Familial Risks Between Urolithiasis and Cancer

Kari Hemminki1,2, Otto Hemminki3,4, Asta Försti1,2, Jan Sundquist2,5, Kristina Sundquist2,5 & Xinjun Li2

Urolithiasis (UL, urinary tract stone disease) has been reported to increase subsequent cancers in the urinary tract. Recently, we showed data that surveillance bias may be an important confounder in the reported associations. In the present approach we want to address the question of possible cancer risk posed by UL mechanistically. Both UL and cancer have strong genetic components and we hypothesize that familial association between UL and cancer may be plausible. We thus assess familial risks between UL and cancer, hoping to find an explanation why UL may pose a risk of cancer. UL patients were identified from hospital inpatient and outpatient records and they were organized in families based on the Multigeneration Register into which also national cancer data were linked. Standardized incidence ratios were calculated for cancer in the offspring generation when parents were diagnosed with UL, and conversely for UL when parents were diagnosed with cancer. Familial risks between UL and cancer were generally small and inconsistent providing no convincing support of genetic sharing between UL and cancer. However, bladder UL was associated weakly with prostate cancer, and ureter and bladder UL were associated with salivary gland cancer. Potential mechanisms for these findings are proposed.

Urolithiasis (UL, urinary tract stone disease) includes stones found in the kidney, ureter and urinary bladder. UL is a common disease affecting up to 15% of population and many patients have recurrent episodes1,2. Kidney stones (nephrolithiasis) form in the kidney and leave the body in the urine stream. Small stones may pass without causing symptoms but stones measuring more than 5 mm tend to generate obstruction of the ureter causing severe pain. Some stones do not enter the ureter, instead they can grow to fill up the renal pelvis and cause kidney damage if untreated. Stones in the bladder have another etiology which usually relates to long term retention of urine in the bladder, typically through obstruction caused by prostate hyperplasia. Thus bladder stones are far more common among men than women. Bladder stones may form in the bladder but also seed on small stones originating from kidney with urine1,2. Reasons for UL are thought to be a combination of genetic and environmental factors. Risk factors include high urine calcium levels, calcium supplements, hyperparathyroidism, gout, obesity, dehydration, urinary stasis and some foods and medications. Genetic causes of UL include many rare monogenic metabolic disorders, such as adenine phosphoribosyltransferase deficiency, cystinuria, Dent disease, familial hypomagnesemia and primary hyperoxaluria1.

There are a number of papers on UL patients reporting subsequent risks of various cancers. For example, a meta-analysis evaluated the association between personal history of kidney stones and kidney cancer, and collected results from 7 studies which gave an overall relative risk (RR) of 1.76, higher for transitional cell carcinoma than for renal cell carcinoma, and for renal cell carcinoma only men were at risk4. A Taiwanese case-control study on bladder stone patients found an RR of 3.42 for bladder cancer5. Another case-control study associate prostate cancer with prior kidney and bladder stones6. However, the reports are not only limited to urological cancers but a study from Taiwan’s National Health Insurance Research Database reported that UL was associated with a high risk of many systemic cancers, for example of breast and lung cancers (RRs 1.84 and 1.82)7.

We recently completed a study reconsidering the above results of ULs possible role in subsequent cancers8. To our surprise the associations were strong with practically all cancers. However, they decreased with the length of the follow-up time since the last UL episode but for many cancers RRs remained significant even after 10 years of follow-up. We could not exclude that patients with recurrent UL disease might have contributed to the elevated

1 Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 580, D-69120, Heidelberg, Germany. 2 Center for Primary Health Care Research, Lund University, 205 02, Malmö, Sweden. 3 Department of Urology, Helsinki University Hospital, Helsinki, Finland. 4 Cancer Gene Therapy Group, Faculty of Medicine, University of Helsinki, Helsinki, Finland. 5 Department of Family Medicine and Community Health, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai, New York, USA. Correspondence and requests for materials should be addressed to K.H. (email: kari.hemminki@dkfz.de)
risks after the long follow-up. We concluded that exclusion of surveillance bias is extremely difficult in conditions for which prior medical contacts have taken place. As UL is a common disease it would be of high importance to unravel and settle the possible cancer risks because, if real, their population burden would be considerable and prevention would be at least in part possible. Here we decided to approach the problem through a mechanistic reasoning and addressing two research questions: 1) directly assessing whether UL and cancer share familiar links, and 2) indirectly using the results from 1) to conclude whether UL may be associated with individual cancer risk. As both UL and cancer have a genetic component we hypothesized that they share familial risks, i.e., in families with UL certain cancers should be in excess, and conversely, in families with cancer UL should be in excess. When UL and cancer would be assessed in different generations, surveillance bias should be non-existent.

