Journal of the Formosan Medical Association (2015) 114, 52–57

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Increased risk of urothelial cancer in young and middle aged patients with end-stage renal disease

Shuo-Meng Wang [a,b], **Ming-Nan Lai** [c], **Pau-Chung Chen** [b], **Jung-Der Wang** [d,e,*]

[a] *Department of Urology, National Taiwan University Hospital, Taipei, Taiwan*
[b] *Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University, Taipei, Taiwan*
[c] *Department of Statistics, Feng Chia University, Taichung, Taiwan*
[d] *Department of Public Health, National Cheng Kung University Medical College, Tainan, Taiwan*
[e] *Departments of Internal Medicine and Occupational and Environmental Medicine, National Cheng Kung University Hospital, Tainan, Taiwan*

Received 18 August 2013; received in revised form 5 October 2013; accepted 25 October 2013

KEYWORDS
end-stage renal disease;
standardized incidence ratio;
upper tract urothelial cancer;
urothelial cancer

Background/Purpose: End-stage renal disease (ESRD) may increase the likelihood of malignancy. The aim of this study is to evaluate the characteristics of increased urothelial cancer (UC) risk in patients with ESRD in Taiwan by a population-based study.
Methods: The standardized incidence ratios (SIRs) for UC among a registered cohort of ESRD in Taiwan during 1997–2002 were calculated using reimbursement data obtained from the Bureau of National Health Insurance (NHI), with the incidence rates of UC in the general population as the reference.
Results: During the study period we identified 58,739 patients with ESRD, 20,939 patients with UC, and 1305 patients with ERSD and UC. Among the 1305 patients with both diseases, 687 developed UC after ESRD had been diagnosed. Using the general population as the reference group, SIRs were 12.9 [95% confidence interval (CI)]: 12.0–13.9) for all UC cases, 13.9 (95% CI: 12.4–15.0) for bladder cancer, 11.9 (95% CI: 8.6–16.0) for renal cell carcinoma, and 11.6 (95% CI: 10.1–13.1) for upper tract urothelial cancer.
Conclusion: Patients with ESRD are at increased risk for UC in Taiwan, especially women age 50 years and younger. Early and lifelong surveillance of UC is recommended after diagnosis of ESRD.

* Corresponding author. No. 1, University Road, Tainan 701, Taiwan.
E-mail address: jdwang121@gmail.com (J.-D. Wang).

0929-6646/$ - see front matter
http://dx.doi.org/10.1016/j.jfma.2013.10.022

Introduction

Various studies carried out in different regions around the world have found that the incidence of malignancy is generally higher in patients suffering from end-stage renal disease (ESRD),[1–4] and renal cell carcinoma (RCC) is especially high in renal cancer after exclusion of cases related to analgesic nephropathy.[2] In Taiwan, several studies have revealed that the incidence rate for urothelial cancer (UC), especially transitional cell carcinoma (TCC), among patients undergoing renal replacement therapy ranges from 0.89% to 1.69%, but RCC is even lower.[5–8]

In our previous study the accumulated incidence rate for UC in the general population using a 200,000 randomized person dataset from the National Health Insurance (NHI) was approximately 0.12%, whereas in patients with ESRD it was much higher (2.1%). Because patients with either major cancer or ESRD in Taiwan can be registered in the "Catastrophic Illness" category, making them exempt from copayments, there is a strong financial incentive for the comprehensive inclusion of such cases. The registry generally requires valid documentation to prevent any potential abuse, thereby preserving the financial system of the NHI. Thus, with this valuable reimbursement database we can initiate a nationwide study to determine whether there is any discernible increase in UC, especially those in the upper tract, in patients with ESRD. The aim of this study is to evaluate the characteristics of UC incidence in this specific population and to select the patients who are at higher risk.

