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Cancer risk in patients receiving renal replacement therapy: A meta-analysis of cohort studies

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Abstract. It has been reported that patients receiving renal replacement therapy (RRT), including dialysis and kidney transplantation, tend to have an increased risk of cancer; however, studies on the degree of this risk have remained inconclusive. The present meta-analysis was therefore performed to quantify the cancer risk in patients with RRT. Cohort studies assessing overall cancer risk in RRT patients published before May 29, 2015 were included following systematic searches with of PubMed, EMBASE and the reference lists of the studies retrieved. Random-effects meta-analyses were used to pool standardized incidence rates (SIRs) with 95% confidence intervals (CIs). Heterogeneity tests, sensitivity analyses and publication bias assessment were performed. A total of 18 studies including 22 cohort studies were eventually identified, which comprised a total of 1,528,719 patients. In comparison with the general population, the pooled SIR for patients with dialysis including non-melanoma skin cancer (NMSC), dialysis excluding NMSC, transplantation including NMSC, transplantation excluding NMSC and RRT were 1.40 (95% CI, 1.36-1.45), 1.35 (95% CI, 1.23-1.50), 3.26 (95% CI, 2.29-4.63), 2.08 (95% CI, 1.73-2.50) and 2.01 (95% CI, 1.70-2.38), respectively. The cancer risk was particularly high in subgroups of large sample size trials, female patients, younger patients (age at first dialysis, 0-34 years; age at transplantation, 0-20 years), the first year of RRT and non-Asian transplant patients. A significant association was also found between RRT and the majority of organ-specific cancers. However, neither dialysis nor transplantation was associated with breast, body of uterus, colorectal or prostate cancer. Significant heterogeneity was found regarding the association between RRT and overall cancer as well as the majority of site-specific cancer types. However, this heterogeneity had no substantial influence on the pooled SIR for overall cancer in RRT according to the sensitivity analysis. Compared with the general population, RRT patients have a significantly increased risk of overall cancer and the majority of specific cancer types, particularly Kaposi sarcoma (KS), lip cancer and NMSC in patients subjected to kidney transplantation and cancer of the thyroid gland and kidney as well as myeloma in dialysis patients. Considering the high heterogeneity encountered, further high-quality studies are required.

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Introduction

The prevalence of end-stage renal disease (ESRD) is increasing, with the population of the affected individuals in the USA almost doubling every 10 years (1). ESRD has now become a major health problem worldwide. Dialysis is the most common treatment for ESRD, while kidney transplantation is the most ideal treatment. However, dialysis and transplantation have adverse effects, including cardiovascular disease, infection and cancer (2,3). In addition, cancer is increasingly recognized as a complication and a major cause of mortality in patients with ESRD receiving renal replacement therapy (RRT) (4). Since the association between chronic uremia and malignant disease was first reported in 1970 (5), it has been supported by an increasing number of studies. In 1993, the association between malignancy and dialysis was assessed by a meta-analysis of 15 studies, whose results, however, were contradictory (6). The pooled data from 10 of the studies suggested an average relative risk of malignancy of 7.6 for dialysis patients, while it was 0.98 according to the 5 remaining studies showing an unchanged risk (6). The shortcomings of the above mentioned meta-analysis were that the sample size of the majority of the studies included was small and only a few types of cancer were assessed, rendering the risk estimates obtained unreliable. In addition, all the studies included were on Western populations, while the analysis lacked information on non-Western patients. In 2007, a meta-analysis of 5 studies on the cancer risk in renal transplant recipients (RTRs) showed that an extensive variety of cancer types occurred with an increased incidence in RTRs (7). However, the study did not specifically evaluate

the risk of overall cancer or risk factors, including age, gender, follow-up time or country. Moreover, the number of studies included was small and all studies assessed were on Western populations.

In the past few years, several studies using registry data have provided convincing evidence for the increased incidence of certain cancer types in patients receiving RRT (4,8-16). However, it remains to be determined whether meta-analysis of these studies and others may provide results that are different from those of previous meta-analyses. Although certain reviews have reported on the association between RRT and the occurrence of cancer (2,17,18), meta-analysis of data from previous studies can increase statistical power by pooling the results of individual studies. Therefore, the present meta-analysis was performed to quantify the cancer risk in patients receiving RRT, which may provide a realistic perspective on the cancer risk associated with RRT in the clinical setting.

Materials and methods

Conducting the study. The analysis and data presentation of the study were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement checklist (19).

