Increased risk of cancer in chronic dialysis patients: a population-based cohort study in Taiwan

Hsuen-Fu Lin, Yi-Hwei Li, Chih-Hsien Wang, Chu-Lin Chou, De-Jhen Kuo and Te-Chao Fang

Abstract

Background. An increased incidence of cancer in chronic dialysis patients has not been confirmed in the Chinese population. The aim of this population-based study was to examine the risk of various types of cancers in chronic dialysis patients in Taiwan.

Methods. Data of 92,348 chronic dialysis patients extracted from the National Health Institutes Research Database during 1997–2008 were analyzed. Patients newly diagnosed with end-stage renal disease, free of cancer and receiving dialysis for >3 months were eligible for inclusion in the study.

Results. After a mean follow-up of 4.4 years, a new cancer was diagnosed in 4,328 chronic dialysis patients. The standardized incidence ratio (SIR) of chronic dialysis patients was 1.4 [95% confidence interval (CI): 1.3–1.4] and annual incidence of cancer was 1.1%. A trend of an increased SIR was observed in young patients and within the first year of dialysis. Bladder cancer carried the highest SIR (SIR: 8.2, 95% CI: 6.7–9.9) and had the highest frequency (21.2%). Importantly, the frequency (15.3%) of liver cancer in chronic dialysis patients was higher than that of their healthy counterparts. Unexpectedly, chronic dialysis patients had a significantly reduced risk of developing lung cancer.

Conclusion. Increased risk of cancer in chronic dialysis patients is confirmed in the Taiwanese population and it is necessary to develop different strategies for cancer screening in chronic dialysis patients among different ethnicities.

Keywords: cancer risk; chronic dialysis; population-based study

Introduction

Impaired function of the immune system, impaired DNA repair, reduced antioxidant defense, accumulation of carcino-
information about the risk of cancers in chronic dialysis patients in Taiwan to supplement the earlier international collaborative study [6].

Materials and methods

Data collection

We used a longitudinal health insurance database provided by the Taiwan National Health Research Institute (NHRI). Taiwan launched its compulsory social insurance program, NHRI, to provide health care for all of the island’s residents in 1995. As of 2007, 22.6 million of Taiwan’s 22.96 million citizens were enrolled in this program; a coverage of >99% [11]. The database of this program contains registration files and original claim data for reimbursement. The identification of all individuals with reimbursement data in the NHRI database was encoded to protect the privacy of the individuals by NHRI. The NHRI was delegated to maintain the National Health Insurance Research Database (NHIRD) and to provide data upon request by scientists in Taiwan for research purposes (source: http://w3.nhri.org.tw/nhird/date_01.html).

In the NH system, the government defined several major diseases, such as ESRD and cancer, as ‘catastrophic illnesses’, and provided guidelines and regulations for the insured to apply for a catastrophic illness certificate. The application is formally reviewed, and if approved, the information is entered into the individuals’ certified card. Patients with catastrophic illness certification, who receive care for the insured or its related conditions within the validity period of the certificate, do not pay any out-of-pocket expenses (http://www.nhi.gov.tw/english/webdata.asp?menu=11&menu_id=596&webdata_id=3180).

We used a longitudinal health insurance database for people with ‘catastrophic illnesses’ provided by the NHRI. The database consisted of all the chronological applications and transitional information from the ‘catastrophic illness certificate’, including death dates for the deceased, as well as outpatient and inpatient claim data during the period from 1995 to 2008.

Study populations

This study was carried out with prior approval from the Ethics Committee and Human Subjects Institutional Review Board of Tzu Chi Hospital, Hualien. To select potential case subjects for this study, we first obtained the NHRI catastrophic illness registry files for all patients from 1 January 1997 to 31 December 2008. Patients newly diagnosed with ESRD [International Classification of Diseases (ICD)-9 code 585], free of cancer and receiving dialysis for >3 months were eligible in our study. To ensure the identity of the ESRD cases (ICD-9 code 585), we only selected data from the 98,133 individuals who received their first ever issuance of ESRD certification during the period 1997–2008 from the longitudinal catastrophic illness database. We excluded those patients with missing data regarding date of birth or sex; those diagnosed with cancer prior to certification; those whose dialysis lasted >3 months; those with a follow-up time of <3 months; those who received renal transplantation either before or after dialysis and those who had acquired immune deficiency syndrome. The first-ever cancer status, including type of cancer and date of diagnosis, of the study subjects was also obtained by linkage to the catastrophic illness database. A cytological or pathological report or evidence supporting the diagnosis of the malignancy is required to apply for a catastrophic illness certificate for cancer. Benign tumors, in situ malignancies, Kaposi’s sarcoma and metastatic cancers were excluded. All cancers were coded according to the ninth edition of the ICD (ICD-9 codes: 140–208).

