developing cancer. In addition, the observation that kidney stones had no influence on the risk of bladder cancer indicated that it was local irritation that created regional inflammation, which then led to carcinogenesis. This phenomenon has been observed in animal models, where hyperplasia in the urinary tract, dysplasia, and even neoplasms could be induced by urolithiasis through specific diet conditions.[27–30] For example, in a study performed in the 1970s, the implantation of paraffin wax pellets into mouse bladders was shown to induce calculi, which was associated with an increased incidence of subsequent tumors.[31] In present study, we found that the UUT was more susceptible to urolithiasis-related cancer compared to the LUT, which is a reasonable finding given the higher incidence and prevalence of urolithiasis at the kidney, renal pelvis, ureter and bladder reported in most parts of world,[1] including Taiwan.[18] This may be due to chronic inflammation induced by the retention of stones in the relatively long ureter, which runs from the renal pelvis to the bladder. Similarly, the low or nonsignificant risk of prostate and urethral cancer related to urolithiasis observed in our study may be related to the rapid passage of stones beyond the bladder, via the relatively short urethra.

With regard to the differences between early and late-intervention cohorts, 3 groups of patients with clinical presentations of urolithiasis should be described. The first group consists of patients who have urolithiasis with complications, such as hydronephrosis, urinary tract infection or obstruction, and would accept intervention immediately after a definite diagnosis. The second category of urolithiasis patients present intermittent symptoms that wax and wane depending on the location of calculi, especially when stones pass via the ureter. Thus, intervention for these patients is not urgently required. The third group consists of patients who are given an incidental diagnosis of urolithiasis, and should receive medicine or medical observation until symptoms present. The early intervention cohort tended to be comprised of the first 2 groups, whereas the late-intervention cohort was comprised of the latter 2 groups. Thus, the early intervention group suffered from a higher risk of inflammation and infection compared to the late-intervention group, indicating that we may have underestimated the risk.

There were some limitations in the present study. First, occupational dye exposure and the exact degree of smoking of each participant, which are well-known causes of UTC, were not available in the NHIRD. Furthermore, participants' height and weight were also not available for the evaluation of BMI. Though obesity and alcohol usage were taken into account, only the extremely severe cases were registered in the claims data. Thus, we performed a sensitivity analysis to take into account any potential unmeasured confounding factors. Second, because pathology reports and stone component data were unavailable in the NHIRD, we were unable to identify the specific cancer histologies that were more strongly associated with the various types of stones. Third, there was a surveillance bias where an increased frequency of outpatient visits by participants who had urinary stones may have increased the probability of detecting UTC. Fourth, differences in the baseline condition between the early and late-intervention cohorts introduced a selection bias. Fifth, in Fig. 1, the difference in the follow-up period between the early and late-intervention cohorts may have influenced the length of cancer-free survival; screening bias from a longer follow-up time in the late-intervention cohort compared to the early intervention cohort may have led to an overestimation of the cancer risk in late-intervention group. Finally, the post-lithotripsy status of the patients (e.g., completely clear, residual fragmented stones, or calculus relapse) was unknown. In general, the success of 1 ESWL treatment was as high as 80%,[32] and among patients with residual stones, 21.4% needed retreatment or invasive intervention.[33] Depending on size and site, residual stones may regrow, become silent, or be spontaneously passed via the urinary tract, all of which may in turn affect the cancer-free rate.

If residual calculi after intervention play a pivotal role in subsequent UTC, then further study of such a phenomenon is warranted. In addition, stone composition (e.g., calcium oxalate, uric acid, magnesium ammonium phosphate, and ammonium acid urate) is influenced by etiology, metabolic status, and environment, and should be taken into account for further studies.

5. Conclusion

In the present study, we found that patients with a antecedent diagnosis of urolithiasis are at an increased risk of developing

subsequent UTC compared with the general population, and that the most common calculi-related malignancies occur at the kidney, ureter, bladder, and prostate gland. In addition, women have a higher risk of developing subsequent urolithiasis-related UTC compared to men. These findings suggest that early intervention for urolithiasis may reduce the risk of UTCs.

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