Methods

The NHI scheme was established in Taiwan in March 1995. The National Health Research Institute (NHRI) transforms NHI reimbursement data into files for research. These files have proved invaluable in providing detailed information on the healthcare services used by each patient, including outpatient visits, hospitalizations, and prescriptions. Data collection began in 1996 and by January 1997, the database had already become extremely comprehensive. The records show that the system covered approximately 96% of the total population in Taiwan during 1997—2002.[9] For each outpatient visit, the data contain up to three diagnoses (coded under the International Classification of Diseases, ICD-9), comprising all prescription drugs and dosages (both conventional medicines and Chinese herbal products), any special treatment obtained (including dialysis and kidney transplantation), and the dates of such orders. For hospitalization, up to five diagnoses are recorded. To protect the privacy of all persons registered in the scheme, the identification numbers of all persons contained within the NHI database are encrypted and converted into research files by the NHRI.

Study population

The files in the "Registry of Catastrophic Illness" were obtained for the years 1997—2002; these files include basic records on all patients with catastrophic illnesses, including ESRD, kidney transplants, and UC. A histopathology report is required as a validation document.

Files on patients with diagnoses of ESRD and UC made during the period 1997—2002 were obtained from the registry. UC was identified as bladder cancer (ICD-9 code 188), upper tract urothelial cancer (UT-UC; ICD-9 codes 189.1 and 189.2), and RCC (ICD-9 code 189.0). Cases with ICD-9 code 189.9 were excluded because they did not contain detailed pathological data. Data on patient demographics (sex, date of birth), diagnoses and treatment (the date treatment began and the date of death or transplantation), and duration of renal replacement therapy prior to diagnosis of UC were obtained from the databases and used to calculate the incidence rates of the different types of urinary cancer.

The reference group included all people enrolled in the NHI, or the general population of Taiwan. Thus, patients with UC categorized as ICD-9 codes 188, 189.0, 189.1, and 189.2 were taken as the numerators for the reference population or ESRD patient cohorts. The entire procedure for the selection of the patients is illustrated in the flowchart in Fig. 1.

This study was approved by the Ethics Review Board of the National Taiwan University Hospital, Taipei, Taiwan. In addition, the study complied with personal data protection regulations.

Statistical analysis

The total number of new cases and the incidence rates of UC among patients with ESRD and the reference (general) population were calculated as the number of new patients with UC per 100,000 person-years at risk. The age-stratified incidence rates for UC in the reference population were used to calculate the number of expected cases under the assumption that the reference population had the same cancer experience as patients with ESRD for each age strata. The total number of observed UC cases summed up across all age strata divided by the total number of expected cases was then defined as the standardized incidence ratio (SIR). We then calculated the 95% confidence intervals (95% CIs) under the assumption of Poisson distribution. Potential risk factors, including age and sex, were assessed for any independent association with new occurrences of UTC, concluding with the calculation of age- and sex-stratified incidence rates. All of the above analyses were carried out using the SAS software package, version 8.2 (SAS Institute Inc. Cary, NC, USA).

Results

There were approximately 22 million people registered with the NHI system between the years 1997 and 2002 (as summarized in Fig. 1). Patients with missing information were excluded. During the 6-year cross-sectional study (1997—2002) of the 22 million individuals in the reference group without ESRD, 20,171 developed UC. Among them, 6,816 (34%) were women and 13,355 (66%) were men. The mean age was 65.6 $\pm$ 13.9 years. In the reference population, 7% had renal cancer, 34% had renal pelvic and ureteral cancers, and 59% had bladder cancer. Among patients with ESRD, 6% had renal cancer, 30% had renal pelvic and ureteral cancers, and 64% had bladder cancer.

