Original Article

Cancer Among End-Stage Renal Disease Patients on Dialysis

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Abstract

Introduction: The aim of this study is to investigate the risk of cancer among end-stage renal disease (ESRD) patients on dialysis in Singapore. Materials and Methods: The study looks at a retrospective cohort of 5505 ESRD patients who had received dialysis between 1998 and 2007. The cancer risk of these patients would be compared against the risk of the general population. Results: During a median follow-up time of 3.9 years, 267 (4.9%) dialysis patients developed cancer. The risk of cancer (excluding non-melanoma skin cancer) is 1.66 times higher in dialysis patients than the general population, and is highest at age less than 35 years old and at first year after dialysis. Cancer risk was found to be significantly higher among Chinese dialysis patients, followed by Malays, compared to the general population. The 3 sites with highest elevated cancer risks among dialysis patients compared to the general population are kidney, tongue and multiple myeloma. Conclusion: The finding of elevated cancer risk among younger dialysis patients is similar to other international studies. High cancer risks among specific cancer sites were also consistent with other studies. In view of the lack of screening procedures for these cancers and shortened expected survival of ESRD patients, cancer screening of ESRD patients should be individualised and based on a reasonable life expectancy and transplant candidacy, keeping in mind the competing risk of cardiovascular mortality.

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Key words: Chronic dialysis, Chronic kidney disease, Malignant neoplasms

Introduction

The age standardised incidence rate (ASIR) of end-stage renal disease (ESRD) patients on dialysis in Singapore increased from 176.1 (95% CI, 171.7 to 180.6) per million population (pmp) in 1999 to 211.3 pmp in 2007. Due to increased longevity, it is expected that malignant neoplasms will become an increasingly relevant health issue in this population. Previous studies have suggested that the frequency of cancer is higher in patients with ESRD than the general population.[1-5] This increase in cancer risk could be due to several reasons such as greater exposure to hepatitis B and C viruses, chronic infection, a weakened immune system and treatment with immunosuppressive or cytotoxic drugs.[6] The cancer incidence among ESRD patients in Singapore had not been looked at previously. There has been a recent study done on ethnic Chinese patients in Taiwan.[3] Singapore's population is unique in that apart from the ethnic Chinese majority, it also includes a significant proportion of ethnic Malay and Indian minorities. Against this background, the aim of the study is to investigate the risk of cancer in ESRD patients on dialysis.

Materials and Methods

A retrospective cohort of 5505 ESRD patients who had received dialysis between 1998 and 2007 for at least 3 months was assembled from the population-based Singapore Renal Registry. Case notification in Singapore was event-driven and cases are identified based on serum creatinine >10 mg/dL or 880 umol/L or on initiation of renal replacement therapy, with the exception of Singapore General Hospital, which had provided listings of patients with estimated glomerular filtration rate (eGFR) <15 mL/min (corrected for body surface area (BSA) 1.73 m^2) since 2007. Data submission by dialysis centres was voluntary and was estimated at 95% of all dialysis patients in Singapore.

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Patients in whom the diagnosis of cancer preceded dialysis or those who received renal allograft or started dialysis after renal allograft were excluded. Additionally, benign tumours, non-melanoma skin cancers and metastatic cancers were also excluded.

The standardised incidence ratio (SIR) of observed: expected incidence rate of cancers in the cohort versus the general population was used to estimate relative risk. Patients were censored at time of death, at date of last follow-up or the end of the follow-up period (31 October 2010). It is assumed that the observed cancer cases follow a Poisson distribution. Data analysis was performed using STATA 10.0.

Results

Baseline Characteristics of ESRD Patients with Cancers

Among the 5505 ESRD patients on dialysis, 267 (4.8%) developed cancers, with a median follow up of 3.9 years (Table 1). A slightly higher proportion of females developed cancers (52.4%) compared to males. Majority of the cancer patients were Chinese (80.1%). Among the 267 ESRD patients on dialysis with cancers, about one third (33.3%) had cancer diagnosed in the first year of dialysis with a majority (86.5%) of them receiving haemodialysis. Diabetes nephropathy was the most common cause of ESRD among this group of patients.

Compared to Korea (45%), USA (32.8%), Europe (13.2%) and Australia (14.3%), a higher proportion of dialysis patients in Singapore had diabetes (Table 1).

