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Risk of bladder cancer in renal transplant recipients: a meta-analysis

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Background: Renal transplantation has been associated with a significantly increased risk of developing cancers during long-term follow-up, but for bladder cancer, this risk is less clear. We therefore performed a meta-analysis to determine whether bladder cancer risk in renal transplant recipients was increased.

Methods: Eligible studies were identified through searches of PubMed and other public resources. Random-effects meta-analyses were used to pool overall estimates for standardised incidence ratios (SIRs). Heterogeneity test, sensitivity analysis, and assessment of publishing bias were also performed.

Results: We identified a 3.18-fold higher SIR (95% confidence intervals (CI): 1.34–7.53, $P=0.008$) of bladder cancer in patients following renal transplantation compared with the general population, based on data from 79 988 patients with a total follow-up of 308 458 patient-years. When stratified by ethnicity, the SIRs for bladder cancer were 2.00 (95% CI: 1.51–2.65, $P=0.001$) and 14.74 (95% CI: 3.66–59.35, $P<0.001$) between European and Asian renal transplant recipients, respectively.

Conclusions: Our study demonstrated that the risk of developing bladder cancer in transplant populations was increased. Such association suggests that physicians should be more vigilant in checking for bladder cancer in transplantation recipient population.

Renal transplantation is the treatment offered for patients with end-stage renal failure. The outcomes of renal transplantation have improved considerably over the past decades, especially with the introduction of highly active immunosuppressive drugs that dramatically decrease the incidence of acute graft rejection and improve graft and patient survival rates (O'Grady *et al*, 2002; Knight *et al*, 2009). However, treatment of renal transplant recipients (RTRs) with immunosuppressive agents was considered to lead to malignancy by supporting oncogenesis caused by certain viruses or by impairing immune surveillance resulting in faster tumour growth (Rama and Grinyo, 2010). As a matter of fact, malignancy is the third leading cause of death among RTRs after transplation, following cardiovascular disease and infection (Briggs, 2001). Compared with the general population, an overall two- to seven-fold elevated risk of malignancies was documented among RTRs (Kyllonen *et al*, 2000; Adami *et al*, 2003; Vajdic *et al*, 2006; Villeneuve *et al*, 2007; Krynitz *et al*, 2013). The most frequent malignancies are skin cancers and lymphomas, followed by Kaposi's sarcoma, lip, cervical, perineal, renal, hepatocellular carcinomas, and other sarcomas (Penn, 2000; Kauffman *et al*, 2006). Increased incidence of other malignancies, such as thyroid and lung in transplant recipients, has also been reported (Grulich *et al*, 2007; Karamchandani *et al*, 2010).

Several studies have showed increased risk of bladder cancer after renal transplantation (Hoshida *et al*, 1997; Cheung *et al*, 2012; Li *et al*, 2012). However, not all studies have shown a similar

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association (Serraino *et al*, 2005; Vegso *et al*, 2007). In this study, we performed a meta-analysis to determine whether the overall SIR of bladder cancer is increased in RTRs compared with the general population, which might be helpful in determining whether conclusive recommendations for bladder cancer screening in RTRs are needed.

MATERIALS AND METHODS

Identification of eligible studies. A comprehensive literature search was performed via public database PubMed (http://www.ncbi.nlm.nih. gov/pubmed/), Embase (http://www.embase.com), and ISI Wed of Knowledge (http://isiknowledge.com), with the last update in September 2013. The search was restricted to studies published in English. The key search terms used were 'renal', 'kidney', 'transplantation', 'bladder', and 'cancer'. The search results were restricted to the presence of these keywords in the title or abstract of the articles. A manual search of the references from eligible studies was performed afterwards to check for additional potentially relevant studies for inclusion.