Data sources and searches. Two of the investigators (W.S. and L.H.) searched the PubMed and EMBASE databases for studies published before May 29, 2015 using search term combinations of 'transplant OR transplantation OR dialysis OR hemodialysis', 'neoplasia OR neoplasm OR neoplasms OR carcinoma OR cancer OR cancers OR malignancy OR malignancies OR tumor OR tumors', 'standardized incidence rate (SIR) OR standardized incidence ratio', and 'RR OR relative risk'. All eligible studies were retrieved and their references were reviewed to identify additional relevant studies.

Inclusion criteria. Studies were included in the present meta-analysis when meeting the following criteria: i) Population-based cohort studies on chronic dialysis patients or RTRs; ii) chronic dialysis or renal transplantation were defined as exposure interests and cancer as the outcome of interest; iii) SIR/standardized mortality rate or relative risk with their 95% confidence intervals (CIs) of overall cancer (or with data to calculate them) were provided; iv) the patient cohort mainly comprised adults.

Exclusion criteria. The following types of study were excluded: Case reports, reviews, conference reports, editorials, studies not written in English, as well as studies on transplantation of organs other than kidneys. Studies were excluded when the cancer diagnosis had not been submitted to a cancer registry. If multiple studies on the same trial were encountered, only the most recent study was included in the present meta-analysis.

Data extraction and quality evaluation. Two investigators (W.S. and L.H.) independently extracted the following variables from the selected studies: Name of first author, publication year, country, cohort entry criteria, study period, sample size, mean age, percentage of males, patient-years, mean follow-up time, number of cancers observed in the cohort, as well as the SIRs and their 95% CIs of commonly known cancer types and overall cancer. If the overall-cancer SIR estimate including non-melanoma skin cancer (NMSC) as well as that excluding NMSC were provided, both values were considered. The quality of the cohort studies was assessed by each investigator independently using the Newcastle-Ottawa quality assessment scale (NOS) (20). The NOS reflects the quality of published non-randomized studies with regard to selection, comparability and outcome. Studies meeting ≥5 NOS criteria were considered to be of high quality. Discrepancies between the findings of the two investigators were resolved by discussion.

Data synthesis and analysis. SIRs with 95% CIs for overall cancer were pooled using a random-effects model for possible heterogeneity among studies. Risks for specific cancer types were only combined in the same method if data from ≥2 studies were available for a given type of cancer. Heterogeneity was assessed by means of the χ^2 test and quantified using I^2 statistics. I^2-values of 25, 50 and 75% were considered to indicate low, moderate and severe statistical heterogeneity, respectively. To assess any potential confounding factors, including sample size, gender, age, follow-up time and geographical region, subgroup analyses were performed if ≥1 study took the above factors into account; furthermore, combined cohort data were stratified into those including or excluding NMSC. In addition, a sensitivity analysis was performed to assess the influence of any individual study on the overall estimate. Publication bias was evaluated using Egger's test (21). All the analyses were performed using Stata 10.0 software (StataCorp LP, College Station, TX, USA) and all P-values were calculated as two-sided. Unless otherwise specified, $P<0.05$ was considered to indicate a statistically significant difference.

Results

Description of included studies. A total of 4,424 studies were identified via the search strategy applied, which is outlined in Fig. 1, and the full-text version of 57 studies was retrieved. Of these, 39 were excluded, as they comprised 3 duplicate studies, 2 studies not written in English, 1 review, 21 from which the SIR and 95% CI could not be calculated, 10 studies on hospital-based cohorts and 2 on irrelevant topics. Finally, 22 cohort studies contained in 18 studies were included in the present meta-analysis (8-16,22-30). The main characteristics of the studies included are presented in Table I. The earliest study began in 1989 (22) and the latest ended in 2015 (11). All the studies were population-based. Of the patients included, 1,443,684 received dialysis and 85,035 were RTRs. On average, dialysis patients were 15.8 years older than RTRs. The average duration of follow-up was more than twice as long after transplantation (7.17 years) compared to patients on dialysis (2.60 years from first dialysis). The present meta-analysis included 75,336 cases of cancer identified in a total of 1,528,719 individuals. According to the NOS, all cohort studies were of high quality (data not shown).