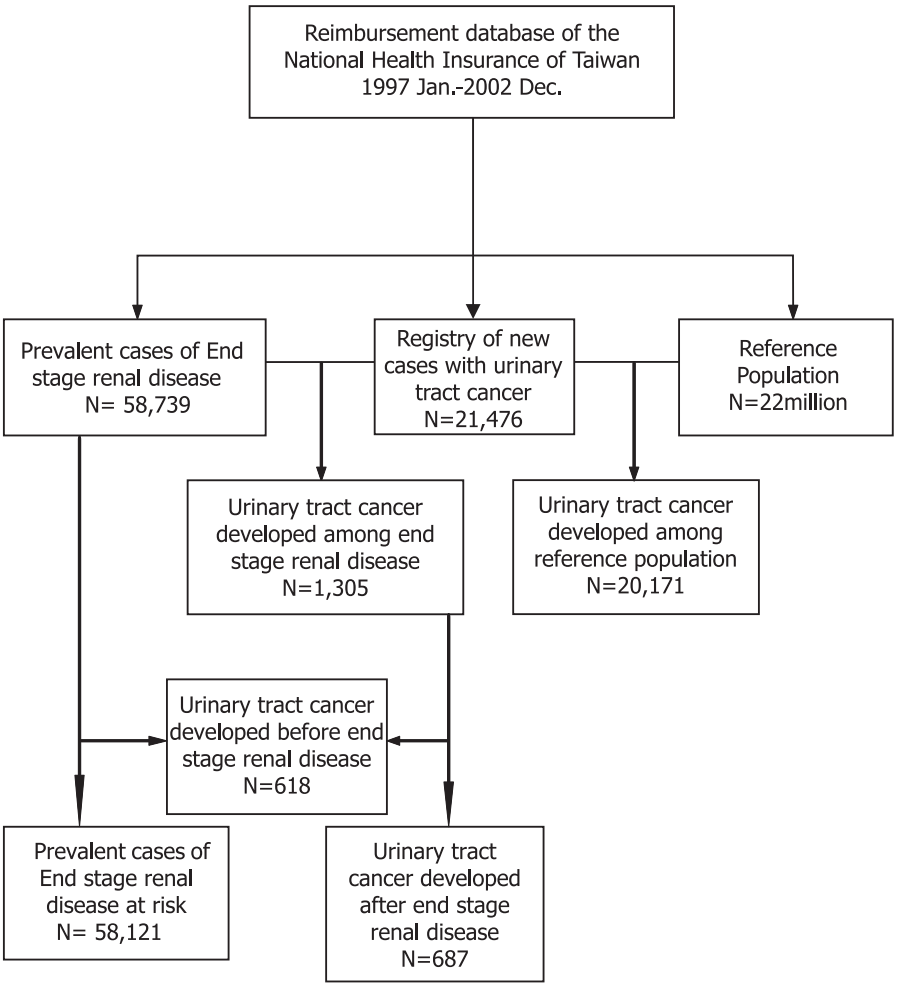

Figure 1 Flowchart of recruitment of cases.

Among 58,739 patients with ESRD, 1305 patients had UC. However, 618 individuals who developed ESRD after the diagnosis of UC were excluded from the numerators. One patient with incomplete data was also excluded. Thus, a total of 58,120 patients with ESRD were at risk of developing UC during the follow-up period, and in 687 of them UC had developed at the 6-year follow-up. Among patients with ESRD without UC, 52.3% were women ($n = 30,027$) and 47.3% were men ($n = 27,406$). Among the 687 patients in whom UC developed, 62% were women ($n = 426$) and 38% were men ($n = 261$). The odds ratio of men and women to develop UTC was statistically significant ($p < 0.0001$). The mean age of the patients was 60.8 ± 11.1 years. UC comprised RCC in 41 patients, bladder cancer in 436 patients, and UT-UC in 210 patients. Among the patients with ESRD, 1834 underwent kidney transplantation and UC developed in 28 of them after transplantation. Only three of the 365 patients with ESRD who later developed UC resided in arsenic-endemic areas, namely, the townships of Peimen, Hsuechia, Putai, and Ichu in southwestern Taiwan.[10,11] The odds ratio of developing UTC did not differ significantly between patients living in arsenic-endemic areas and patients living in nonarsenic-endemic areas ($p = 0.51$).