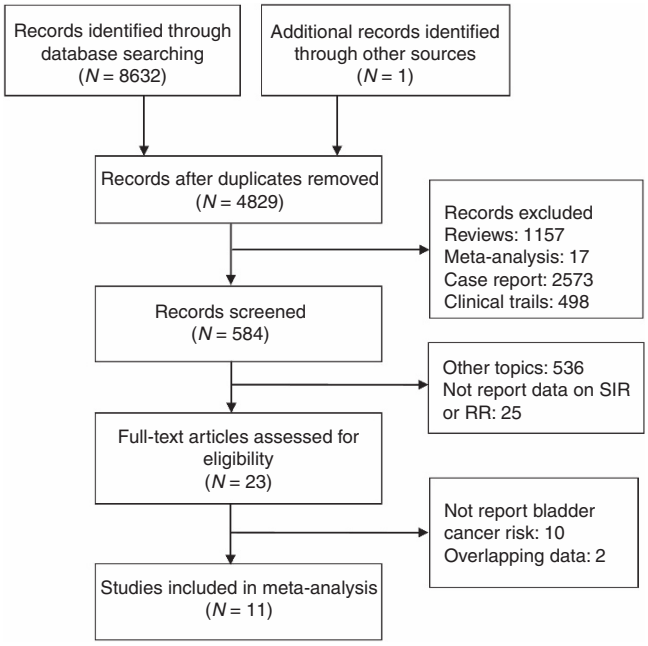

Figure 1. Flowchart of article selection.

Inclusion and exclusion criteria. Eligible studies were selected according to the following inclusion criteria: (a) studies should be population-based cohort studies of RTRs; (b) studies matched the transplant population to a standardised population to calculate a standardised incidence ratio (SIR); (c) Sufficient information on SIR, relative risk (RR), or observed cases of bladder cancer in RTRs had to be provided in the studies. The following exclusion criteria were used: (a) other organ transplantation studies; (b) case series and case reports; and (c) studies that collected data on incident cancer through cancer registries in the developed countries. Those studies that merely accepted bladder cancer or other cancer diagnoses without confirming that these were notified to a cancer registry were excluded.

Data extraction. Two investigators (LY and PC) independently extracted the data and reached consensus on all items. All retrieved data were organised into a data extraction tables. Parameters extracted from the studies included: the first author, publication year, geographic origin, data source, number of patients, number of renal transplant cases, number of all cancers, length of follow-up time, mean follow-up time (years), patient-years (years), mean age at transplantation (years), mean age at diagnosis of malignancy (years), median time to development of any type of cancer (months), number of expected cases of bladder cancer, number of observed cases of bladder cancers, the SIRs of commonly known cancers and bladder cancer, and mean time to development of bladder cancer (months), if available.

Statistical analysis. In this meta-analysis, the unadjusted RR with 95% confidence intervals (CIs) was estimated. Because of possible heterogeneity between studies, a random-effects model was used to pool effects for RR (DerSimonian and Kacker, 2007). Between-study heterogeneity was calculated using the chi-squared-based Q-statistic (significance level at $P<0.1$) and by estimating I^2, which was documented for the percentage of the observed between-study variability due to heterogeneity rather than chance, with ranges from 0% to 100% ($I^2=0$–25%, no heterogeneity; $I^2=25$–50%, moderate heterogeneity; $I^2=50$–75%, large heterogeneity;

Table 1. Summary of studies included in the analysis

Study	Multicentre	Type of transplant	Geographic origin	Data source	Number of pantients	Number of renal transplant cases
Birkeland *et al*, 2000	Yes	Renal	Denmark	Danish registry	1821	1821
Cheung *et al*, 2012	Yes	Renal	China	Hong Kong Renal Registry	4674	4895
Collett *et al*, 2010	Yes	Multiorgan	UK	UK Transplant Registry	25 104	25 104
Hoshida *et al*, 1997	Yes	Renal	Japan	Multicentre, Japan	1744	1744
Krynitz *et al*, 2013	Yes	Multiorgan	Sweden	Swedish National Patient Register	7952	7952
Kyllonen *et al*, 2000	No	Renal	Finland	Finland Transplant Registry	2890	3440
Li *et al*, 2012	Yes	Renal	China	Taiwan National Health Insurance Research Database (NHIRD)	4716	4716
Piselli *et al*, 2013	Yes	Renal	Italy	Italian KT centre	7217	7299
Vajdic *et al*, 2006	Yes	Renal	Australia and New Zealand	Australia and New Zealand Dialysis and Transplant Registry (ANZDATA)	10 180	10 180
Vegso *et al*, 2007	No	Renal	Hungary	Budapest transplantation center	2535	2852
Villeneuve *et al*, 2007	Yes	Renal	Canada	Canadian Organ Replacement Registry	11 155	11 391
Total					79 988	81 394

$I^2 = 75–100\%$, extreme heterogeneity). In addition, one-way sensitivity analyses were performed after the sequential removal of each study, and the new pooled results reflected the influence of that deleted study to the overall RR. The Begg's funnel plot and Egger's test were performed to statistically analyse the publication bias (Egger *et al*, 1997). All statistical analyses were performed using the STATA 11.0 software (STATA Corp, College Station, TX, USA).

