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**Original Article**

# The Association Between Malignancy and End-stage Renal Disease in Taiwan

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**Objective:** Patients with end-stage renal disease are suggestive to have a higher risk for the development of some kinds of cancer. The aim of this study is to evaluate the possible association between malignancy and end-stage renal disease in Taiwan.
**Methods:** We used the data of the National Health Insurance system of Taiwan to assess this issue. The end-stage renal disease cohort contained 21 817 patients, and each patient was randomly frequency-matched with two people from the general population without end-stage renal disease based on their age and sex. The Cox proportional hazard regression analysis was conducted to estimate the effects of end-stage renal disease on the cancer risk.
**Results:** In patients with end-stage renal disease, the risk of developing overall cancer was significantly higher than the normal healthy subjects (adjusted hazard ratio = 1.64, 95% confidence interval = 1.54–1.74). This was also true when we analyzed males and females separately. For individual cancer, the risks for developing urinary tract cancers, liver cancer and breast cancer among patients with end-stage renal disease were significantly higher. On the contrary, lung, prostate and esophageal cancer risks were significantly lower when compared with the normal healthy subjects.
**Conclusions:** Our study found Taiwanese patients with end-stage renal disease to have a higher risk to develop urinary tract, liver and breast cancer. We unexpectedly discovered these patients to have a lower risk to get lung, prostate and esophageal cancer.

*Key words: malignancy – end-stage renal disease – association*

## INTRODUCTION

The case number of end-stage renal disease (ESRD) continues to steadily increase in western countries, as well as in Asia (1–4). The growing prevalence of patients with ESRD is mostly attributed to prolonged life span with the aid of modern medical treatment techniques. As a result of the increasing survival in ESRD patients, the incidence of chronic co-morbidities, such as malignancy, had been rising. Although cardiovascular disease is the most common cause of death in patients with ESRD (5), investigators were interested in evaluating the issue of the possible association between ESRD and cancer. Patients with dialysis are prone

to develop cancer based on the following possible reasons: an underlying disease leading to renal failure, a chronic infection by an oncogenic virus, a weakened immune system, a prior treatment with immunosuppressive or cytotoxic drugs, a nutritional deficiency and an altered DNA repair (6,7). In fact, the results from several studies found that patients with ESRD were indeed at an increased risk for some types of cancer compared with the general population (7–11). Renal cell carcinoma (RCC) especially showed an excess incidence in ESRD patients (6,12,13).

To the best of our knowledge, there are no large, population-based studies which outline the relationship between malignancy and ESRD in Taiwan. The aim of this study is to determine whether there is the same pattern of cancer risk for patients with ESRD in Taiwan. These results, presented in this paper, were from a retrospective cohort study to assess the possibility of a higher risk of developing malignancy in patients with ESRD. The original database was derived from the National Health Insurance (NHI) system in Taiwan.

## PATIENTS AND METHODS

### Data Sources

This study used data retrieved from the medical claims database of Taiwan's NHI program reformed in March 1995. The NHI has covered more than 96% of the country's population and contracted with 97% of hospitals and clinics since the end of 1996. We obtained the claims data of 1996–2008 from the National Health Research Institute (NHRI), Department of Health, consisting of registries and claims reported from contracted health-care facilities. With approval from NHRI, we were able to use the encrypted patient identification to link files, including the registry of Catastrophic Illness Patient Database, medical facilities, details of inpatients orders, ambulatory cares, dental services and prescriptions. The International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) was used to identify patient's disease.

### Study Population

The study cohort was identified from the registry of Catastrophic Illness Patient Database with newly diagnosed ESRD (ICD-9-CM code 585) in the period from 1997 to 1999 (in NHI program, patients with chronic renal failure and registered in the Catastrophic Illness Patient Database were the ESRD patients).