The incidence rates of UC among patients with ESRD and the reference population, after stratification by age, are illustrated in Fig. 2. The SIRs for all types of UC were much higher among the patients with ESRDs than among those in the reference population across all age groups. As summarized in Table 1, the SIRs for the ESRD cohort were 12.9 (95% CI: 12.0—13.9) for all UC cases, 13.9 (95% CI: 12.4—15.0) for bladder cancer, 11.9 (95% CI: 8.6—16.0) for renal cancer, and 11.6 (95% CI: 10.1—13.1) for renal pelvic and ureteric cancers. Discernibly higher SIRs were noted

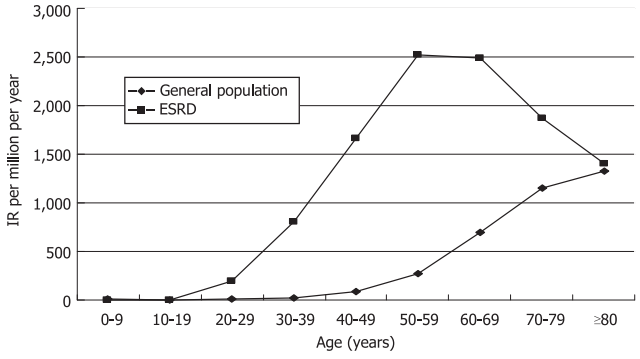

Figure 2 Incidence rates of urinary tract cancer in patients with ESRD (end stage renal disease) and general population of Taiwan.

among women and patients with age below 50–60 than those above that age, especially for bladder cancer. We also found that the SIRs for the different types of UC declined among patients older than 70 years, with the rate coming close to 1 (Fig. 2).

The average duration between the diagnosis of UC and the diagnosis of ESRD was 2.17 years (0.003–5.9 years). The average duration was 2.4 years for patients with RCC, 2.3 years for patients with bladder cancer, and 1.8 years for patients with UT-UC. In addition, UC developed earlier in the upper tract than in the bladder and developed earlier than RCC after renal replacement therapy.

Discussion

This study indicates, for the first time, that patients with ESRD in Taiwan are at increased risk for developing UC, with women and those below 50–60 years old at a particularly high risk. Further inference is necessary to evaluate possible etiologies.

Prior to making further inference, however, we must examine all potential confounding factors. First, we need to rule out the possibility of overdiagnosis. In order for patients with UC to be registered under the "catastrophic illness" category, every patient is required to submit a histopathology report as a validation document, although a very minor proportion (<5–10%) of patients with inoperable cancer is allowed to submit a cytology report plus evidence of imaging in lieu of submitting a pathology report. The data obtained from the National Cancer Registry of Taiwan showed that 90–95% of the diagnoses of UC were verified by histopathologic proof. Moreover, the annual incidence rates calculated from the cancer registry for UT-UC and bladder cancer were 3.5 cases per 100,000 persons and 7.1 cases per 100,000 persons, respectively, in the year 2001, rates that are close to the rates of 3.6 and 6.23, respectively, calculated from the catastrophic registry. Thus, the potential bias of overdiagnosis cannot explain our finding. Second, the possibility of diagnosis bias must be considered. In general, patients with ESRD often experience hematuria prior to when the diagnosis of UC is made.[12] In Taiwan, the convenience of our NHI system makes the accessibility to healthcare services relatively easy and equal.[13] Although cancer is definitively diagnosed, patients can be registered under the catastrophic illness category, making them eligible for a copayment waiver. Thus, every patient with cancer and persistent hematuria will ultimately be detected, thereby minimizing the likelihood of an erroneous diagnosis. Therefore, we tentatively conclude that the increased SIR of UC in patients with ESRD is real and deserves further exploration into the possible etiological mechanism.