RESULTS

Study characteristics. A total of 11 studies met our inclusion criteria (Hoshida *et al*, 1997; Birkeland *et al*, 2000; Kyllonen *et al*, 2000; Vajdic *et al*, 2006; Vegso *et al*, 2007; Villeneuve *et al*, 2007; Collett *et al*, 2010; Cheung *et al*, 2012; Li *et al*, 2012; Krynitz *et al*, 2013; Piselli *et al*, 2013), comprising a total of 81 394 renal transplants performed on 79 988 patients. A diagram schematising the selection process of identified studies is presented in Figure 1. The studies and their details are listed in Table 1. All the studies were retrospective, and the largest study had 25 104 renal transplant patients. These studies were based on patients in several countries, including one in Denmark (Birkeland *et al*, 2000), two in China (Cheung *et al*, 2012; Li *et al*, 2012), one in the UK (Collett *et al*, 2010), one in Japan (Hoshida *et al*, 1997), one in Sweden (Krynitz *et al*, 2013), one in Finland (Kyllonen *et al*, 2000), one in Italy (Piselli *et al*, 2013), one in Australia and New Zealand (Vajdic *et al*, 2006), one in Hungary (Vegso *et al*, 2007), and one in Canada (Villeneuve *et al*, 2007). All were multicentre-based studies except two (Kyllonen *et al*, 2000; Vegso *et al*, 2007).

Table 2 showed the demographic details of the included studies. As noted, the 79 988 RTRs included in this analysis were followed-up for a total of 308 458 person-years, with a mean follow-up duration of 7.6 years (range: 4.8–9.8 years). The mean age at transplantation and diagnosis of malignancy were 43.7 (range: 38.9–53.1) and 46.8 (range: 40.0–53.1) years old, respectively.

Table 2. Demographic details of the included studies

Study	Number of all cancers	Length of follow-up time	Mean follow-up time (years)	Patient-years (years)	Mean age at trans-plantation (years)	Mean age at diagnosis of malignancy (years)	Number of expected cases of bladder cancer	Number of observed cases of bladder cancers	Mean time to development of bladder cancer (months)
Birkeland *et al*, 2000	209	NR–1995	7.5	13 734	38.9		3.06	5	
Cheung *et al*, 2012	299	1972–2011	8.2	40 246	43.7	53.1	1.46	12	57.6
Collett *et al*, 2010	4422	1980–2007					31.90	76	
Hoshida *et al*, 1997	46	1970–1995	7.4	12 982		40.0	0.30	2	63.0
Krynitz *et al*, 2013	2774	1970–2008	9.7	77 288			21.00	42	
Kyllonen *et al*, 2000	230	1964–1997	7.2	20 817	41.5	47.2	2.47	8	
Li *et al*, 2012	320	1997–2008	4.8	22 556	44.1		1.68	72	
Piselli *et al*, 2013	395	1997–2009	5.5	39 598			18.10	20	
Vajdic *et al*, 2006	1236	1982–2003	8.5		41.0		12.61	42	105.6
Vegso *et al*, 2007	193	1973–2007	9.8		53.1		3.80	3	
Villeneuve *et al*, 2007	778	1981–1998	7.3	81 237			12.10	24	
Total	10902		7.6	308 458	43.7	46.8	108.48	306	75.4