For each ESRD case, two controls without ESRD were selected from a sub-dataset randomly composed of one million insured population created by NHRI using a systematic random sampling method, frequency-matched with the distributions of age and sex during the same period. The index date for the ESRD patients was the date of their first registry. The index date for the controls was created by matching the year of case's index date. The age of each study subject was measured by the difference in time between the index date and the date of birth. Subjects with the history of malignant cancer (ICD-9-CM 140–230) diagnosed before the index date or with missing information on age or sex were excluded.

### Study Endpoint

With the unique patient's identification number, we linked study subjects to the registry for catastrophic illness patient claim data to identify the newly diagnosed cancer (ICD-9-CM 140–230) as the outcome of this study during the follow-up period which ended at 31 December 2008. The diagnosis of cancer in the National Health Insurance Research Database (NHIRD) needs histological confirmation and report in the Catastrophic Illness Patient Database. Person-years (PY) of follow-up time were calculated for each person until cancer diagnosed or censored. The date of censoring was defined as: the date of study subjects died in follow-up period, the date of last withdrawal from NHI or the date of termination of follow-up, whichever came first.

### Statistical Analysis

We compared the socio-demographic data including distributions of categorical age, gender, occupation, urbanization level and income between ESRD and non-ESRD patients using $\chi^2$ tests. We also calculated the incidence density with PY by these variables in the ESRD and non-ESRD cohorts. The crude hazard ratio (cHR) of cancer was calculated by each variable. We conducted the Cox proportional hazard regression analysis to assess the effects of ESRD on the risk of cancer, adjusting for variables that were significantly related to ESRD from the prior $\chi^2$ analyses. The sex- and cancer type-specific HRs of cancer were also examined by Cox's proportional hazard regression analysis. A value of $P < 0.05$ was considered statistically significant. All analyses were performed with SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

### Subject Characteristics

Table 1 summarizes the demographic characteristics of the ESRD cohort and the comparison cohort. Similar distribution of sex was observed in both case and control groups, with the female subjects were slightly predominant in both groups. Most subjects were ≥50 years of age (73.4% both in non-ESRD and ESRD cohorts). Patients with ESRD were more likely to be blue-collar occupation (45.5 vs. 43.7%, $P < 0.0001$), living in higher urbanization level (57.1 vs. 54.9%, $P < 0.0001$) and have lower income (37.0 vs. 35.2%, $P < 0.0001$).

**Table 1.** Comparisons in demographic characteristics between ESRD patients and non-ESRD patients in 1997–99

| Variables | ESRD | | *P* value[a] |
|---|---|---|---|
| | No, $N = 43\,634$ [*n* (%)] | Yes, $N = 21\,817$ [*n* (%)] | |
| Sex | | | |
| Women | 22 957 (52.6) | 11 494 (52.7) | 0.86 |
| Men | 20 677 (47.4) | 10 323 (47.3) | |
| Age (years) | | | |
| <40 | 5110 (11.7) | 2555 (11.7) | 1.00 |
| 40–49 | 6950 (15.9) | 3475 (15.9) | |
| 50–59 | 8783 (20.0) | 4369 (20.0) | |
| 60–69 | 11 722 (26.9) | 5861 (26.9) | |
| ≥70 | 11 114 (26.5) | 5557 (26.5) | |
| Occupation | | | |
| White collar | 19 021 (43.7) | 9282 (42.6) | <0.0001 |
| Blue collar | 19 041 (43.7) | 9896 (45.5) | |
| Others | 5506 (12.6) | 2594 (11.9) | |
| Urbanization level | | | |
| 1 | 12 190 (28.2) | 5988 (27.8) | <0.0001 |
| 2 | 11 548 (26.7) | 6323 (29.3) | |
| 3 | 7213 (16.7) | 3624 (16.8) | |
| 4 | 12 306 (28.5) | 5632 (26.1) | |
| Income | | | |
| <15 000 | 15 352 (35.2) | 8081 (37.0) | <0.0001 |
| 15 000–29 999 | 22 875 (52.4) | 11 860 (53.1) | |
| ≥30 000 | 5407 (12.4) | 1876 (11.1) | |

Urbanization level: 1 indicates the highest level of urbanization and 4 the lowest. ESRD, end-stage renal disease.
[a]$\chi^2$ test.