In general, relatively little is known about the pathophysiological mechanisms of and risk factors for UC and renal cancer. Indeed, UC among patients with ESRD and among those who undergo kidney transplantation only recently attracted the attention of clinicians, when sporadic case reports of UC began to be seen in the early 1990s; since then, there has been a rapid increase in such reports in Taiwan.[8,14–16] Studies from Western countries indicate that the incidence of pelvic tumor among all urinary cancer is 5%,[17] and ureteral tumors are even less, or, about a quarter in upper tract cancer,[18] and the odds ratio of developing UC among ESRD is generally less than three times.[19–21] In this study we found that proportions of bladder cancer, UT-UC, and RCC among ESRD were 59%, 34% and 7%, respectively, which are similar to those of general population of 64%, 30% and 6%, respectively. In addition to high proportions of UT-UC in renal cancer among the

Table 1 Distribution of cancers of the urinary tract, bladder, kidney, ureter and pelvis in patients with end-stage renal disease in Taiwan.*

Sample	All urinary tract cancer			Bladder urothelial cancer			Ureter and pelvic urothelial cancers			Renal cell carcinoma		
	Obs.	Exp.	SIR (95% CI)	Obs.	Exp.	SIR (95% CI)	Obs.	Exp.	SIR (95%CI)	Obs.	Exp.	SIR (95% CI)
Male	261	32.7	7.9 (7.1, 9.0)	166	21.5	7.7 (6.6, 9.0)	75	9.2	8.1 (6.5, 10.2)	19	1.8	10.5 (6.7, 16.5)
Female	426	19.3	22.1 (20.1, 24.3)	270	8.9	29.6 (26.3, 33.3)	134	8.9	15.2 (12.7, 17.9)	22	1.7	13.4 (8.8, 20.3)
Total	687	53.1	12.9 (12.0, 13.9)	436	31.4	13.7 (12.4, 15.0)	209	18.2	11.5 (10.1, 13.1)	41	3.5	11.7 (8.6, 16.0)
Male												
<40	13	0.3	46.7 (1.7, 27.1)	3	0.1	24.7 (8.0, 76.6)	8	0.1	65.3 (32.7, 130.7)	1	0.03	31.8 (4.5, 225.4)
40–49	38	3.3	11.5 (8.4, 15.9)	24	2.0	12.3 (8.3, 18.4)	11	1.1	10.1 (5.6, 18.2)	3	0.2	12.6 (4.1, 38.9)
50–59	62	12.4	5.0 (3.9, 6.4)	34	7.4	4.6 (3.3, 6.4)	20	4.0	5.0 (3.2, 7.7)	8	1.0	8.5 (4.2, 16.9)
60–69	86	37.8	2.3 (1.8, 2.8)	55	24.1	2.3 (1.8, 3.0)	26	11.4	2.3 (1.6, 3.4)	5	2.2	2.3 (0.9, 5.5)
>70	62	58.4	1.1 (0.8, 1.4)	50	42.8	1.2 (0.9, 1.5)	10	13.5	0.7 (0.4, 1.4)	2	2.2	0.9 (0.2, 3.6)
Female												
<40	11	0.2	74.5 (1.8, 41.2)	8	0.04	205.4 (102.7, 410.8)	3	0.1	35.5 (11.1, 107.1)	0	0.02	
40–49	59	2.0	29.9 (23.2, 38.6)	36	0.8	46.0 (33.2, 63.7)	22	1.0	22.7 (14.9, 34.5)	1	0.2	4.6 (0.6, 32.9)
50–59	122	7.0	17.4 (14.6, 20.1)	79	3.1	25.4 (20.3, 31.6)	34	3.2	10.7 (7.6, 14.9)	9	0.7	13.9 (7.2, 26.7)
60–69	149	26.6	5.6 (4.8, 6.6)	98	12.1	8.1 (6.6, 9.8)	41	12.1	3.4 (2.5, 4.6)	10	2.2	4.6 (2.5, 8.6)
>70	85	36.2	2.4 (1.9, 2.9)	49	18.4	2.7 (2.0, 3.5)	34	15.1	2.3 (1.6, 3.2)	2	2.5	0.8 (0.2, 3.2)

Note: *The table provides details of the total number of observations (Obs), the expected number of cases (Exp,) the standardized incidence ratio (SIR) and the 95 per cent confidence interval (95 per cent CI).