Background cancer incidence

We calculated background cancer incidence rates for the general population from the cancer registry database provided by the Bureau of Health Promotion, Department of Health in Taiwan. The cancer registry database includes the patient’s age, sex, birth date, age at diagnosis, date of initial diagnosis, primary sites, histology, grading and stage. In the present study, age- and gender-specific cancer incidence rates for each location of the general population in Taiwan were collected for each year from 1997 until 2007.

Because the database used in this study consisted of de-identified secondary data released to the public for research purposes, the study was exempt from full review by the Institutional Review Board.

Statistical analysis

The follow-up time for cancer, defined as person-years at risk, began on the issue date of ESRD catastrophic illness certificate and ended on the date on which a cancer catastrophic illness certificate was issued, death or the end of the study period (31 March 2009), whichever came first. We calculated the expected number of cancers in patients with ESRD by multiplying the number of person-years accumulated in each stratum of age, sex and follow-up time by the corresponding specific rate of the general Taiwanese population. The SIR, taken as the ratio of observed to expected number of cancer cases, was used as a measure of relative risk, and 95% confidence intervals (CIs) were calculated after assuming a Poisson distribution of the observed number of cancers. SAS statistical software (SAS System for Windows, version 9.1.3; SAS Institute, Cary, NC) was used to perform the statistical analysis.

Results

Between January 1997 and December 2008, a total of 98,133 patients newly diagnosed with ESRD were identified. From this number, 5,279 patients were excluded because they had a cancer diagnosis preceding ESRD and 506 patients were excluded because of missing data and insufficient follow-up. Characteristics of chronic dialysis patients are summarized in Table 1. The cohort, comprised of 92,348 patients with ESRD, was analyzed with a mean follow-up of 4.4 years. The annual incidence of chronic dialysis patients was 1.1%.

Table 2 shows the overall risk of cancer in chronic dialysis patients. The SIR of overall cancer in chronic dialysis patients was significantly higher than in the general population (SIR: 1.4, 95% CI: 1.3–1.4). Young patients (≤34 years old) had a high SIR of cancer development (SIR: 9.2, 95% CI: 5.3–16.0). During the first 5 years of dialysis, patients had a higher SIR of cancer, particularly in the first year (SIR: 8.3, 95% CI: 7.6–9.0). After 8 years of dialysis, the SIR of overall cancer in chronic dialysis patients was negatively related to the duration of dialysis (SIR: 0.3, 95% CI: 0.2–0.3).

The site-specific cancer risk in chronic dialysis patients is summarized in Table 3. The urinary bladder, followed by the kidney, thyroid and liver were the most common sites of cancer development, in order of their SIR scores. With regard to the events of cancer in chronic dialysis patients, the highest ranking was urinary bladder cancer, followed by liver, kidney, colorectal and female breast cancers. Whether male or female, urinary tract cancers were the most commonly seen in patients with ESRD. However,
prostate cancer was a notable exception. Unexpectedly, chronic dialysis patients had a reduced SIR (SIR: 0.5, 95% CI: 0.5–0.6) of developing lung cancer than the general population.

Table 4 shows the top three cancers ranked by number in chronic dialysis patients. Bladder cancer had the highest frequency of cancers in ESRD patients (919/4328, 21.2%), and liver cancer had the second highest frequency (664/4328, 15.3%). There was a higher SIR of urinary bladder and kidney cancers in female dialysis patients than in male dialysis patients. The SIR gradually declined in proportion to the duration of dialysis treatment. The SIR for liver cancer was higher in males than in females and it was also reduced with the duration of dialysis. Young chronic dialysis patients had a high SIR of urinary bladder, liver and kidney cancers, and this trend was consistent within the whole cohort. With increased age in chronic dialysis patients, the SIRs of kidney and urinary bladder cancers were decreased but were still higher than those of the general population. In contrast, elderly (≥65 years old) chronic dialysis patients had a lower SIR of liver cancer than the general population.