### Risk and HR of Cancer

Table 2 presents the incident densities and cHR of cancer by the baseline factors. During the follow-up period through 2008, the incidence of cancer was higher in the ESRD cohort than in the non-ESRD cohort (122.2 vs. 90.5 per 10 000 PY; cHR = 1.42, $P < 0.0001$; Table 2). The incidence densities of cancer were consistently higher in the ESRD cohort than in the non-ESRD cohort for both women (128.9 vs. 75.0 per 10 000 PY, cHR = 1.82, $P < 0.0001$) and men (114.2 vs. 113.3 per 10 000 PY, cHR = 1.10, $P = 0.047$). Among <40 years of age, the incidence of cancer in the ESRD cohort (59.4 per 10 000 PY) was 3.98 times higher than in the non-ESRD cohort (16.1 per 10 000 PY).

The further analysis by Cox's proportional regression model showed that the adjusted HR (aHR) of cancer was significantly greater in the ESRD cohort than that in the non-ESRD cohort after controlling for age, sex and socio-demographic variables [aHR = 1.64, 95% confidence interval (CI) = 1.54–1.74; Table 3]. After stratification analysis by sex, the ESRD cohort had 2.03-fold risk to developed cancer (95% CI = 1.86–2.21) in women and 1.27-fold risk to developed cancer (95% CI = 1.16–1.39) in men, respectively (Table 3).

Compared with the subjects without ESRD, the cancer type-specific analysis also showed that the aHR of patients with ESRD increased consistently in liver cancer (aHR = 1.48, 95% CI = 1.25–1.74), breast cancer (aHR = 1.36, 95% CI = 1.07–1.74), bladder cancer (aHR = 10.5, 95% CI = 8.60–12.9), urinary organ cancer (aHR = 9.52, 95% CI = 7.45–12.2) and renal pelvis and ureter cancer (aHR = 11.1, 95% CI = 7.08–17.5), but decreased in lung cancer (aHR = 0.49, 95% CI = 0.37–0.65), prostate cancer (aHR = 0.65, 95% CI = 0.43–0.97) and esophagus cancer (aHR = 0.40, 95% CI = 0.19–0.83; Table 3). Interestingly, after stratification analysis by sex in Table 3, the aHR of bladder cancer was significantly strengthened in women (aHR = 26.4, 95% CI = 18.5–37.7) than in men (aHR = 4.77, 95% CI = 3.61–6.30).

## DISCUSSION

Cancer has been the leading cause of death in the general population of Taiwan since 1982, and it occurs predominantly in older people. The cancer registry data from Taiwan showed that more than 61% of the cancer patients were diagnosed at or after the age of 60, and more than a quarter of cases in people aged 75 and over (14). The incidence of cancer is also expected to grow in patients with ESRD due to increased life span. This study focused on whether the cancer incidence is higher in patients with ESRD than in the normal healthy subjects.

To the best of our knowledge, this is the first population-based study with collection of 21 817 ESRD patients in Taiwan. This data source was from the NHI system which covers more than 96% of whole population in Taiwan and contracted with 97% of hospitals and clinics of Taiwan since the end of 1996. It represents the majority of people in Taiwan, so the generalizability is undoubted. The control group was randomly frequency-matched each patient with two people from the general population without ESRD based on age and sex. Unlike other papers, we used the HR instead of standardized incidence ratio (SIR) to estimate the cancer risk. HR is more reasonable because we did not pick the data from whole population to compare, and people from the control group are definitely without ESRD. Using the HR to estimate the endpoint for the two groups with and without the clear-cut risk factor (here means the ESRD) is appropriate. For the comparisons in demographic characteristics between the two groups, our data show that ESRD patients generally tend to have a higher ratio of blue-collar occupation, lower income, live in Southern Taiwan. It is not difficult to understand because lower socio-economic status is generally associated with an increased risk of ESRD (15).