general population (83%) and ESRD (82%), Taiwan has the world's highest incidence and second highest prevalence of ESRD.[22] Thus, we attempted to determine possible pathogens for these phenomena, albeit they might share the same mechanism. Most strikingly, our results showed that women with ESRD and patients younger than 50 years are at increased risk for developing UC. Because few women in Taiwan are engaged in occupations that would expose them to carcinogens and based on the fact that the prevalence of cigarette smoking has consistently been lower than 5% during the past four decades, it is unlikely that occupational exposure to carcinogens or smoking is responsible for the increased incidence of UC among women. Genetic alternation in upper urinary tract urothelial carcinoma with more copy number variants is noted in patients with ESRD.[23] Arsenic exposure has been associated with an increased incidence of kidney and bladder cancer in Taiwan since 1920.[11,24–26] Chen et al[27] reported their findings that more than 20% female patients with nonmuscle-invasive bladder UC had synchronous ESRD and required permanent dialysis. However, bilateral nephroureterectomy from renal or ureteral UC is not the major reason to dialysis. There is limited evidence to address the association of ESRD and bladder cancer in Western countries. In Taiwan, another group identified the unusual association between chronic dialysis and the development of UC in Taiwan.[6] They also reported that the SIR of UC for patients receiving chronic dialysis was 48.2 compared with that of the general population. It is remarkably higher in women (65.1) than in men (38.1).[6] However, the mechanism to explain the strong association among female predominance, chronic dialysis, and UC remained elusive. In this study, the incidence of UC in arsenic-endemic areas (including four townships with blackfoot disease) was high. During the 6-year study period we found that the SIRs were 3.2 ($n = 19$) for RCC, 55.5 ($n = 333$) for bladder cancer, and 26.1 ($n = 157$) for UT-UC. A total of 355 patients with ESRD lived in those endemic areas; however, only three developed UC. The exclusion of those three patients did not change the summary results, indicating that the development of UC is not associated with arsenic exposure.

In a recent population-based case–control study in Taiwan, we found that UC was associated with cumulative prescriptions of aristolochic acid (AA)-related Chinese herbal products even after limiting the analysis to those who consumed fewer than 500 pills of nonsteroidal anti-inflammatory drugs or acetaminophen.[28] The study appears to corroborate the findings reported in studies from Belgium and the Balkan states.[29–32] Given that more than 25% of all Taiwanese citizens are known to regularly consume Chinese herbal products containing AA, a chemical that is associated with the development of CKD,[33] ESRD,[34] and UC,[28] it seems logical to assume that the increased risk for the development of UC in patients with ESRD in Taiwan might be related to the consumption of AA-associated herbal products.[32–34] Racial and etiologic differences might partially explain the different ratios in RCC and UC.

The major limitation of this study is its cross-sectional design and the limitation of the NHI database. Because the data from that database do not include the history of smoking or specific exposures to toxic materials precludes us from making detailed analysis or further inference. Therefore, our conjecture that the increased incidence of UC might be associated with the consumption of AA-related herbal products needs more corroborative study and must be interpreted with caution.

In conclusion, with a national database, we found that SIRs of UT-UC, bladder cancer, and RCC among dialysis patients with ERSD are much higher than those that occurred in the general population of Taiwan. In the diagnosis of ESRD, UT-UC comprised 37% of all UC, higher than 30% in the general population, and both much higher than 5% in Western countries. In ESRD patients below 50 years of age, SIRs of bladder UC and UT-UC are about more than 10 times in males and 30 times in females if compared to general population. Those of RCC were about 10 times higher in both genders, which were lower than the reported SIR 30–40 times in western countries. In exposure, we hypothesized that Chinese herbal products might play an important role in the development of UTC in patients with ESRD. We recommend that clinicians who care for patients with ESRD in countries where Chinese herbal products are commonly used conduct similar studies to corroborate the aforementioned hypothesis. In addition, special attention may be paid to any sign of UC, such as hematuria and hydronephrosis, for early detection of disease.