Table 1. Characteristics of ESRD Patients and ESRD Patients Who Developed Cancer

	Total ESRD patients (n = 5505)		**ESRD patients with cancer (n = 267)**	
Mean age, years (SD)	58.1	(13.0)	60.9	(13.1)
Gender	Number	%	Number	%
Male	2875	52.23	140	47.57
Female	2630	47.77	127	52.43
Ethnicity				
Chinese	3848	69.90	214	80.15
Malay	1201	21.82	41	15.36
Indian	396	7.19	11	4.12
Others	60	1.09	1	0.37
Time on dialysis				
1 year	1283	23.31	89	33.33
2 years	644	11.70	49	17.23
3 to 5 years	2142	38.91	76	29.96
6 to 10 years	1236	22.45	45	19.10
>10 years	200	3.63	1	0.37
Dialysis Mode				
Haemodialysis	4627	84.05	231	86.52
Peritoneal dialysis	878	15.95	36	13.48
Cause of ESRD				
Diabetes	3206	58.24	108	40.45
Glomerular Nephritis	1203	21.85	79	29.59
Hypertension	503	9.14	40	14.98
Others*	444	8.07	30	11.24
Unknown	149	2.71	10	3.75
Mean Time to cancer discovery in months (SD)			43.6	(30.8)

ESRD: End-stage renal disease

*Others refers to polycystic kidney disease / other cystic diseases, vesicoureteric reflex / chronic pyelonephritis, obstruction, stone disease, etc

Comparison of Cancer Sites Between General Population and ESRD Patients

The most common cancer sites were breast (12.3%), lung (11.6%), colon (10.9%) and kidney (10.9%). Compared to the general population, the 3 leading cancer sites with higher frequencies among dialysis patients were kidney, bladder and multiple myeloma cancer (Table 2).

Table 2. Comparison of Selected Cancer Types Between the General Population and ESRD Patients on Dialysis

Cancer Sites	General Population		ESRD Patients	
	Number	%	Number	%
Kidney	1712	2.5	30	10.9
Myeloma	504	0.7	5	1.8
Colon	8150	11.9	31	10.9
Stomach	4689	6.8	14	5.1
Liver	4352	6.3	18	6.5
Bladder	1710	2.5	10	3.6
Female Breast	12,361	18.0	34	12.3
Lung	10,941	15.9	32	11.6
Thyroid	1699	2.5	9	3.3
Tongue	442	0.6	3	1.1

ESRD: End-stage renal disease

Mean Duration for Development of Cancer in ESRD Patients

The mean duration from initiation of dialysis to the discovery of cancer was the shortest for myeloma (15.4 months) and longest for thyroid cancer (70.6 months) (Table 3).

Table 3. Mean Interval (months) to Discovery of Selected Cancers in ESRD Patients on Dialysis

Cancer Sites	Mean interval (Months)	Standard Deviation
Myeloma	15.4	15.5
Bladder	33.3	24.6
Lung	33.5	18.9
Liver	35.8	31.2
Colon	34.5	32.0
Tongue	43.1	19.7
Stomach	44.1	28.4
Female Breast	54.3	28.8
Kidney	58.9	36.8
Thyroid	70.6	40.1
Small intestines	119.1	-

ESRD: End-stage renal disease

Risk of Developing Cancer in ESRD Patients

The risk of cancer (excluding non-melanoma skin cancer) was 1.66 times higher in dialysis patients than the general population, and was highest at age of dialysis initiation less than 35 and at first year after dialysis (Table 4). Among the various causes of ESRD, 'other' causes, which include infective and obstructive nephropathies, congenital disease and toxic nephropathies, confer the highest cancer risk. The risk of cancer decreases with increasing time after dialysis. It is interesting to note the risk of cancer among the dialysis population was lower than the general population when the duration of dialysis was more than 6 years. In addition, cancer risk is significantly higher compared to the general population among Chinese dialysis patients, followed by Malays.

Table 4. Overall Risk of Cancer in ESRD Patients on Dialysis

	SIR	95% CI
Overall	1.66	1.42, 1.95
Gender		
Male	1.53	1.23, 1.90
Female	1.84	1.47, 2.30
Ethnicity		
Chinese	1.79	1.51, 2.14
Malay	1.52	1.04, 2.21
Indian	0.74	0.28, 1.98
Others	0.00	-
Age at first dialysis		
0 to 34 years	8.93	3.35, 23.80
35 to 64 years	1.86	1.51, 2.29
≥ 65 years	1.38	1.08, 1.77
Cause of ESRD		
Diabetes	1.40	1.11, 1.77
Glomerulonephritis	2.05	1.55, 2.71
Hypertension	1.63	1.00, 2.67
Others	2.22	1.32, 3.75
Unknown	1.90	0.85, 4.23
Time after dialysis		
<1 year	7.60	5.93, 9.75
2 years	3.52	2.45, 5.07
3 to 5 years	1.39	1.04, 1.86
>6 years	0.44	0.29, 0.69

SIR: Standardised incidence ratio; ESRD: End-stage renal disease

Site Specific Cancer Risk in ESRD Patients on Dialysis

The 3 sites with highest elevated cancer risks among dialysis patients compared to the general population are kidney, tongue and multiple myeloma cancer (Table 5). Many other sites showed increase in risk but the increase in risk was not statistically significant for example stomach, lung and liver. As only kidney cancer had a substantial number of cases among the top 3 sites with elevated cancer risk, we only present the site-specific cancer risk for kidney cancer (Table 6).