**Table 2.** Comparisons of incidence density of cancer between cohorts with and without ESRD by socio-demographic factor

| Variables | ESRD | | | | | | | | Crude HR | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| | No | | | | Yes | | | | | |
| | *N* | Cases | Person-years | Rate[†] | *N* | Cases | Person-years | Rate[†] | | |
| All | 43 634 | 3670 | 405 714 | 90.5 | 21 817 | 1482 | 121 264 | 122.2 | 1.42 | <0.0001 |
| Sex | | | | | | | | | | |
| Women | 22 957 | 1635 | 218 118 | 75.0 | 11 494 | 852 | 66 099 | 128.9 | 1.82 | <0.0001 |
| Men | 20 677 | 2125 | 187 596 | 113.3 | 10 323 | 630 | 55 164 | 114.2 | 1.10 | 0.047 |
| Age (years) | | | | | | | | | | |
| <40 | 5110 | 84 | 52 058 | 16.1 | 2555 | 135 | 22 713 | 59.4 | 3.98 | <0.0001 |
| 40–49 | 6950 | 295 | 71 607 | 41.2 | 3475 | 353 | 26 433 | 133.5 | 3.59 | <0.0001 |
| 50–59 | 8783 | 712 | 88 441 | 80.5 | 4369 | 380 | 26 533 | 143.2 | 2.00 | <0.0001 |
| 60–69 | 11 722 | 1384 | 111 077 | 124.6 | 5861 | 420 | 28 429 | 147.7 | 1.32 | <0.0001 |
| ≥70 | 11 114 | 1285 | 82 531 | 155.7 | 5557 | 194 | 17 156 | 113.1 | 0.81 | 0.007 |
| Occupation | | | | | | | | | | |
| White collar | 19 021 | 1513 | 181 895 | 83.2 | 9282 | 673 | 54 105 | 124.4 | 1.61 | <0.0001 |
| Blue collar | 19 041 | 1762 | 176 539 | 99.8 | 9896 | 685 | 54 134 | 126.5 | 1.36 | <0.0001 |
| Others | 5506 | 484 | 46 702 | 103.6 | 2594 | 124 | 13 008 | 95.3 | 0.98 | 0.87 |
| Urbanization level | | | | | | | | | | |
| 1 | 12 190 | 1026 | 115 055 | 89.2 | 5988 | 419 | 34 114 | 122.8 | 1.48 | <0.0001 |
| 2 | 11 548 | 967 | 109 174 | 88.6 | 6323 | 478 | 36 243 | 131.9 | 1.60 | <0.0001 |
| 3 | 7213 | 570 | 67 059 | 85.0 | 3624 | 242 | 20 632 | 117.3 | 1.51 | <0.0001 |
| 4 | 12 306 | 1159 | 110 995 | 104.4 | 5632 | 332 | 29 130 | 114.0 | 1.15 | 0.02 |
| Income | | | | | | | | | | |
| <15 000 | 15 352 | 1414 | 134 443 | 105.2 | 8081 | 416 | 38 664 | 107.6 | 1.10 | 0.10 |
| 15 000–29 999 | 22 875 | 1980 | 215 765 | 91.8 | 11 860 | 864 | 69 047 | 125.1 | 1.46 | <0.0001 |
| ≥30 000 | 5407 | 366 | 55 507 | 65.9 | 1876 | 202 | 13 553 | 149.0 | 2.50 | <0.0001 |

HR, hazard ratio.
[†]Per 10 000 person-year.

There was an arseniasis-endemic area in Southern Taiwan and long-term arsenic exposure has been reported to be associated with chronic renal disease (16,17).

The results also show that ESRD patients in Taiwan have a significantly higher overall cancer occurrence. The risk is higher in both male and female ESRD patients. This finding is consistent with one international collaborative study (7) which showed that the SIR of cancer for all ESRD patients is 1.18 (95% CI = 1.17–1.20). Both male and female patients with ESRD had a significantly higher risk of cancer except for male patients in Europe. Another population-based cohort study from Australia found that men, but not women, with at least Stage 3 chronic kidney diseases have a significantly increased risk for cancer (8).