Acknowledgments

This study was supported by a grant from the Department of Health — DOH94-TD-D- 113-044-(2), Center of Excellence for Cancer Research, and another grant from the National Science Council (NSC 94-2314-B-002-235) for which we are grateful. We are also further indebted to the Bureau of National Health Insurance, the Department of Health, and the National Health Research Institutes for kindly providing us with the data for analysis in this study. The interpretation and conclusions contained herein are not, in any way, representative of those of the Bureau of National Health Insurance, the Department of Health, or the National Health Research Institutes.

References

1. Maisonneueve P, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, et al. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. *Lancet* 1999;**354**:93–9.
2. Stewart JH, Buccianti G, Agodoa L, Gellert R, McCredie MR, Lowenfels AB, et al. Cancers of the kidney and urinary tract in patients on dialysis for end-stage renal disease: analysis of data from the United States, Europe, Australia and New Zealand. *J Am Soc Nephrol* 2003;**14**:197–207.
3. Akiyama T, Imanishi M, Matsuda H, Nishioka T, Kunikata S, Kurita T. Difference amongst races in post-transplant malignancies: report from an oriental country. *Transplant Proc* 1998;**30**:2058–9.
4. Agraharkar ML, Cinclair RD, Kuo YF, Daller JA, Shahnian VB. Risk of malignancy with long-term immuno-suppression in renal transplant recipients. *Kidney Int* 2004;**66**:383–9.
5. Chuang CH, Lee CT, Tsai TL, Chen JB, Hsu KT, Hsieh HH. Urological malignancy in chronic dialysis patients. *Acta Nephrologica* 2002;**16**:19–24.