Discussion

The deficiency of information pertaining to Asian populations, particularly the Chinese, in an international study on the overall risk of cancer in chronic dialysis patients [6] led us to investigate the risk of long-term dialysis in Taiwan. There are two major advantages in our population-based cohort study. The first advantage is that the registries of chronic dialysis patients and the cancer database are for practical purposes complete because the Taiwan NHI program covers >99% of Taiwanese residents [11]. The second advantage is that our cohort study is a Chinese population-based study.

Our study has six major findings. Firstly, the annual incidence of cancer development in chronic dialysis patients was 1.1%. Secondly, there is an increment in the SIR of developing overall cancer in chronic dialysis patients (SIR: 1.4, 95% CI: 1.3–1.4) that is independent of age, sex and duration of dialysis. Thirdly, patients aged <35 years old and patients having a duration of dialysis of <5 years had a higher risk of cancer. Fourthly, the highest SIR of cancers in our study was attributed to genitourinary tract cancers. Fifthly, the cancers with the highest rates of incidence in our study were bladder, liver and kidney cancers. Sixthly, our study showed that chronic dialysis patients had a reduced SIR (SIR: 0.5, 95% CI: 0.5–0.6) of developing lung cancer than the general population.

The SIR of overall cancers in female patients with chronic dialysis was higher than that in male patients with chronic dialysis, and this is consistent with the previous international collaborative study [6]. Our study showed young dialysis patients (<35 years old) had the highest SIR of cancer development and this is consistent with the report from international collaborative study [6]. The reason for a higher SIR of cancers in young dialysis patients than in their healthy counterparts is unclear. Heiland et al. [12] hypothesize that this age phenomenon, defined as a situation in which tumor promotion and progression are faster in younger patients, might be due to a considerably more serious viral-associated malignancy in the young [12]. The deterioration of the cancer defense system and
inactivation of important tumor suppressor genes are observed in advanced age and in patients either with or without chronic kidney disease. Therefore, the difference in cancer risk could disappear with advancing age [12]. Similarly, the age phenomenon is also shown in cardiovascular (CV) mortality of chronic dialysis patients [13]. The ratio of CV mortality in chronic dialysis patients to that in their healthy counterparts is higher in young patients than that in elderly patients [13].

Another interesting finding in our cohort was that elderly dialysis patients (≥65 years old) had a lower SIR of cancer (SIR: 0.8, 95% CI: 0.7–0.8) compared to their healthy aged counterparts. This is different from previous international collaborative studies [6, 14, 15] that found that the SIR of cancer risk in elderly chronic dialysis patients was higher than in their healthy counterparts. The reason for the discrepancy between our cohort and the international collaborative study [6] is unclear and may be due to ethnic difference and/or enhanced mortality. The enhanced mortality is because the age-dependent decline of enhanced SIR in cancer of dialysis patients will result in both a smaller number of new cases and a shorter exposure time (long-standing cases) to chronic dialysis with less malignant cell transformation.

Our study showed that the highest SIR of cancer risks occurred in the first year of dialysis and that the risk gradually declined with the duration of dialysis. Several other studies have also shown similar results [6, 16]. For example, the international collaborative study [6] demonstrated that the risk of cancer in chronic dialysis patients was higher in the first year, particularly in the populations of Australia and New Zealand [6]. The reason for this might be that ESRD is an important promoting factor of malignancies [17], suggesting that a better surveillance method is needed for these dialysis patients [12]. Regarding both chronic renal disease and ESRD as risk factors for carcinogenesis, several studies demonstrated that impairment of DNA repair during chronic renal disease [18] and chromosomal abnormalities in the uremic state [19] contributed to the development of cancer. Considering the better surveillance of chronic dialysis patients as a cause of increasing cancer incidence, i.e. lead time bias, an international collaborative study [6] and several studies from Taiwan [20–23] showed that an aggressive surveillance in chronic dialysis patients could explain the higher incidence of recognized cancer. However, this effect needs to be further investigated.