As for the individual cancer risk, most papers showed that ESRD patients are at an increased risk for RCC (6,12,13,18,19), as well as for other urinary tract malignancies (7–9). The preexistent renal disease is considered as a predisposing factor contributing to the increased tumor formation (12,13,20). From the experience in Taiwan, a high proportion of upper urinary tract urothelial carcinoma was observed in patients with ESRD (10,21). Our data showed significantly higher risks for the development of kidney cancer, renal pelvic/ureter cancer and bladder cancer in Taiwanese ESRD patients. Although we cannot specify the morphology types from our database, we can assume that the majority are RCCs for kidney cancer, and urothelial carcinomas for renal pelvic/ureter and bladder cancer. As for the prostate cancer, the results from prior papers are controversial. Port *et al*. (22) found that the SIR was significantly higher for invasive tumors of the prostate, and Kamata and Fushimi (23) found that the prevalence of prostate cancer in ESRD patients was equal or higher compared with that of normal healthy subjects. On the other hand, the results from

**Table 3.** HRs and 95% confidence interval (CI) of cancer associated with ESRD in Cox's regression analysis in different cancer by sex

| Variables | Overall | Women | Men |
|---|---|---|---|
| | HR[a] (95% CI) | HR[b] (95% CI) | HR[b] (95% CI) |
| Overall | 1.64 (1.54–1.74)*** | 2.03 (1.86–2.21)*** | 1.27 (1.16–1.39)*** |
| Cancer types-specific | | | |
| Hematological malignancy[b,c] | 0.95 (0.64–1.39) | 0.94 (0.55–1.58) | 0.94 (0.53–1.67) |
| Colorectal cancer | 1.12 (0.93–1.35) | 1.01 (0.76–1.33) | 1.22 (0.95–1.56) |
| Lung cancer | 0.49 (0.37–0.65)*** | 0.58 (0.37–0.90)* | 0.45 (0.31–0.64)*** |
| Liver cancer | 1.48 (1.25–1.74)*** | 1.44 (1.09–1.90)* | 1.48 (1.20–1.82)** |
| Breast cancer (women only) | — | 1.36 (1.07–1.74)* | — |
| Uterus, cervical, ovary and vagina cancer | — | 1.06 (0.80–1.41) | — |
| Prostate cancer (men only) | — | — | 0.65 (0.43–0.97)* |
| Head and neck cancer | 1.13 (0.87–1.47) | 1.22 (0.64–2.34) | 1.12 (0.84–1.48) |
| Esophagus cancer | 0.40 (0.19–0.83)* | —[d] | 0.44 (0.21–0.91)* |
| Bladder cancer | 10.5 (8.60–12.9)*** | 26.4 (18.5–37.7)*** | 4.77 (3.61–6.30)*** |
| Kidney and other urinary organ cancer | 9.52 (7.45–12.2)*** | 14.4 (10.2–20.5)*** | 5.64 (3.92–8.11)*** |
| Renal pelvis and ureter | 11.1 (7.08–17.5)*** | 16.2 (8.68–30.2)*** | 6.47 (3.20–13.1)*** |
| Cervical cancer | — | 0.96 | — |

[a]Adjusted for age, sex, occupation, urbanization and income.
[b]Adjusted for age, occupation, urbanization and income.
[c]ICD-9-CM: hematological malignancy, 200.xx-203.xx and 205.xx-208.xx; colorectal cancer, 153.xx and 154.xx; lung cancer, 162.xx; liver cancer, 155. xx; breast cancer, 174.xx and 175.xx; uterus, cervical, ovary and vagina cancer, 179.xx-184.xx; prostate cancer, 185.xx; head and neck cancer, 140.xx -149.xx and 161.xx; esophagus cancer, 150.xx; bladder cancer, 188.xx; kidney and other urinary organ cancer including kidney, 189.0, renal pelvis, 189.1, ureter, 189.2, urethra, 189.3, paraurethral glands, 189.4, other specified sites of urinary organs, 189.8, urinary organ, site unspecified, 189.0; renal pelvis and ureter, 189.1 and 189.2; and cervical cancer, 180.xx.
[d]No/any female patient with ESRD got esophageal cancer.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.0001$.