6. Chang CH, Yang CM, Yang AH. Renal diagnosis of chronic hemodialysis patients with urinary tract transitional cell carcinoma in Taiwan. *Cancer* 2007;**109**:1487—92.
7. Ou JH, Pan CC, Lin SN, Tzai TS, Yang WH, Chang CC, et al. Transitional cell carcinoma in dialysis patients. *Eur Urol* 2000; **37**:90—4.
8. Chen KS, Lai MK, Huang CC, Chu SH, Leu ML. Urologic cancers in uremic patients. *Am J Kidney Dis* 1995;**25**:694—700.
9. Tan HF, Chang CK, Tseng HF, Lin W. Evaluation of the national notifiable disease surveillance system in Taiwan: an example of varicella reporting. *Vaccine* 2007;**25**:2630—3.
10. Chen CJ, Wu MM, Lee SS, Wang JD, Cheng SH, Wu HY. Atherogenicity and carcinogenicity of high-arsenic artesian well water. Multiple risk factors and related malignant neoplasms of blackfoot disease. *Arteriosclerosis* 1988;**8**:452—60.
11. Chen CJ, Chuang YC, Lin TM, Wu HY. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. *Cancer Res* 1985;**45**:5895—9.
12. Wen CP, Tsai SP, Chung WSI. A 10-year experience with universal health insurance in Taiwan: measuring changes in health and health disparity. *Ann Intern Med* 2008;**148**:258—67.
13. Jiaan BP, Yu CC, Lee YH, Huang JK. Uraemia with concomitant urothelial cancer. *Br J Urol* 1993;**72**:458—61.
14. Boon NA, Michael J. Multiple neoplasia in a patient on dialysis presenting with haematuria. *Br J Urol* 1984;**56**:96—7.
15. Tsai HJ, Hsieh HH. Adult polycystic kidneys associated with transitional cell carcinoma: A case report. *Chang Keng I Hsueh Tsa Chih* 1987;**10**:257—62.
16. Fraley EE. Cancer of the renal pelvis. In: Skinner DG, deKernion JB, editors. *Genitourinary cancer*. Philadelphia: WB Saunders; 1978. p. 134.
17. Chou YH, Huang CH. Unusual clinical presentation of upper urothelial carcinoma in Taiwan. *Cancer* 1999;**85**:1342—4.
18. Matas AJ, Simmons RL, Kjellstrand CM, Buselmeier TJ, Najarian JS. Increased incidence of malignancy during chronic renal failure. *Lancet* 1975;**1**:883—6.
19. Port FK, Ragheb NE, Schwartz AG, Hawthorne VM. Neoplasms in dialysis patients: a population-based study. *Am J Kidney Dis* 1989;**14**:119—23.
20. Kjellstrand CM. Are malignancies increased in uremia? *Nephron* 1979;**23**:159—61.
21. Yang WC, Hwang SJ. Taiwan Society of Nephrology. Incidence, prevalence and mortality trends of dialysis end-stage renal disease in Taiwan from 1990 to 2001: the impact of national health insurance. *Nephrol Dial Transplant* 2008;**23**:3977—82.
22. Wu CF, Pang ST, Shee JJ, Chang PL, Chuang CK, Chen CS, et al. Identification of genetic alterations in upper urinary tract urothelial carcinoma in end-stage renal disease patients. *Genes Chromosomes Cancer* 2010;**49**:928—34.
23. Hsieh YF, Ling GC, Lu YB, Yeh MT, Chiang CP. Incidence of tumor of the renal pelvis in Taiwan. *J Formos Med Assoc* 1979; **78**:749—53.
24. Wu MM, Kuo TL, Hwang YH, Chen CJ. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular disease. *Am J Epidemiol* 1989;**130**: 1123—32.
25. Arsenic and arsenic compounds. *IARC monographs on the evaluation of carcinogenic risk of chemicals to humans; Suppl 7. Overall evaluations of carcinogenicity: updating of IARC monographs volumes 1-42*. Lyon: France: World Health Organization, International Agency for Research on Cancer; 1987. p. 29—33.
26. Lai MN, Wang SM, Chen PC, Chen YY, Wang JD. Population-based case—control study of Chinese herbal products containing aristolochic acid and urinary tract cancer risk. *J Natl Cancer Inst* 2010;**102**:179—86.
27. Chen CH, Shun CT, Huang KH, Huang CY, Yu HJ, Pu YS. Characteristics of female non-muscle-invasive bladder cancer in Taiwan: association with upper tract urothelial carcinoma and end-stage renal disease. *Urology* 2008;**71**:1155—60.
28. Vanherweghem JL, Depierreux M, Tielemans C, Abramowicz D, Dratwa M, Jadoul M, et al. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. *Lancet* 1993;**341**:387—91.
29. Cukovic C, Djukanovic L, Jankovic S, Stanojcić A, Dragićević P, Radmilović A, et al. Malignant tumor in hemodialysis patients. *Nephron* 1996;**73**:710—2.
30. Arlt VM, Stiborova M, Simoes ML, Simões ML, Lord GM, Nortier JL, et al. Aristolochic acid mutagenesis: molecular clues to the aetiology of Balkan endemic nephropathy-associated urothelial cancer. *Carcinogenesis* 2007;**28**:2253—61.
31. Grollman AP, Shibutani S, Moriya M, Miller F, Wu L, Moll U, et al. Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *PNAS* 2007;**104**:12129—34.
32. Lai MN, Lai JN, Chen PC, Tseng WL, Chen YY, Hwang JS, et al. Increased risks of chronic kidney disease associated with prescribed Chinese herbal products suspected to contain aristolochic acid. *Nephrology (Carlton)* 2009;**14**:227—34.
33. Lai MN, Lai JN, Chen PC, Hsieh SC, Hu FC. Wang JD. Risks of kidney failure associated with consumption of herbal products containing mu tong or fangchi: a population-based case-control study. *Am J Kidney Dis* 2010;**55**:507—18.
34. Arlt VM, Stiborova M, Schmeiser HH. Aristolochic acid as a probable human cancer hazard in herbal remedies: a review. *Mutagenesis* 2002;**17**:265—77.