Table 1. Population and case numbers for urolithiasis and cancer. *Age adjusted for the European standard population.

| Cancer site in offspring | Kidney | Ureter | Bladder | All |
|--------------------------|--------|--------|---------|-----|
|                          | O      | SIR    | 95% CI  | O   | SIR    | 95% CI  | O   | SIR    | 95% CI  | O   | SIR    | 95% CI  |
| Upper aerodigestive tract| 57     | 0.93   | 0.71    | 1.21 | 71    | 0.84   | 0.65    | 1.06 | 40    | 0.94   | 0.67    | 1.28 | 195   | 0.95   | 0.82    | 1.09 |
| Salivary gland           | 13     | 1.48   | 0.78    | 2.53 | 23    | 1.97   | 1.25    | 2.97 | 7     | 1.52   | 0.60    | 3.16 | 48    | 1.74   | 1.28    | 2.30 |
| Stomach                  | 24     | 0.75   | 0.48    | 1.12 | 51    | 1.15   | 0.85    | 1.51 | 23    | 0.93   | 0.59    | 1.40 | 111   | 1.01   | 0.83    | 1.22 |
| Small intestine          | 24     | 1.90   | 1.21    | 2.82 | 18    | 1.04   | 0.62    | 1.65 | 13    | 1.47   | 0.78    | 2.52 | 60    | 1.42   | 1.08    | 1.83 |
| Colon                    | 172    | 1.15   | 0.98    | 1.33 | 217   | 1.05   | 0.92    | 1.20 | 107   | 0.99   | 0.81    | 1.20 | 535   | 1.06   | 0.97    | 1.15 |
| Rectum                   | 81     | 0.90   | 0.71    | 1.12 | 132   | 1.05   | 0.88    | 1.24 | 68    | 0.98   | 0.76    | 1.24 | 305   | 0.99   | 0.88    | 1.10 |
| Liver                    | 88     | 1.26   | 1.01    | 1.55 | 86    | 0.88   | 0.70    | 1.09 | 50    | 0.97   | 0.72    | 1.28 | 254   | 1.06   | 0.94    | 1.20 |
| Pancreas                 | 31     | 0.89   | 0.61    | 1.27 | 55    | 1.11   | 0.83    | 1.44 | 28    | 0.97   | 0.64    | 1.40 | 125   | 1.02   | 0.85    | 1.21 |
| Lung                     | 127    | 1.05   | 0.88    | 1.25 | 148   | 0.87   | 0.73    | 1.02 | 90    | 0.87   | 0.70    | 1.07 | 399   | 0.93   | 0.84    | 1.03 |
| Breast                   | 665    | 1.05   | 0.98    | 1.14 | 903   | 1.05   | 0.98    | 1.12 | 450   | 1.06   | 0.96    | 1.16 | 2195  | 1.05   | 1.01    | 1.09 |
| Cervix                   | 1572   | 1.00   | 0.95    | 1.05 | 1978  | 0.98   | 0.94    | 1.03 | 437   | 0.94   | 0.85    | 1.03 | 4478  | 0.99   | 0.96    | 1.02 |
| Endometrium              | 67     | 0.95   | 0.74    | 1.21 | 84    | 0.89   | 0.71    | 1.11 | 71    | 1.26   | 0.99    | 1.60 | 240   | 1.00   | 0.88    | 1.13 |
| Prostate                 | 289    | 1.08   | 0.96    | 1.21 | 384   | 0.98   | 0.89    | 1.09 | 292   | 1.12   | 0.99    | 1.25 | 1044  | 1.06   | 0.99    | 1.12 |
| Kidney                   | 57     | 1.02   | 0.78    | 1.33 | 78    | 1.06   | 0.83    | 1.32 | 31    | 0.85   | 0.58    | 1.21 | 188   | 1.04   | 0.89    | 1.20 |
| Urinary bladder          | 68     | 1.05   | 0.82    | 1.34 | 96    | 1.06   | 0.86    | 1.29 | 44    | 0.82   | 0.59    | 1.10 | 221   | 0.98   | 0.85    | 1.11 |
| Melanoma                 | 404    | 1.07   | 0.97    | 1.18 | 533   | 1.06   | 0.96    | 1.16 | 219   | 1.16   | 1.01    | 1.32 | 1254  | 1.07   | 1.01    | 1.13 |
| Nervous system           | 226    | 1.04   | 0.93    | 1.19 | 318   | 1.14   | 1.02    | 1.27 | 89    | 1.02   | 0.82    | 1.25 | 692   | 1.07   | 0.99    | 1.15 |
| Endocrine glands         | 70     | 0.94   | 0.73    | 1.19 | 99    | 1.01   | 0.82    | 1.23 | 36    | 0.93   | 0.65    | 1.28 | 218   | 0.94   | 0.82    | 1.07 |
| Bone                     | 25     | 1.06   | 0.68    | 1.56 | 30    | 1.02   | 0.69    | 1.46 | 1     | 0.17   | 0.00    | 0.99 | 69    | 1.05   | 0.81    | 1.32 |
| Hodgkin disease          | 56     | 1.03   | 0.78    | 1.34 | 67    | 0.99   | 0.77    | 1.26 | 14    | 1.01   | 0.55    | 1.70 | 157   | 1.03   | 0.88    | 1.21 |
| Leukemia                 | 126    | 0.93   | 0.77    | 1.10 | 172   | 1.00   | 0.85    | 1.16 | 53    | 0.94   | 0.70    | 1.23 | 389   | 0.96   | 0.87    | 1.06 |
| Unspecified primary      | 52     | 0.98   | 0.73    | 1.29 | 74    | 1.01   | 0.80    | 1.27 | 34    | 0.85   | 0.59    | 1.19 | 171   | 0.95   | 0.81    | 1.10 |
| All                      | 5013   | 1.02   | 0.99    | 1.05 | 6642  | 1.02   | 0.99    | 1.04 | 2615  | 1.02   | 0.98    | 1.06 | 15729 | 1.02   | 1.01    | 1.04 |