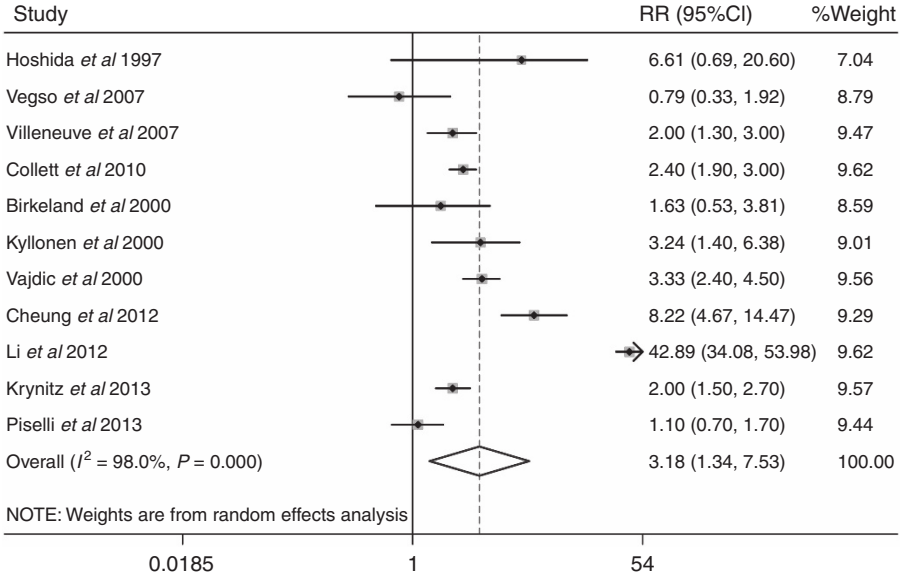

Figure 2. Forest plot of overall bladder cancer risk, showing the relative ratio (RR) and 95% confidence intervals (CI). The squares and horizontal lines correspond to the study-specific RR and 95% CI. The area of the squares reflects the study-specific weight.

Table 3. Cancer-specific standardised incidence ratios (SIRs)