Our study showed that the highest SIR of cancer in chronic dialysis patients was for bladder cancer (SIR: 8.2, 95% CI: 6.7–9.9) compared to that in their healthy counterparts. This is different from the international collaborative studies [6, 14, 24] which found that kidney cancer had the highest SIR of cancers in chronic dialysis patients. The reason for this discrepancy is unknown, but it may be associated with the heavy consumption of some Chinese herbal products or compound analgesics in the Taiwanese population [22, 25]. Additionally, other studies have indicated analgesic nephropathy, cystic kidney disease and pyelonephritis could evoke the development of urologic cancer in dialysis patients [20, 21]. Taken together, concerning the high incidences of urologic tumors in Taiwan, we hypothesized that these causes may be derived from analgesic abuse, Chinese herbs, renal stones and infectious or obstructive nephropathy, etc.

Urinary bladder, liver and kidney cancers, in that order, had the highest incidences in our study. However, chronic dialysis patients in Japan had a high frequency of gynecological and urinary tract cancers, whereas chronic dialysis patients in Korea had a high frequency of gastrointestinal tract and urinary tract cancers [7, 8].

Paradoxically, our study showed that chronic dialysis patients had a lower SIR (SIR: 0.5, 95% CI: 0.5–0.6) of developing lung cancer compared with the general population, although the frequency of lung cancer in chronic dialysis patients was in the top six cancers, with an incidence of

### Table 4. The top three cancers ranked by number in chronic dialysis patients

<table>
<thead>
<tr>
<th></th>
<th>Bladder</th>
<th></th>
<th>Liver</th>
<th></th>
<th>Kidney</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>SIR</td>
<td>95% CI</td>
<td></td>
<td>N</td>
<td>SIR</td>
</tr>
<tr>
<td>All</td>
<td>919</td>
<td>8.2</td>
<td>6.7–9.9</td>
<td></td>
<td>664</td>
<td>1.4</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>350</td>
<td>4.5</td>
<td>3.5–5.8</td>
<td></td>
<td>452</td>
<td>1.4</td>
</tr>
<tr>
<td>Female</td>
<td>569</td>
<td>16.2</td>
<td>11.5–22.8</td>
<td></td>
<td>212</td>
<td>1.2</td>
</tr>
<tr>
<td>Age at first dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0–34 years</td>
<td>26</td>
<td>203.0</td>
<td>0.8–492018</td>
<td></td>
<td>26</td>
<td>20.0</td>
</tr>
<tr>
<td>35–54 years</td>
<td>334</td>
<td>46.2</td>
<td>22.1–96.6</td>
<td></td>
<td>231</td>
<td>4.1</td>
</tr>
<tr>
<td>55–65 years</td>
<td>252</td>
<td>12.0</td>
<td>7.7–18.8</td>
<td></td>
<td>202</td>
<td>1.5</td>
</tr>
<tr>
<td>≥65 years</td>
<td>307</td>
<td>3.6</td>
<td>2.9–4.6</td>
<td></td>
<td>205</td>
<td>0.7</td>
</tr>
<tr>
<td>Time after first dialysis</td>
<td></td>
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</tr>
<tr>
<td>Year 1</td>
<td>78</td>
<td>25.0</td>
<td>18.6–33.5</td>
<td></td>
<td>135</td>
<td>10.0</td>
</tr>
<tr>
<td>Year 2</td>
<td>123</td>
<td>18.7</td>
<td>14.4–24.2</td>
<td></td>
<td>130</td>
<td>4.5</td>
</tr>
<tr>
<td>Year 3</td>
<td>145</td>
<td>18.1</td>
<td>14.1–23.2</td>
<td></td>
<td>219</td>
<td>2.6</td>
</tr>
<tr>
<td>Year 4</td>
<td>222</td>
<td>13.5</td>
<td>10.5–17.4</td>
<td></td>
<td>222</td>
<td>2.2</td>
</tr>
<tr>
<td>Year 5</td>
<td>232</td>
<td>10.8</td>
<td>8.3–14.0</td>
<td></td>
<td>232</td>
<td>1.4</td>
</tr>
<tr>
<td>Years 6–8</td>
<td>245</td>
<td>8.0</td>
<td>6.4–10.0</td>
<td></td>
<td>245</td>
<td>0.8</td>
</tr>
<tr>
<td>&gt;Year 8</td>
<td>85</td>
<td>1.9</td>
<td>1.4–2.5</td>
<td></td>
<td>94</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*N = number.
Cancer risk in chronic dialysis patients