Table 2. SIR of cancer in offspring when parents were diagnosed with UL. Bold type: 95% CI does not include 1.00. O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval. Column 'All' includes data for mixed stones which are not shown separately. They included 1459 cases for this table.
results

Person numbers and characteristics of the UL and cancer patients are shown in Table 1 separately for the offspring (8.5 million) and parental (7.8 million) generations. Respective numbers of UL patients were 130,091 and 15,729; note that case numbers were much lower than in Table 1 because only familial cases were included in Table 2 and subsequent Tables. For 4 individual cancers SIRs were significant for all types of UL combined. The highest overall SIRs were observed for small intestinal cancer (1.42; 1.90 when parents had kidney stones) and salivary gland cancer (1.74; 1.97 when parents had ureter stones). Any significant association was observed for one UL type only. The overall SIR for prostate cancer was increased to 1.06 (95% CI: 0.99–1.12) but no individual UL subtype showed an association.

Table 2 includes data for mixed stones which is not shown separately. They included 9031 cases for this table. Bold type: 95% CI does not include 1.00.

or minimal. Demonstration of familial risk between UL and cancer would offer unbiased evidence and a plausible mechanism for individuals risks, i.e., why UL patients have an increased risk of cancer. We use the nation-wide Swedish Family-Cancer Database for the study.