Cancer site	Birkeland *et al*, 2000	Cheung *et al*, 2012	Collett *et al*, 2010	Hoshida *et al*, 1997	Krynitz *et al*, 2013	Kyllonen *et al*, 2000	Li *et al*, 2012	Piselli *et al*, 2013	Vajdic *et al*, 2006	Vegso *et al*, 2007	Villeneuve *et al*, 2007	Overall SIR
Lip	13.02 (10.75–15.63)		65.6 (49.9–84.6)		46 (35–59)	22.95 (12.55–38.51)		9.4 (3.1–22.0)	47 (41.76–52.91)		31.3 (23.5–40.8)	29.45 (17.85–48.59)
Stomach		2.85 (1.62–5.02)	2.0 (1.4–2.6)	1.40 (0.45–2.68)	1.8 (1.0–2.9)		1.84 (0.83–4.09)	1.4 (0.8–2.3)			2.1 (1.2–3.4)	1.93 (1.60–2.34)
Colon		1.75 (1.22–2.52)	1.8 (1.6–2.1)		2.3 (1.8–2.9)	3.94 (2.10–6.74)	2.04 (1.13–3.54)		1.71 (1.38–2.09)	0.34	1.4 (1.0–1.8)	1.89 (1.61–2.22)
Liver		2.53 (1.63–3.91)	2.4 (1.5–3.8)	1.36 (0.24–3.36)	2.7 (1.6–4.1)		5.07 (3.89–6.42)	0.4 (0.1–1.1)	3.19 (1.53–5.8)	3.25	1.8 (0.6–4.3)	2.63 (1.91–3.62)
Pancreas		1.57 (0.51–4.87)	1.5 (1.2–2.1)		2.2 (1.3–3.5)			0.9 (0.3–2.0)			1.1 (0.4–2.2)	1.55 (1.24–1.93)
Lung[a]		1.68 (1.17–2.42)	1.4 (1.2–1.6)		1.7 (1.3–2.2)		4.81 (2.73–8.48)	1.1 (0.8–1.6)		0.65	2.1 (1.7–2.5)	1.70 (1.30–2.21)
Melanoma	1·35 (0·28–3·93)	9.09 (2.27–36.34)					5.40 (0.76–38.18)	1.8 (0.9–3.3)				2.33 (1.39–3.92)
Non-melanoma skin	10.68 (8.84–12.79)		16.6 (15.9–17.3)		54 (52–56)	39.10 (29.20–51.27)	2.30 (0.86–6.13)			2.58		11.93 (4.84–29.45)
Breast	1.45 (0.72–2.60)	1.66 (1–2.75)	1.0 (0.8–1.2)	1.53 (0.18–5.27)	1.2 (0.9–1.5)	1.20 (0.64–2.05)		0.8 (0.5–1.2)	1.03 (0.78–1.34)	0.86	1.3 (1.0–1.7)	1.12 (1.00–1.24)
Ovary		3.29 (1.37–7.9)	1.4 (0.9–2.0)		1.9 (1.1–3.1)		1.14 (0.64–1.89)	1.1 (0.2–3.1)	1.15 (0.46–2.38)		1.5 (0.6–3.0)	1.50 (1.19–1.89)
Prostate		0.88 (0.39–1.95)	1.1 (0.9–1.4)		1.1 (0.9–1.3)			1.7 (1.2–2.3)	0.95 (0.68–1.29)	0.65	0.9 (0.6–1.3)	1.11 (0.99–1.25)
Kidney	4.08 (1.50–8.88)	12.5 (8.51–18.36)	7.9 (6.7–9.3)	79.96 (39.98–114.95)	6.2 (4.8–7.9)	7.97 (5.00–12.07)		4.9 (3.4–6.8)	7.3 (5.69–9.22)	6.77	7.3 (5.7–9.2)	8.61 (6.73–11.02)
Bladder	1.63 (0.53–3.81)	8.22 (4.67–14.47)	2.4 (1.9–3.0)	6.61 (0.69–20.60)	2.0 (1.5–2.7)	3.24 (1.40–6.38)	42.89 (34.08–53.98)	1.1 (0.7–1.7)	3.33 (2.4–4.5)	0.79	2.0 (1.3–3.0)	3.18 (1.34–7.53)
Thyroid	0·91 (0·02–5·09)	4.35 (2.41–7.85)	7.0 (4.8–9.8)	12.43 (2.38–33.70)	4.1 (2.1–7.2)	8.09 (4.04–14.47)	2.41 (1.08–5.34)	1.9 (0.9–3.6)	6.9 (4.69–9.8)	8.95	5.0 (3.1–7.4)	5.29 (3.87–7.24)
Hodgkin's lymphoma	8.0 (1.65–23.38)		7.4 (5.3–10.2)					2.3 (0.5–6.8)	3.74 (1.51–7.71)		3.6 (1.7–6.9)	5.92 (4.53–7.73)
Non-Hodgkin lymphoma	5.48 (2.37–10.80)		12.5 (11.2–13.8)						9.86 (8.37–11.54)	1.32	8.8 (7.4–10.5)	6.59 (4.33–10.04)
All cancers	3.59 (3.12–4.11)	2.94 (2.62–3.29)	4.5	2.78 (1.8–3.28)	6.5 (6.3–6.8)	3.33 (2.92–3.79)	3.75 (3.36–4.18)	1.7 (1.6–1.9)	3.4 (3.22–3.59)	1.33	2.5 (2.3–7.1)	3.19 (2.22–4.60)

[a]Includes trachea, bronchus, and lung.

During the period of observation, the overall diagnosed cancers and haematological malignancies was 10 902.

In this meta-analysis, 306 cases of bladder cancer were identified, compared with 108.48 expected cases.

Evidence synthesis. Meta-analysis for the SIR for bladder cancer suggested a significantly increased risk (SIR = 3.18, 95% CI: 1.34–7.53; $P = 0.008$). Figure 2 shows the forest plot for individual and overall RR measures. Table 3 shows the cancer-specific SIRs. Cancers caused by viral infections, including liver cancer (hepatitis C and B viruses), non-Hodgkin lymphoma and Hodgkin lymphoma (both due to Epstein Barr virus), lip, and non-melanoma skin cancer (both possibly due to human papillomavirus virus (HPV)), were found to be significantly increased among RTRs. Thyroid and kidney cancers also had an increased risk of 5.29 and 8.61 times more than the general population, respectively, whereas common epithelial cancers such as breast, ovary, prostate, and pancreas cancers occurred almost at the same rate as the general population.

Sensitivity analysis indicates that the omission of any of the studies led to changes in estimates between 2.36 (95% CI: 1.69–3.30) and 3.64 (95% CI: 1.48–8.94) (Table 4). The changes were not significant.