the collaborative study showed that patients with ESRD in the USA had a significantly lower risk for the development of prostate cancer (7). Horinaga *et al.* (24) found that hemodialysis men had lower prostate-specific antigen levels than those of controls as well. Our results revealed that ESRD is a protective factor for prostate cancer; however, we also found that the cHR is lower in the ESRD group for age $\geq$70. Prostate cancer patients tend to be diagnosed in the elderly, and it could be the same reason for the decrease in the risk of prostate cancer as the decreased trend of the cancer risk in the elderly.

Besides the urinary tract cancer, dialysis patients are more susceptible to viral-mediated cancers, including human papillomavirus-associated cancer, such as cervical cancer and tongue cancer (7) and hepatitis B and C virus-associated liver cancer (7,13). Our study demonstrated that there are significantly more liver cancer patients in the ESRD cohort than in the non-ESRD cohort, but neither for cervical cancer nor for head and neck cancer. The results derived from our data demonstrated a significantly higher risk for developing breast cancer in ESRD patients than in normal healthy subjects, which is compatible with the data source from the Australia and New Zealand, but not for the USA (7). ESRD patients are known to have a higher prevalence of breast calcification and may lead to an increased biopsy referral rate for breast cancer (25,26). This may partially explain the higher breast cancer detection in our ESRD patients. The association between ESRD and the hematologic malignancies is not very clear. The international collaborative study found that the risks for ESRD patients to develop the overall hematologic malignancies, as well as multiple myeloma, are consistently higher in all the three data sources (7); however, our results did not reveal this pattern. We were interested in exploring more when we discovered that our ESRD patients had a significantly lower risk to develop lung cancer and esophageal cancer. The Europe data source from the international collaborative study also disclosed less lung cancer patients in the ESRD group, but that study did not specify esophageal cancer. There are some possible undetermined protecting factors for some malignancies in ESRD patients that need to be further investigated.

Table 2 shows that ESRD patients have a lower cancer incidence than the normal healthy subjects in the age group equal or older than 70 years. It is unexpected because cancer tends to develop in older people. One of the possible reasons for this contradiction is that our study identified the ESRD cases

diagnosed in the period from 1997 to 1999, but the cancer cases were collected till 2008. The expected remaining lifetime of most dialysis patients is shorter than the time lived to develop malignancy; therefore, our older ESRD patients might not have enough time to develop cancer when compared with the control cohort at the same age level. In fact, the median survival of ESRD patients who were older than 75 years was <2 years after first dialysis worldwide (27,28).

In this study, we used new diagnosis of cancer to be the endpoint. If patient had double or triple cancer, we only considered the first one to calculate the follow-up time. For example, if one patient was diagnosed with prostate cancer after diagnosis of bladder cancer, we used bladder cancer as the endpoint; therefore, the follow-up period was the time between the index date and the diagnosis date of bladder cancer. To ensure that the double or triple cancer patients would not affect the results in Table 3, we re-analyzed Table 3 by excluding patients with two or more cancers (exclude 203 cases in the non-ESRD cohort and 105 cases the in ESRD cohort, data not shown), and the results show that the HR of any cancer in the table was barely changed or not changed. For this reason, we supposed that the risk trend was not changed; no matter how many cancers they carried with.

In conclusion, our study discovered the positive association between some malignancies and ESRD, and most of the relationships are well known. On the other hand, we also unexpectedly found the negative interaction between ESRD and some cancers. Further larger studies to support it with exploration the possible underlying mechanisms are mandatory.

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## Conflict of interest statement

None declared.

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