Table 3. SIR of UL in offspring when parents were diagnosed with cancer. O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval. Column 'All' includes data for mixed stones which are not shown separately. They included 9031 cases for this table. Bold type: 95% CI does not include 1.00.
| Cancer site in parents |Kidney |Urter |Bladder |All |
|---|---|---|---|---|
| |O|SIR|95% CI|O|SIR|95% CI|O|SIR|95% CI|O|SIR|95% CI|
|Upper aerodigestive tract|331|1.10|0.99|1.23|336|0.99|0.89|1.10|29|1.10|0.74|1.58|802|1.06|0.99|1.13|
|Salivary gland|36|1.29|0.91|1.79|37|1.17|0.82|1.61|5|1.98|0.63|4.66|91|1.29|1.04|1.58|
|Stomach|441|1.08|0.98|1.19|500|1.04|0.95|1.13|62|1.42|1.09|1.82|1163|1.10|1.04|1.16|
|Small intestine|79|1.13|0.90|1.41|83|1.04|0.83|1.29|7|1.08|0.43|2.24|182|1.02|0.88|1.18|
|Colon|1435|1.08|1.02|1.13|1683|1.09|1.04|1.14|141|1.09|0.92|1.29|3699|1.08|1.05|1.12|
|Rectum|800|1.04|0.97|1.12|941|1.06|0.99|1.13|80|1.10|0.87|1.37|2049|1.04|1.00|1.09|
|Liver|412|1.08|0.98|1.19|502|1.13|1.03|1.23|32|0.81|0.55|1.14|1067|1.09|1.02|1.15|
|Pancreas|407|1.08|0.98|1.19|448|1.03|0.93|1.13|44|1.18|0.86|1.59|1018|1.06|0.78|1.48|
|Lung|1293|1.14|1.08|1.20|1442|1.11|1.05|1.17|102|1.03|0.84|1.25|3233|1.12|1.08|1.16|
|Breast|1951|0.93|0.89|0.97|2298|0.98|0.94|1.02|159|0.90|0.76|1.05|5066|0.96|0.93|0.98|
|Cervix|609|1.12|1.03|1.21|555|1.06|0.98|1.15|44|1.15|0.84|1.55|1416|1.11|1.05|1.16|
|Endometrium|548|1.09|1.00|1.18|609|1.05|0.97|1.14|45|1.01|0.74|1.35|1376|1.07|1.02|1.13|
|Prostate|2763|1.01|0.97|1.05|3265|1.04|1.01|1.08|266|1.10|0.97|1.24|7164|1.03|1.00|1.05|
|Kidney|408|1.13|1.02|1.24|490|1.18|1.08|1.29|42|1.25|0.90|1.69|1074|1.16|1.10|1.24|
|Urinary bladder|810|1.06|0.98|1.13|915|1.03|0.97|1.10|67|0.94|0.73|1.21|2052|1.05|1.00|1.09|
|Melanoma|634|0.91|0.84|0.98|745|0.97|0.90|1.04|56|1.00|0.76|1.30|1632|0.93|0.89|0.98|
|Nervous system|393|1.17|1.05|1.29|400|1.08|0.98|1.19|36|1.33|0.93|1.84|947|1.13|1.06|1.20|
|Endocrine glands|237|1.03|0.90|1.17|279|1.08|0.96|1.22|22|1.09|0.68|1.65|606|1.04|0.96|1.13|
|Bone|15|1.02|0.57|1.68|17|1.05|0.61|1.69|1|0.82|0.00|4.70|40|1.09|0.78|1.48|
|Hodgkin disease|36|1.16|0.81|1.61|55|1.62|1.22|2.11|2|0.74|0.07|2.73|105|1.36|1.11|1.64|
|Leukemia|498|1.04|0.95|1.14|565|1.03|0.94|1.12|54|1.19|0.89|1.55|1265|1.04|0.98|1.09|
|Unspecified primary|614|1.14|1.06|1.24|692|1.10|1.02|1.19|63|1.16|0.89|1.49|1544|1.12|1.06|1.17|
|All|18181|1.04|1.02|1.05|20846|1.04|1.03|1.06|1701|1.06|1.01|1.12|46143|1.04|1.03|1.05|

Table 4. SIR of cancer in parents when offspring were diagnosed with UL. Bold type: 95% CI does not include 1.00. O = observed number of cases; SIR = standardized incidence ratio; CI = confidence interval Column ‘All’ includes data for mixed stones which are not shown separately. They included 5685 cases for this table.

Discussion

Our goal was to investigate the possible familial association of UL and cancer. If such an association could be demonstrated it would offer one possible mechanism for a personal history of UL being a risk factor for cancer. The demonstration of the association would require that positive results should be found in complementary two-way analyses, shown in Tables 2 to 5. Positive two-way results were found for salivary gland and prostate cancers, and also for liver cancer, however the associated UL sites were different from Table 2.