Table 5. Site-specific Cancer Risk in ESRD Patients on Dialysis

Sites (ICD9 code)	n	SIR (95% CI)
All but skin (140 – 208)	267	1.66 (1.42, 1.95)
Oral Cavity		
All (140 – 149)	10	1.64 (0.85, 3.16)
Tongue (141)	3	5.01 (1.62, 15.53)
Digestive		
All (150 – 158)	95	1.77 (1.41, 2.23)
Stomach (151)	14	1.14 (0.57, 2.27)
Intestinal (152 – 154)	47	1.52 (1.07, 2.15)
Liver (155)	18	1.54 (0.85, 2.78)
Respiratory		
All (160 – 165)	34	1.10 (0.73, 1,68)
Lung (162)	32	1.17 (0.77, 1.80)
Bone, skin and breast		
All (170 – 175)	45	1.52 (0.99, 2.33)
Breast (174)	34	1.63 (1.06, 2.50)
Genitourinary		
All (179 – 189)	56	13.78 (9.69, 19.59)
Cervix of uterus (180)	2	0.45 (0.06, 3.17)
Body of uterus (182)	6	1.48 (0.55, 3.94)
Other female genital (184)	0	
Prostate (185)	6	0.28 (0.07, 1.11)
Penis scrotum (187)	1	3.64 (0.51, 25.82)
Bladder (188)	10	3.02 (1.5, 6.05)
Kidney (189)	30	5.25 (3.11, 8.86)
Other and unspecified		
All (190 – 199)	15	1.09 (0.45, 2.61)
Thyroid and other endocrine (193 – 194)	9	1.90 (0.61, 5.88)
Haemopoietic		
All (200 – 208)	21	1.48 (0.80, 2.75)
Non-Hodgkin Lymphoma (200, 202)	10	0.29 (0.04, 2.03)
Hodgkin's Disease (201)	0	
Multiple Myeloma (203)	5	3.68 (1.19, 11.42)
Leukaemia (204 – 208)	6	2.63 (1.18, 5.86)

ESRD: End-stage renal disease; SIR: Standardised incidence ratio

Table 6. Risk of Kidney Cancer in ESRD Patients on Dialysis

Kidney	n	SIR (95% CI)
All	30	5.25 (3.11, 8.86)
Gender		
Male	17	3.33 (1.50, 7.41)
Female	13	9.24 (4.62, 18.47)
Time after dialysis		
<1 year	7	8.72 (2.18, 34.85)
2 years	4	17.21 (6.46, 45.84)
3 – 5 years	6	2.14 (0.53, 8.55)
>6 years	13	4.72 (2.12, 10.50)
Cause		
Diabetes	6	2.73 (1.03, 7.28)
Glomerulonephritis	14	10.43 (4.97, 21.87)
Hypertension	6	7.18 (1.80, 28.72)
Others	4	5.79 (0.82, 41.12)
Unknown	0	0

ESRD: End-stage renal disease; SIR: Standardised incidence ratio

The risk of kidney cancer is highest within 2 years of dialysis. The risk of cancer by age at initiation of dialysis has been omitted due to the large confidence intervals for the youngest age group.

Conclusion

ESRD patients are known to have high incidence of cancer as a result of their weakened immune system, immuno-suppressive treatment, altered deoxyribo nucleic acid, (DNA) repair and chronic infection. This study determines whether these dialysis patients were at higher risk of developing specific cancers with the view to recommend careful surveillance so that treatment could be instituted early to improve the duration and quality of life.

In agreement with previous studies,[1,3-5] our study showed an overall increased risk of cancer in dialysis patients compared to the general population. Also consistent with previous studies, our study also had a higher risk of cancer in younger dialysis patients which declined with increasing age. This phenomena had been hypothesised to be due to a more serious viral-associated malignancy in younger, compared to older patients, as the former group may not have the necessary antibodies to counter the infections.[3,7] Furthermore, as cancer defense mechanisms are likely to be weakened with advanced age, both in the general population as well as the ESRD patient population, this will result in a lower differential risk of cancer with advanced age. Finally, this could also be due to competing risks of the older population being diagnosed with other chronic illnesses such as cardiovascular disease.