Overall cancer risk in RRT. As shown in Fig. 2, RRT was significantly associated with an increased risk for overall cancer. The pooled SIR of overall cancer for patients

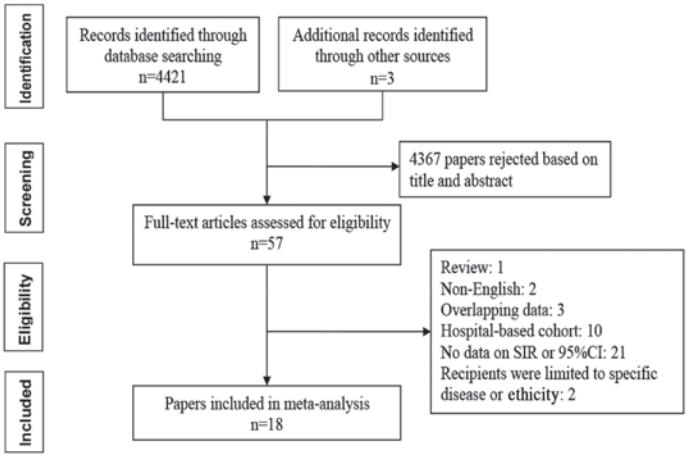

Figure 1. Literature search flow diagram. SIR, standardized incidence rate; CI, confidence interval.

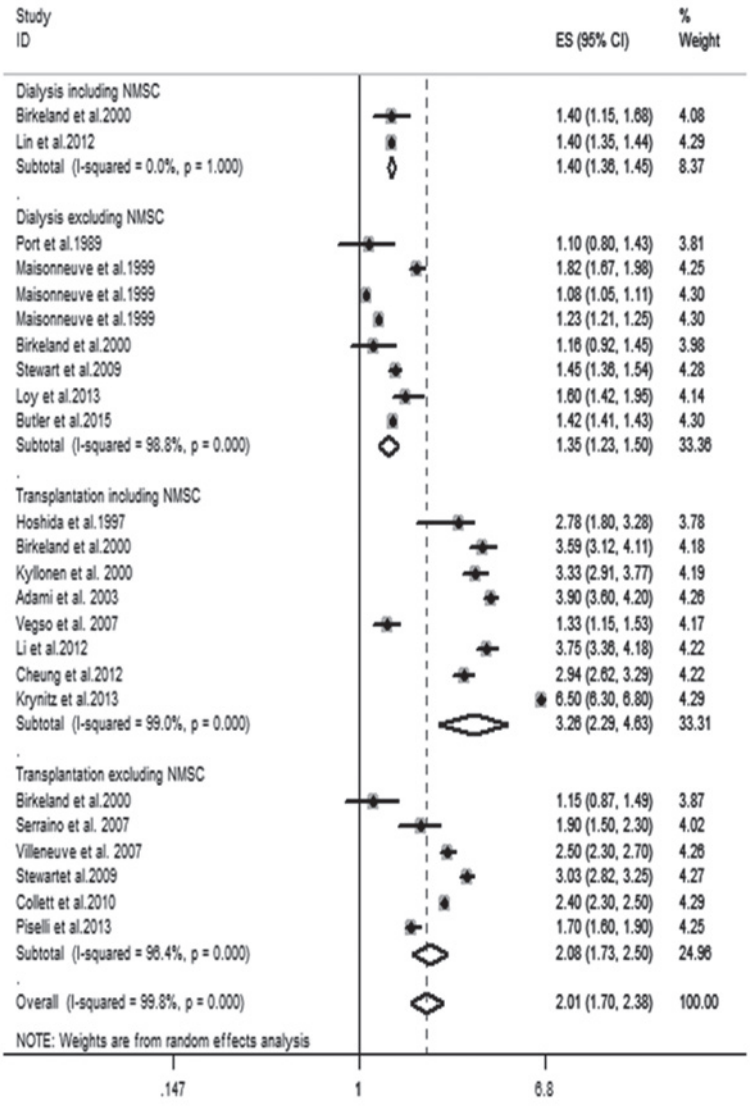

Figure 2. Standardized incidence rates for all cancers in renal replacement therapy. NMSC, non-melanoma skin cancer; CI, confidence interval; ES, effect size.

receiving dialysis including NMSC, dialysis excluding NMSC, transplantation including NMSC and transplantation excluding NMSC and RRT were 1.40 (95% CI, 1.36-1.45), 1.35 (95% CI, 1.23-1.50), 3.26 (95% CI, 2.29-4.63), 2.08 (95% CI, 1.73-2.50), 2.01 (95% CI, 1.70-2.38), respectively. Significant heterogeneity was observed in the pooled analysis

Table I. Characteristics of studies included in the present meta-analysis.