Significant heterogeneity existed ($I^2 = 98.0\%$, $P_{heterogeneity} < 0.001$) in the pooled analysis. When stratified by ethnicity, the SIRs for bladder cancer were 2.00 (95% CI: 1.51–2.65, $P = 0.001$, $I^2 = 70.50\%$, $P_{heterogeneity} = 0.001$) for European RTRs and 14.74 (95% CI: 3.66–59.35, $P < 0.001$, $I^2 = 93.70\%$, $P_{heterogeneity} < 0.001$) for Asian RTRs (Figure 3). With the limited information available, we could not detect any sources contributing to the substantial heterogeneity. Furthermore, no evidence of publication bias was observed by Egger's test ($P = 0.373$) or Begg's test ($P = 0.276$, Figure 4).

Table 4. Sensitivity analysis

Study omitted	RR	95% confidence intervals		$P_{heterogeneity}$	I^2	P_{bias}
Birkeland *et al*, 2000	3.39	1.37	8.39	<0.001	98.2	0.422
Cheung *et al*, 2012	2.89	1.14	7.30	<0.001	98.2	0.344
Collett *et al*, 2010	3.28	1.20	8.94	<0.001	98.1	0.204
Hoshida *et al*, 1997	3.01	1.23	7.38	<0.001	98.2	0.310
Krynitz *et al*, 2013	3.34	1.28	8.72	<0.001	98.1	0.342
Kyllonen *et al*, 2000	3.18	1.27	7.95	<0.001	98.2	0.394
Li *et al*, 2012	2.36	1.69	3.30	<0.001	80.0	0.969
Piselli *et al*, *2013*	3.55	1.44	8.79	<0.001	98.1	0.461
Vajdic *et al*, 2006	3.17	1.19	8.44	<0.001	98.2	0.393
Villeneuve *et al*, *2007*	3.34	1.31	8.51	<0.001	98.2	0.433
Vegso *et al*, *2007*	3.64	1.48	8.94	<0.001	98.2	0.483
Combined	3.18	1.34	7.53	<0.001	98.0	0.373

Abbreviation: RR = relative risk.

DISCUSSION

The aim of this meta-analysis was to determine whether the risk of bladder cancer among RTRs is increased such that separate surveillance recommendations would be warranted. Our results showed a significantly increased risk of developing bladder cancer in transplant populations compared with the general population (SIR = 3.18, 95% CI: 1.34–7.53, $P = 0.008$). When stratified by ethnicity, the SIRs for bladder cancer were 2.00 (95% CI: 1.51–2.65, $P = 0.001$) among European and much higher (14.74) among Asian RTRs (95% CI: 3.66–59.35, $P < 0.001$), suggesting the presence of ethnicity-based differences.

Most bladder cancers in RTRs are transitional cell carcinoma (TCC). However, in RTRs, some studies reported an invasive and fatal nature of bladder cancers (Buzzeo *et al*, 1997), a factor that should impact on intensive surveillance during the post-transplant period. The exact reason for the increased risk of bladder cancer in RTRs still remains unknown. Several possible factors have been proposed. Both viral and nonviral factors are involved in the