The high risk of cancer diagnosis, especially within 1

year of dialysis, could be partly explained by undetected cancers being already present before dialysis. This is most likely true of cancers that cause little or no symptoms until the advanced stages, such as myeloma and lung cancer. The peculiarity of cancer risk elevation in the general population relative to the ESRD patient population after 6 years could be due to survival of the fittest, whereby the patients on dialysis who survive long term could be healthier than selected individuals from the general population.

In terms of risk of cancers among various causes of ESRD, the highest risk ratios were seen in patients with 'other' disease, followed by glomerulonephritis and hypertension. This is similar to findings from the international collaborative study where infective and obstructive nephropathies, congenital disease and toxic nephropathies were found to have the highest SIRs.

Ethnic differences in cancer risk could possibly be attributed to genetic differences or differential distributions in competing risks of comorbidities. For instance, deletion loci on the CYP2A6 gene has been found to be associated with reduced susceptibility to lung cancer in the Japanese population. Interestingly, the highest frequency of this deletion is found among the Malays (35.2%), followed by the Chinese (18.3%) and Indians (7.1%).[8] This association is worth investigating, as Malay males in Singapore have the highest smoking prevalence but lower age-standardised lung cancer rates compared to Chinese males. The ASIR of acute myocardial infarction among Malays or Indians is about twice that of Chinese.[9] The ASIR of stroke among Malays is greater than 1.5 times and that of Indians is greater than 1.2 times that of Chinese. Given that cardiovascular mortality is the leading cause of death among dialysis patients, it may be that compared to their Chinese counterparts, proportionately more Malays and Indians develop cardiovascular disease rather than cancer.

The risk of bladder cancer in Singapore was not as greatly elevated as compared to Taiwan. It had previously been postulated that the high SIR for bladder cancer among Taiwanese patients may be related to heavy consumption of Chinese herbal or analgesic products.[3] The use of complementary and alternative medicine (including traditional medicines, acupuncture and health supplements) in Singapore is also fairly common at 76%[10] over a 1-year period with Chinese herbs although consumption patterns may differ from those in Taiwan.

The elevated risk of kidney cancer is a consistently seen observation in the international collaborative study, Denmark[1] and Taiwan. Both inherited and acquired renal cystic disease seem to increase kidney cancer risk, though acquired disease appears to increase risk to a greater extent compared to inherited disease.[6]

The risk of multiple myeloma among dialysis patients has been found to be elevated in Australia and New Zealand, as well as in Europe and the US. There are currently no well-established lifestyle or disease-related risk factors for multiple myeloma, although this may be in part due to difficulties in conducting studies of sufficient power.[11] However, some evidence of cancer association has been found for AIDs, herpes zoster/shingles and hepatitis C. The annual incidence of hepatitis C virus among dialysis patients has been found to be much higher among dialysis patients than in the general population and this could be attributed to nosocomial infection.[12] It had been suggested that the SIR of multiple myeloma is the most elevated among all cancers as myeloma could have been a cause of ESRD[13] rather than the other way round. Investigators from Australia and New Zealand have re-derived the SIR excluding cases of myeloma diagnosed within 2 years and found the new SIR to be 1.9, which was 5-fold less in magnitude compared to the original value.[5] In our study, only 1 out of 5 diagnosed cases of myeloma was diagnosed after 2 years.

In our study, we had excluded patients who had been on dialysis for less than 3 months. This group is made up of patients who had recovered, ceased dialysis or died. Additionally, patients who had recovered or ceased dialysis beyond 3 months were also excluded. These exclusions alleviate the issue of causality at least partially, as the cancer may actually have been present before the renal patient started dialysis; it may just have been undetected. The excluded patients comprised 13.3% of the original study population. The only other study that mentioned a similar exclusion was the Taiwanese study.[3]

There has been concern that closer cancer surveillance could have given rise to increased detection of cancers in the dialysis patient population. However, a study on dialysis patients from the US has found that the likelihood of non-localised cancer stage at diagnosis was not significantly different for patients with ESRD versus the general population after controlling for age at diagnosis, race, gender, geographical region of residence, year of diagnosis and cancer site.[14] Although this study found a 1.66-fold increase in cancer risk among the ESRD patients on dialysis compared with the general population, general population cancer screening among dialysis patients has not been found to be cost-effective.[15] Cardiovascular disease is the leading cause of death among ESRD patients. Cancer screening of ESRD patients should be individualised and based on a reasonable life expectancy and transplant candidacy, keeping in mind the competing risk of cardiovascular mortality.

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