First author, year	Country	Cohort entry criterion	Study period	Sample size, n	Mean age, years	Men,%	Patient-years, n	Mean follow-up time, years	Cancers, n	(Refs.)
Port, 1989	United States	Dialysis	1973-1984	4,161	52	56.8	NA	NA	63	(22)
Maisonneuve, 1999	Australia and New Zealand	Dialysis	1980-1994	13,497	49	55.7	34,456	2.6	500	(30)
	Europe	Dialysis	1980-1994	296,903	52	58.4	858,532	2.9	6,849	
	United States	Dialysis	1980-1994	521,404	58	53.4	1,152,047	2.2	17,695	
Birkeland, 2000	Denmark	Dialysis	NA-1995	3,592	50.2	60	8,043	2.26	110	(23)
Stewart, 2009	Australia	Dialysis	1982-2003	23,764	54.5	54	63,431	2.7	1,018	(8)
Lin, 2012	China	Dialysis	1997-2008	92,348	60.4	48.5	409,909	4.4	4,328	(9)
Loy, 2013	Singapore	Dialysis	1998-2007	5,505	58.1	52.23	NA	3.9	267	(10)
Butler, 2015	United States	Dialysis	1996-2009	482,510	67	51.6	988,395	2.5	35,767	(11)
Hoshida, 1997	Japan	Transplantation	1970-1995	1,744	36[a]	66.2	12,982	7.4	46	(24)
Birkeland, 2000	Denmark	Transplantation	NA-1995	1,821	39	60.6	13,734	7.5	209	(23)
Kyllönen, 2000	Finland	Transplantation	1964-1997	2,890	41.5	59.5	20,817	7.2	230	(25)
Adami, 2003	Sweden	Transplantation	1970-1997	5,004	46	60	36,963	6.8	639	(26)
Végso, 2007	Hungary	Transplantation	1973-2007	2,535	53.1	NA	NA	9.8	193	(27)
Villeneuve, 2007	Canada	Transplantation	1981-1998	11,155	NA	63.2	81,237	7.3	778	(28)
Serraino, 2007	Italy	Transplantation	1988-2004	1,829	NA	65.3	16,196	7.3[a]	104	(29)
Stewart, 2009	Australia	Transplantation	1982-2003	8,173	41.9	59	49,357	6	770	(8)
Collett, 2010	United Kingdom	Transplantation	1980-2007	25,104	NA	NA	NA	NA	1,982	(12)
Li, 2012	China	Transplantation	1997-2008	4,716	44.1	52.5	22,556	4.8	320	(13)
Cheung, 2012	China	Transplantation	1972-2011	4,895	43.7	58.6	40,246	8.2	299	(14)
Piselli , 2013	Italy	Transplantation	1997-2009	7,217	NA	64.2	NA	5.5	395	(15)
Krynitz, 2013	Sweden	Transplantation	1970-2008	7,952	47[a]	62	NA	9.7	2,774	(16)

[a]Median value. NA, not available.

Table II. Subgroup analyses of overall cancer risk in patients who received renal replacement therapy.

	Including NMSC					Excluding NMSC				
				Heterogeneity					Heterogeneity	
Characteristic	No. studies	(Refs.)	Pooled SIR (95%CI)	I^2 (%)	P-value[a]	No. studies	(Refs.)	Pooled SIR (95%CI)	I^2 (%)	P-value[a]
Sample size, n										
Dialysis										
<10,000	1	(23)	1.40 (1.15-1.68)	NA	NA	3	(10,22,23)	1.29 (1.00-1.67)	74.8	0.019
≥10,000	1	(9)	1.40 (1.35-1.44)	NA	NA	5	(8,11,30)	1.37 (1.22-1.54)	99.3	<0.001
Transp										
<5,000	6	(13,14,23-25,27)	2.81 (2.07-3.82)	96.7	<0.001	2	(23,29)	1.49 (0.91-2.43)	87.8	0.004
≥5,000	2	(16,26)	5.04 (3.06-8.32)	99.3	<0.001	4	(8,12,15,28)	2.36 (1.94-2.87)	97.1	<0.001
Gender										
Dialysis										
Men	2	(9,23)	1.45 (1.23-1.71)	0.0	0.464	5	(10,23,30)	1.36 (1.13-1.65)	86.3	<0.001
Women	2	(9,23)	1.59 (1.50-1.69)	0.0	0.585	5	(10,23,30)	1.50 (1.28-1.76)	95.0	<0.001
Transp										
Men	4	(13,14,23,24)	2.95 (2.54-3.42)	56.1	0.077	2	(23,28)	2.10 (1.32-3.35)	87.9	0.004
Women	4	(13,14,23,24)	3.84 (3.03-4.86)	78.9	0.003	2	(23,28)	2.28 (2.03-2.57)	0.0	0.777
Age at first dialysis, years										
0-34	1	(9)	9.20 (7.68-10.93)	NA	NA	4	(10,30)	4.09 (2.59-6.47)	93.0	<0.001
35-64	0	NA	NA	NA	NA	4	(10,30)	1.88 (1.41-2.50)	96.9	<0.001
≥65	1	(9)	0.80 (0.76-0.84)	NA	NA	4	(10,30)	1.21 (1.11-1.32)	78.2	0.003
Age at transp, years										
0-20	2	(13,14)	21.97 (5.72-84.4)	61.5	0.107	0	NA	NA	NA	NA
30-45	1	(24)	4.78 (2.73-8.38)	NA	NA	1	(28)	3.33 (2.87-3.83)	NA	NA
>60	1	(13)	2.31 (1.74-3.07)	NA	NA	1	(28)	1.69 (1.44-1.96)	NA	NA
Follow-up time										
Within 1 year of first dialysis	1	(9)	8.30 (7.70-8.92)	NA	NA	4	(10,30)	2.16 (1.53-3.04)	94.0	<0.001
Year 2 after first dialysis	1	(9)	3.90 (3.62-4.19)	NA	NA	4	(10,30)	1.47 (1.22-1.77)	95.4	<0.001
Years 3-5 after first dialysis	0	NA	NA	NA	NA	4	(10,30)	1.32 (1.07-1.63)	96.8	<0.001
Within 1 year of transp	3	(13,14,24)	24.75 (7.63-80.21)	95.6	<0.001	1	(28)	2.97 (1.42-1.95)	NA	NA
Years 1-5 after transp	3	(13,14,24)	6.45 (4.16-9.99)	90.3	<0.001	1	(28)	2.39 (2.13-2.67)	NA	NA
Years 5-10 after transp	3	(13,14,24)	2.40 (1.28-4.53)	93.9	<0.001	1	(28)	2.61 (2.30-2.94)	NA	NA