In Table 5 gives SIRs for parental UL when offspring were diagnosed with cancers, thus reversing parents and offspring from Table 3; total case numbers decreased to 14,418. The two Tables shared overall increased association between UL and salivary gland and prostate cancers, and even the types of UL (ureter for salivary gland cancer and bladder for prostate cancer) were shared. Shared overall associations in Tables 5 and 3 were observed also for colon, cervical and nervous system cancers.

The present incidence of UL was about 80/100,000 in the parental and offspring generations. Surprisingly, incidence rates of UL are rarely reported in the global literature even in studies which refer to incidence in the
yet to be demonstrated.

and urinary tract stones but the necessary final link between salivary gland stones and salivary gland cancer needs bladder UL with salivary gland cancers. The likely initial link was familial predisposition to both salivary gland genetic or familial prostate hyperplasia mechanisms. Unexpected findings showed associations of ureter and 

Table 5. SIR for UL in parents when offspring were diagnosed with cancer. Bold type: 95% CI does not include 

| Cancer site in offspring | Kidney | Ureter | Bladder | All |
|-------------------------|--------|--------|---------|-----|
|                         | O      | SIR    | 95% CI  | O   | SIR    | 95% CI  | O   | SIR    | 95% CI  | O   | SIR    | 95% CI  |
| Upper aerodigestive tract | 58.00  | 0.93   | 0.71    | 1.21 | 73.00  | 0.86   | 0.68    | 1.09 | 41.00  | 1.05   | 0.75   | 1.42 |
| Salivary gland           | 14.00  | 1.55   | 0.85    | 2.63 | 21.00  | 1.90   | 1.20    | 2.86 | 6.00   | 1.34   | 0.84   | 2.15 |
| Stomach                  | 29.00  | 0.93   | 0.62    | 1.34 | 55.00  | 1.28   | 0.97    | 1.67 | 21.00  | 0.97   | 0.60   | 1.48 |
| Small intestine          | 25.00  | 1.90   | 1.23    | 2.81 | 18.00  | 1.00   | 0.59    | 1.58 | 15.00  | 1.75   | 0.97   | 2.89 |
| Colon                    | 172.00 | 1.15   | 0.99    | 1.34 | 223.00 | 1.10   | 0.96    | 1.25 | 106.00 | 1.09   | 0.89   | 1.32 |
| Rectum                   | 90.00  | 0.92   | 0.74    | 1.13 | 145.00 | 1.08   | 0.91    | 1.27 | 66.00  | 0.96   | 0.74   | 1.22 |
| Liver                    | 45.00  | 1.33   | 0.97    | 1.78 | 41.00  | 0.90   | 0.65    | 1.23 | 26.00  | 1.18   | 0.77   | 1.74 |
| Pancreas                 | 29.00  | 0.84   | 0.56    | 1.20 | 52.00  | 1.09   | 0.81    | 1.43 | 26.00  | 1.03   | 0.67   | 1.50 |
| Lung                     | 121.00 | 1.10   | 0.91    | 1.31 | 137.00 | 0.91   | 0.76    | 1.07 | 87.00  | 1.08   | 0.87   | 1.33 |
| Breast                   | 608.00 | 1.05   | 0.97    | 1.14 | 856.00 | 1.08   | 1.01    | 1.45 | 423.00 | 1.12   | 1.02   | 1.23 |
| Cervix                   | 1443.00| 1.04   | 0.99    | 1.10 | 1830.00| 1.04   | 0.99    | 1.09 | 381.00 | 0.98   | 0.88   | 1.08 |
| Endometrium              | 61.00  | 1.10   | 0.84    | 1.42 | 72.00  | 0.94   | 0.74    | 1.19 | 58.00  | 1.40   | 1.06   | 1.80 |
| Prostate                 | 260.00 | 1.06   | 0.94    | 1.20 | 361.00 | 1.05   | 0.95    | 1.17 | 260.00 | 1.27   | 1.12   | 1.44 |
| Kidney                   | 55.00  | 1.03   | 0.77    | 1.34 | 82.00  | 1.16   | 0.92    | 1.44 | 33.00  | 1.04   | 0.71   | 1.46 |
| Urinary bladder          | 68.00  | 1.10   | 0.85    | 1.39 | 102.00 | 1.20   | 0.98    | 1.46 | 41.00  | 0.91   | 0.65   | 1.24 |
| Melanoma                 | 384.00 | 1.08   | 0.98    | 1.20 | 520.00 | 1.10   | 1.01    | 1.20 | 193.00 | 1.11   | 0.96   | 1.28 |
| Nervous system           | 211.00 | 1.11   | 0.97    | 1.27 | 278.00 | 1.14   | 1.01    | 1.28 | 65.00  | 0.88   | 0.68   | 1.13 |
| Endocrine glands         | 67.00  | 0.98   | 0.76    | 1.25 | 106.00 | 1.18   | 0.96    | 1.42 | 36.00  | 1.07   | 0.75   | 1.48 |
| Bone                     | 21.00  | 1.00   | 0.62    | 1.53 | 137.00 | 0.89   | 1.79    | 1.46 | 1.00   | 0.19   | 0.11   | 1.11 |
| Hodgkin disease          | 50.00  | 1.05   | 0.78    | 1.38 | 61.00  | 1.02   | 0.78    | 1.32 | 12.00  | 1.01   | 0.52   | 1.77 |
| Leukemia                 | 116.00 | 0.99   | 0.82    | 1.19 | 158.00 | 1.08   | 0.92    | 1.26 | 46.00  | 1.08   | 0.79   | 1.44 |
| Unspecified primary      | 46.00  | 1.07   | 0.79    | 1.43 | 62.00  | 1.06   | 0.81    | 1.36 | 28.00  | 0.99   | 0.65   | 1.43 |
| All                      | 4589.00| 1.05   | 1.02    | 1.08 | 5141.00| 1.07   | 1.04    | 1.09 | 2330.00| 1.09   | 1.05   | 1.14 |