5.5% (236/4328). However, based on the international collaborative study, the SIR of lung cancer (0.9–1.4) did not have a significant difference between chronic dialysis patients and their healthy counterparts [6]. The reason for this discrepancy between our study and the international collaborative study is unclear and might be due to ethnic differences and geographic variation. For example, several studies have demonstrated that administration of epidermal growth factor receptor tyrosine kinase inhibitors for non-small cell lung cancer resulted in a better response in East Asian patients than in patients from the European Union and North America (i.e. USA and Canada) [26–28].

There was no significant difference in SIR of breast and colorectal cancers between chronic dialysis patients and their healthy counterparts. Similarly, the international collaborative study showed that the SIR of breast and colorectal cancers did not have any significant differences compared to their healthy counterparts [6]. However, the frequency of colorectal and breast cancers in chronic dialysis patients was the fourth and fifth highest cancers, comprising 10.8 and 5.8% of all cancers, respectively. Therefore, we should not overlook these cancer sites as they represent a relatively high proportion of cancers in chronic dialysis patients.

Our study showed that the SIR of kidney and bladder cancer in chronic dialysis patients decreased with increased duration of dialysis. According to the international collaborative study, the SIR of kidney and bladder cancers in chronic dialysis did not have these trends, although the SIR of kidney and bladder cancers in chronic dialysis patients is higher than that of their healthy counterparts [29]. The reason for this discrepancy between our cohort and the international collaborative studies is unclear but might be due to ethnic differences or reduced urine output. It has been suggested that during the progression from the pre-ESRD state to ESRD, reduced urine flow would increase the risk of bladder cancer and other urinary tract cancers [12]. Therefore, with increased duration of dialysis, progressively fewer toxins would be excreted in the urine flow, which might explain why the SIR of kidney and bladder cancers in chronic dialysis patients are reduced with increased duration of dialysis.

The present study showed that the frequency of liver cancer was the second highest found in the dialysis patients and that the SIR of liver cancer in chronic dialysis patients was higher than that of their healthy counterparts. However, the frequency of liver cancer in the international collaborative study was low (0.04%, 357/831804); hence, the SIR of liver cancer in the chronic dialysis patients in our study is not consistent with the results in the international collaborative study [6]. Taiwan is known as a country where infection with hepatitis B and hepatitis C is endemic and the incidence of hepatocellular carcinoma is high [30, 31]. It has been reported that the prevalence of viral hepatitis in continuous ambulatory peritoneal dialysis patients in Taiwan is 75 and 17% for hepatitis B and hepatitis C, respectively [32]. A population-based study showed that liver cirrhosis, alcohol abuse and Asian race were significant risk factors for hepatocellular carcinoma in chronic dialysis patients with chronic hepatitis C virus (HCV) infection, although 37% of these patients were co-infected with hepatitis B virus (HBV) [33]. In our study, a high frequency of liver cancer in chronic dialysis patients might be because HBV and HCV infection is endemic in Taiwan.

There were some limitations in this study, even though we conducted a population-based cohort study from NHIRD. Firstly, information on the primary cause renal disease of ESRD is limited. Therefore, it is difficult to analyze the relationships between underlying renal diseases and the SIR of various types of cancers in chronic dialysis patients. Secondly, some basic lifestyle data were not available, such as tobacco use. It is well known that lung cancer is highly correlated with smoking status. Without the information of smoking status in this database, it is difficult to interpret the lower SIR of lung cancer in our cohort study.

In conclusion, a trend in the increased risk of cancer in young patients and within the first year of dialysis was observed. Several observations in our study are different from the earlier international collaborative study. Firstly, bladder cancer had the highest frequency (21.2%). Secondly, the frequency (15.3%) of liver cancer was second highest and the risk of liver cancer in chronic dialysis patients was higher than that in their healthy counterparts. Thirdly, chronic dialysis patients had a lower SIR of developing lung cancer although the frequency of lung cancer in chronic dialysis patient was high (5.5%).

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Conflict of interest statement. None declared.

References