Table II. Continued.

	Including NMSC					Excluding NMSC				
				Heterogeneity					Heterogeneity	
Characteristic	No. studies	(Refs.)	Pooled SIR (95%CI)	I^2 (%)	P-value[a]	No. studies	(Refs.)	Pooled SIR (95%CI)	I^2 (%)	P-value[a]
Region										
Dialysis										
Asian	1	(9)	1.40 (1.35-1.44)	NA	NA	1	(10)	1.60 (1.42-1.95)	NA	NA
Non-Asian	1	(23)	1.40 (1.15-1.68)	NA	NA	7	(8,11,22,23,30)	1.33 (1.19-1.47)	99.0	<0.001
Transp										
Asian	3	(13,14,24)	3.19 (2.62-3.89)	80.9	0.005	0	NA	NA	NA	NA
Non-Asian	5	(16,23,25-27)	3.33 (2.05-5.41)	99.3	<0.001	6	(8,12,15,23,28,29)	2.08 (1.73-2.50)	96.4	<0.001

[a]P-value for the heterogeneity within each subgroup. Transp, transplantation; NMSC, non-melanoma skin cancer; SIR, standardized incidence rate; 95% CI, 95% confidence interval; NA, not available.

(I^2=99.8%; P<0.001). To explore possible sources of the heterogeneity, subgroup analyses were performed with regard to sample size, gender, age, follow-up time and geographical region. Subgroup analysis with regard to sample size showed that for dialysis, the pooled SIR was increased in studies with a sample size of ≥10,000 patients (excluding NMSC), and that for transplantation, the pooled SIR was increased in studies with a sample size of ≥5,000 patients. Subgroup analysis with regard to gender showed that female patients with RRT had a significantly higher risk for overall cancer compared with that of male patients. Furthermore, subgroup analysis regarding patient age indicated that the risk of cancer was particularly high in the lowest age group and progressively decreased with age. Among RTRs, the risk for cancer was highest in the first year after transplantation with inclusion of NMSC (SIR=24.75; 95% CI, 7.63-80.21) and subsequently decreased in the following years. Furthermore, the risk for cancer excluding NMSC was highest in the first year after dialysis (SIR=2.16; 95% CI, 1.53-3.04) and progressively decreased with follow-up duration compared with the general population. Stratification based on geographical region indicated that the pooled SIR in non-Asian populations of RTRs was higher than that in Asian RTRs. No significant change in the majority of subgroup analyses for heterogeneity was observed (Table II).

Risk of specific cancer types in patients with RRT. Subgroup analyses were performed for specific cancer types reported in ≥1 study (Table III). The meta-analyses showed that myeloma and melanoma as well as cancer of the thyroid gland, kidney, thyroid and other endocrine glands, tongue, bladder, cervix of the uterus, penis scrotum and liver were more frequently observed in dialysis patients compared to the entire population. However, no increase in the risk of leukemia, Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), as well as breast, colorectal, intestinal, stomach, lung, body of uterus or prostate cancer was observed in dialysis patients. Furthermore, the meta-analyses demonstrated that transplantation was associated with an increased risk of KS, NMSC, melanoma, leukemia, malignant lymphoma, myeloma, NHL and HL, as well as cancer of the lip, skin, kidney, anus, thyroid, bladder, liver, cervix, stomach, esophagus, pancreas and lung, whereas no increased risk of cancer of the larynx, ovary, uterus, prostate, breast, body of uterus, colon/rectum and brain was observed. As only 1 study reported on specific cancer types, formal meta-analyses were not performed.