In conclusion, the present study did not provide data in support of UL leading to systemic cancers. Nor did we find any strong support for the induction of local tumors in the urinary tract; however, as the cause for local tumors may be chronic mechanical wear and inflammation, a family study may not find such a link. We found support for a weak familial association of bladder UL and prostate cancer but could not distinguish between genetic or familial prostate hyperplasia mechanisms. Unexpected findings showed associations of ureter and bladder UL with salivary gland cancers. The likely initial link was familial predisposition to both salivary gland and urinary tract stones but the necessary final link between salivary gland stones and salivary gland cancer needs yet to be demonstrated.
Patients and Methods
Family relationships were obtained from the Multigeneration Register, containing the Swedish population in families and spanning more than a century. 'The offspring generation' was born after 1931 and 'the parental generation' was born any time earlier. By the last year of the study, 2012, the offspring generation reached age 80 years. The offspring generation with information of both parents totaled 8.5 million index individuals. UL patients were identified using the nationwide Swedish Hospital Discharge Register (1987–2012) and the Outpatient Register (2001–2012). The first UL diagnosis in either register was included and a patient was only entered once. Information from the registers was linked at the individual level via the national 10-digit civic registration number to the Swedish national Cancer Registry. Both invasive and in situ cancers were included; however in situ cases contributed essentially only to cerebral cancer. In the linked dataset, civic registration numbers were replaced with serial numbers to ensure the anonymity. Revisions 9 (1987–1996) and 10 (1997-) of the International Classification of Diseases (ICD) was used to identify UL diagnostic codes. Only 54,500 patients were diagnosed during the ICD-9 period, compared to 166,600 in the ICD-10 period. The total number of patients diagnosed with UL during years 1987 to 2012 was 211,718, distributed by the most common type, ureter stones (91,397), followed by kidney stones (77,972), mixed stones (23,890) and bladder stones (18,459). For mixed stones the location between kidney and ureter was undefined or stones were present in both.