Sensitivity analysis. Sensitivity analyses were performed by excluding 1 study at a time. The SIRs were similar without significant fluctuation, ranging from 1.99 (95% CI, 1.78-2.24) to 2.17 (95% CI, 1.81-2.59) (data not shown).

Reporting bias. Egger's test indicated the presence of a publication bias regarding the primary outcome (P=0.05).

Discussion

The present meta-analysis demonstrated that dialysis and transplantation were associated with an increased risk of overall cancer and the majority of specific cancer types. Compared with the general population, the risk of overall cancer

Table III. Pooled risks of specific cancer types in patients with renal replacement therapy.

Type/site of malignancy	No. studies	(Refs.)	Pooled SIR (95%CI)	Heterogeneity	
				I^2 (%)	P-value[a]
Dialysis					
Thyroid gland	3	(8,9,23)	4.92 (1.43-16.93)	93.3	<0.001
Kidney	9	(8-11,22,23,30)	4.87 (4.14-5.72)	93.6	<0.001
Myeloma	4	(10,30)	4.15 (3.1-5.56)	90.5	<0.001
Melanoma	2	(22,23)	2.83 (1.28-6.23)	0.0	0.652
Thyroid/other endocrine glands	4	(10,30)	2.57 (1.82-3.63)	77.5	0.004
Bladder	9	(8-11,22,23,30)	2.51 (1.85-3.41)	97.8	<0.001
Tongue	5	(9,10,30)	1.8 (1.43-2.26)	49.0	0.097
Cervix of uterus	5	(9,10,30)	1.76 (1.09-2.86)	94.8	<0.001
Penis scrotum	4	(9,10,30)	1.75 (1.36-2.27)	0.0	0.828
Liver	5	(9,10,30)	1.39 (1.28-1.51)	7.4	0.364
HL	4	(9,30)	1.58 (0.94-2.66)	70.4	0.017
NHL	7	(10,11,22,23,30)	1.16 (0.86-1.55)	91.5	<0.001
Breast	8	(9-11,22,23,30)	1.15 (0.9-1.46)	98.0	<0.001
Colorectal	2	(9,11)	1.13 (0.90-1.43)	95.1	<0.001
Intestinal	4	(10,30)	1.12 (0.91-1.39)	95.8	<0.001
Stomach	6	(9,10,22,30)	1.03 (0.71-1.50)	96.5	<0.001
Leukemia	5	(9,10,30)	1.02 (0.55-1.9)	95.9	<0.001
Lung	7	(9-11,22,30)	0.98 (0.77-1.24)	98.7	<0.001
Body of uterus	6	(9,10,22,30)	0.96 (0.78-1.19)	65.5	0.013
Prostate	7	(9-11,22,30)	0.87 (0.69-1.09)	95.5	<0.001
Transplantation					
Kaposi sarcoma	4	(12,15,16,29)	59.48 (24.43-144.86)	93.1	<0.001
Lip	7	(12,15,16,23,25,26,28)	29.74 (16.96-52.17)	95.7	<0.001
NMSC	6	(12-14,23,25,26)	15.18 (8.08-28.52)	98.9	<0.001
Skin	2	(16,27)	11.84 (0.6-233.25)	99.8	<0.001
Kidney	11	(8,12-16,23-26,28)	9.7 (5.69-16.53)	97.1	<0.001
Anus	2	(12,16)	9.4 (6.5-13.6)	0.0	0.403
Malignant lymphoma	2	(13,24)	6.65 (2.97-14.89)	50.2	0.156
NHL	9	(12-16, 23,26-29)	6.05 (4.11-8.9)	94.8	<0.001
HL	5	(12,15,16,23,28)	4.85 (2.97-7.9)	45.8	0.117
Thyroid gland	11	(8,12-16,23-28)	3.75 (2.5-5.62)	74.8	<0.001
Bladder	11	(8,12-16, 23-28)	3.15 (1.27-7.8)	98.0	<0.001

Table III. Continued.

Type/site of malignancy	No. studies	(Refs.)	Pooled SIR (95%CI)	Heterogeneity	
				I^2 (%)	P-value[a]
Myeloma	3	(12,16,28)	2.96 (1.94-4.52)	47.1	0.151
Liver	9	(12-16,24,27-29)	2.52 (1.71-3.73)	73.7	<0.001
Oral cavity	5	(12-16)	2.38 (1.22-4.64)	86.1	<0.001
Cervix of uterus	3	(12,16,28)	2.20 (1.56-3.10)	0.0	0.732
Melanoma	9	(8,12-16,23,27,28)	2.05 (1.52-2.78)	52.7	0.031
Stomach	8	(12-16,24,26,28)	1.92 (1.6-2.31)	0.0	0.779
Leukemia	7	(12-16,23,28)	1.62 (1.23-2.14)	5.4	0.386
Esophagus	6	(12-16,28)	1.61 (1.22-2.13)	0.0	0.680
Pancreas	6	(12-16,28)	1.55 (1.19-2.0)	0.0	0.511
Lung	8	(12-16,27-29)	1.52 (1.15-1.99)	84.2	<0.001
Larynx	4	(13,15,16,28)	1.53 (0.84-2.79)	18.8	0.297
Ovary	2	(15,28)	1.39 (0.69-2.77)	0.0	0.702
Uterus	4	(12,14,24,28)	1.37 (0.75-2.51)	46.4	0.133
Prostate	6	(12,14-16,27,28)	1.14 (0.94-1.37)	41.5	0.129
Breast	9	(12,14-16,23-25,27,28)	1.13 (0.99-1.29)	9.1	0.360
Body of uterus	2	(15,16)	1.09 (0.66-1.8)	0.0	0.631
Colon/rectum	4	(12,15,27,28)	1.06 (0.66-1.72)	87.7	<0.001
Brain	3	(16,23,28)	1.00 (0.64-1.57)	0.0	0.593

[a]P-value for the heterogeneity within each subgroup. HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; NMSC, non-melanoma skin cancer; SIR, standardized incidence rate; 95% CI, 95% confidence interval.

including NMSC was 1.4-fold increased and that excluding NMSC was 1.35-fold increased for patients receiving dialysis, while the risk of overall cancer including NMSC was 3.26-fold increased and that excluding NMSC was 2.08-fold increased for patients with transplantation. Therefore, the risk of cancer for patients receiving transplantation was higher than that for patients receiving dialysis.

Similar to other published meta-analyses of this type (31,32), the present study had a high level of heterogeneity. Subgroup analyses were performed to explore the sources of this heterogeneity. Stratification of subjects by gender, in agreement with previous studies (9,10,13,14,23,30), showed that the SIR of all cancers in female patients with RRT was higher than that in male patients, suggesting that female RRT patients require a higher level of cancer surveillance. Stratification of subjects by age showed that the risk for all cancers was higher in younger patients and decreased with age in patients with RRT, whether those receiving dialysis or transplantation, similar to the findings of several large studies (9,10,13,14,24,28,30). These age-associated observations may have resulted from the following major aspects: First, the higher cancer risk in younger patients receiving RRT compared with that in older patients was likely to be due to the low incidence rate of cancer among young individuals in the general population. Second, the age phenomenon may be attributed to the fact that younger patients may have been affected by considerably more serious viral-associated cancer, against which they tend to lack immunity compared to older patients. Therefore, the discrepancy in cancer risk may disappear with advancing age (33). Finally, the risk of cancer stands in competition with the risk of other chronic illnesses, such as cardiovascular diseases, in the older population. Thus, younger patients receiving RRT require more intensive cancer surveillance than older patients.

Grouping of studies by follow-up time showed that the cancer risk was highest in the first year of receiving dialysis or after renal transplantation and decreased over subsequent years. This result was compatible with the findings of previous studies (9,10,13,14,24,28,30). Only 1 study reported that the SIR was highest at 10 years post-transplantation (4). The reason for this may be that ESRD is an important risk factor for cancer (34). A further explanation may be the increased amount of medical surveillance. In addition, the increased rate of cancer diagnosis may have been due to undetected cancers being already present prior to RRT. Furthermore, recent increases in the risk of cancer in RTRs may be associated with the effects of more potent immunosuppressive treatments, which are increasingly used for prevention and treatment of acute rejection. The mean duration from initiation of dialysis to the detection of cancer was 2.8 years according to the study by Vajdic *et al* (4) and 3.6 years in the study by Loy *et al* (10). The mean time interval between renal transplantation and tumor development ranged from 4.9 to 9.4 years (4,14,25,27), suggesting that RTRs have a risk of cancer occurring after a number of years. Therefore, regular follow-up is warranted if cancer is not found during early screening.