Standardized incidence ratios (SIRs) were calculated for the offspring generation as the ratio of observed to expected number of cases. SIRs were calculated for cancer in offspring whose parents were diagnosed with UL, or conversely, for UL in offspring whose parents were diagnosed with cancer. The follow-up for cancer was started from January 1st 1958, date of birth or date of immigration whichever came last, and continued until diagnosis of cancer, death, emigration, or the end of the study (December 31st, 2012) whichever came first. Follow-up for UL was started from 1987 and ended at diagnosis of UL, death or end of follow-up, 2012. The expected numbers were calculated for all individuals without a family history of UL or of cancer (essentially the whole Swedish population), and the rates were standardized by 5-year-age, gender, period (5 years group), socioeconomic status (farmers, self-employed, professionals, white collar workers, blue collar workers, others) and residential area (large cities, southern Sweden, northern Sweden). The 95% confidence interval (95%CI) of the SIR was calculated assuming a Poisson distribution. The SAS software version 9.3 was used for the statistical analyses.

The study was approved by the Regional Ethical Review Board of Lund University (no. 2012/795). The ethical permission waived informed consent because anonymous health records were used. The study was conducted following relevant regulations.

References
1. Tiselius, H. G. Epidemiology and medical management of stone disease. BJU Int 91, 758–767 (2003).
2. Morgan, M. S. & Pearle, M. S. Medical management of renal stones. Bmj 352, i52 (2016).
3. Edvardsson, V. O. et al. Hereditary causes of kidney stones and chronic kidney disease. Pediatric nephrology (Berlin, Germany) 28, 1923–1942 (2013).
4. Cheungpasitporn, W. et al. The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis. QJM: monthly journal of the Association of Physicians 108, 205–212 (2015).
5. Chung, S. D., Tsai, M. C., Lin, C. C. & Lin, H. C. A case-control study on the association between bladder cancer and prior bladder calculus. BMC Cancer 13, 117 (2013).
6. Chung, S. D., Liu, S. P. & Lin, H. C. Association between prostate cancer and urinary calculi: a population-based study. PLoS One 8, e57743 (2013).
7. Shih, C. J. et al. Urinary calculus and risk of cancer: a nationwide population-based study. Medicine 93, e342 (2014).
8. Hemminki, K. et al. Surveillance bias in cancer risk after unrelated medical conditions: example urolithiasis. Scientific reports 7, 8073 (2017).
9. Lieske, J. C. et al. Renal stone epidemiology in Rochester, Minnesota: an update. Kidney Int 69, 760–764 (2006).
10. CenterforEpidemiology. Cancer Incidence in Sweden 2009. (eds). The National Board of Health and Welfare (2010).
11. Franke, C., Sundquist, J., Hemminki, A. & Hemminki, K. Familial Associations Between Prostate Cancer and Other Cancers. Eur Urol 71, 162–165 (2017).
12. Stroup, S. P., Palazzi-Churas, K., Kopp, R. P. & Parsons, J. K. Trends in adverse events of benign prostatic hyperplasia (BPH) in the USA, 1998 to 2008. BJU Int 109, 84–87 (2012).
13. Orsted, D. D. & Bojesen, S. E. The link between benign prostatic hyperplasia and prostate cancer. Nature reviews Urology 10, 49–54 (2013).
14. Rakesh, N., Bhoomareddy Kantharaj, Y. D., Agarwal, M. & Agarwal, K. Ultrastructural and elemental analysis of sialoliths and their comparison with nephrolithiasis. Journal of investigative and clinical dentistry 5, 32–37 (2014).
15. Wu, C. C. et al. Sialolithiasis is associated with nephrolithiasis: a case-control study. Acta oto-laryngologica 136, 497–500 (2016).
16. DeLellis, R., Lloyd, R., Heitz, P. & Eng, C. Pathology & Genetics of Tumours of Endocrine Origin. In: World Health Organization Classification of Tumours (ed.3) (IARC Press, Lyon (2004).

Acknowledgements
This study was supported by Deutsche Krebshilfe, Swedish Research Council and ALF grants of Region Skane.

Author Contributions
K.H. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: K.H., O.H., X.L. Statistical analysis: X.L. Acquisition, analysis, or interpretation of data: K.S., J.S., K.H., O.H., A.F.. X.L. Drafting of the manuscript: K.H., O.H. Critical revision of the manuscript for important intellectual content: K.S., A.F., O.H. Final approval of the manuscript for publication: all authors.

Additional Information
Competing Interests: The authors declare no competing interests.
Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2018