Grouping of studies by region showed that the risk for overall cancer remained significantly elevated in the Asian and non-Asian populations receiving RRT, although no significant difference between them was observed. However, the distribution of cancer types in Asian RTRs differed from that in non-Asian RTRs. Numerous studies have shown that in Western countries, RTRs are at greater risk of developing NMSC (16,25,26). By contrast, NHL as well as renal and bladder cancer had the highest SIRs in Hong Kong (14), and kidney cancer was the most common cancer type in Taiwan (13) and Japan (24). These results emphasize the requirement for vigilant cancer surveillance following transplantation.

The present study also observed a strongly increased risk of site-specific cancer in RRT patients. For dialysis patients, the risk was highest for thyroid gland and kidney cancer as well as myeloma (ESRD-associated cancer types) (8). For kidney transplantation, the most common cancer types were KS, lip cancer and NMSC (immune deficiency-associated cancer types) (8); this finding was in agreement with the study by Engels *et al* (35), who reported that the cancer risk was most pronounced for KS, lip cancer and NMSC among solid organ transplant recipients in the USA. Following kidney transplantation, there was an obvious increase in the incidence of a wide variety of cancer types, several of which were also increased in dialysis patients. The magnitude and breadth of the increased cancer risk following transplantation suggested that immune deficiency is the underlying cause. The results of the pooled analysis of the present study are similar to those of the previous meta-analysis by Grulich *et al* (7) for transplantation, with the exception of laryngeal and colorectal cancer. Moreover, the present study further evaluated risk factors, including age, gender and follow-up time, for the development of cancer in RRT recipients. However, the results of the present meta-analysis showed no statistically significant association between RRT and breast, body of uterus, colorectal and prostate cancers. In addition, the present study reported an increased risk of HL, NHL, leukemia and lung cancer for transplantation but not for dialysis. Of note, there was significant heterogeneity among the majority of the studies on various organ-specific cancers.

RRT is linked with cancer via the following potential mechanisms: i) Underlying renal disease is a possible explanation for the increased cancer risk, for example, acquired cystic kidney disease is associated with an increased occurrence of renal cell carcinoma (36). ii) Carcinogenesis is linked to medications administered for treatment of renal disease, such as azathioprine for skin cancers (37) and lymphomas (38). iii) It was reported that long-term hemodialysis may suppress the DNA repair system of lymphocytes (39), and plasma glutathione peroxidase deficiency caused by renal dysfunction may lead to DNA damage (40), which impairs the defense of the organism against oncogenic viral infections and a variety of nonviral tumor antigens. iv) Bioincompatibility of the dialysis membrane may lead to the release of cytokines, predisposing to tumor formation (41). v) Carcinogenesis is also associated with lifestyle and other cancer risk factors, including age, gender and smoking. vi) The correlation of cancer with dialysis may be attributable to a coincidental association due to detection bias. vii) As for RTRs, in addition to all the aforementioned risk factors associated with dialysis, anti-rejection drugs profoundly suppress immunity and may themselves be carcinogenic (42). Other than cancers occurring *de novo* following transplantation, recurrence of preexisting cancers and cancers from donor organs should also be taken into account.

Several limitations of the present meta-analysis should be acknowledged. First, certain studies, which failed to provide data to calculate the SIR were not included in the meta-analysis,

which may have reduced the power of the analysis. Furthermore, significant heterogeneity was observed among the studies. Thus, subgroup analysis was performed to determine the sources of heterogeneity. However, the variables examined did not fully constitute the source of heterogeneity, suggesting that other unknown confounding variables may be the source of heterogeneity. However, sensitivity analyses demonstrated that the results were robust. In addition, the observational nature of the studies included in the present meta-analysis was likely to have caused bias. Specifically, risk factors of cancers, including lifestyle, smoking, alcohol use, immunosuppressive agents and ultraviolet exposure were not taken into account by most studies. As a result, relevant confounding factors could not be considered. Therefore, well-designed studies considering more covariates are required to investigate the association between RRT and the risk of cancer. Furthermore, as certain studies included NMSC, the cancer incidence may have been overestimated. Finally, the present meta-analysis had the limitation of publication bias, as negative trials are less likely to be reported.

In conclusion, the present meta-analysis demonstrated that patients with RRT (particularly transplantation) are at an increased risk of overall cancer as well as a wide range of cancer types, particularly of the thyroid gland, kidney and myeloma for dialysis and KS, lip and NMSC for transplantation. Screening for cancer should be individualized and based on a reasonable life expectancy. However, these conclusions should be drawn cautiously due to high heterogeneity and publication bias as well as the limited amount of data on certain types of cancer. To further assess the link between RRT and cancer, additional large and well-designed prospective studies are required.

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