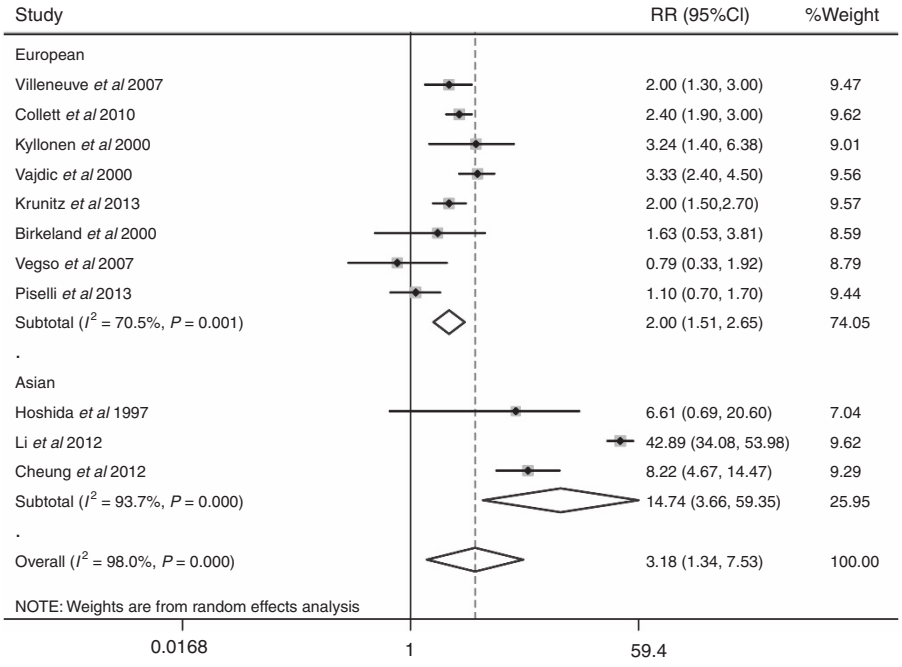

Figure 3. Forest plot of bladder cancer risk stratified by ethnicity.

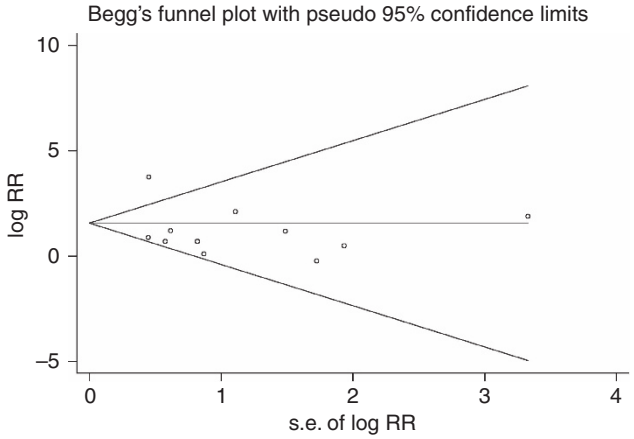

Figure 4. Begg's funnel plot to detect publication bias in overall populations. Each circle represents a separate study for the indicated association.

development of bladder cancer after renal transplantation. The long-term use of immunosuppressive therapy for the graft is another possible factor promoting bladder cancer, as reported for other malignancies. The underlying possible mechanisms include direct cellular damage by immunosuppressants (e.g., cyclophosphamide) and impaired ability to repair damage to cellular DNA or destroy damaged cells due to the immunocompromised state (Buzzeo *et al*, 1997). In this meta-analysis, the incidence of bladder cancer after renal transplantation was much higher in the Asian (specifically Chinese) populations than in European populations. This difference may be due to differences in genetic background and environmental factors. Aristolochic acid in Chinese herbs and chronic arsenic poisoning from underground water intake may both contribute to a high incidence of bladder cancers in transplant patients (Wu *et al*, 2004). Studies in patients from the Chinese mainland showed a RR of 5.85 for developing TCC after kidney transplantation when exposed to Chinese herbs. Furthermore, infection with high-risk HPV (especially HPV16; Li *et al*, 2011) and various gene polymorphisms (Yuan *et al*, 2012; Xie *et al*, 2013) have been postulated to have a role in bladder carcinogenesis.

Some limitation may exist in this study. First, the amount of heterogeneity between studies is high, which may be due to the following reasons: (i) no detail information on the confounders were available that allow us to perform an adjustment for these potential confounders, including cigarette smoking, obesity, aristolochic acid in Chinese herbs, diabetic drug rosiglitazone or pioglitazone, and so on (Wu *et al*, 2004; Holick *et al*, 2007; Hsiao *et al*, 2013; Wyszynski *et al*, 2014); (ii) although all the studies used the general population as the reference population, the criteria used for matching might be differently applied; and (iii) a lack of case–control studies that examined bladder cancer risk following renal transplant to better control of confounding bias. Second, the RTRs were not screened for bladder cancer before transplantation, and the length of time from transplantation to the diagnosis of bladder cancer was very short (from 4.8 to 8.8 years) in our results. Therefore, we could not exclude the presence of possible pre-existing tumours in these recipients. Finally, the pooled increased risk estimate for bladder cancer after transplantation was generated from 11 publications. A larger, multiple-centre prospective study may still be necessary to evaluate the risks of bladder cancer development in RTRs.

In conclusion, in this meta-analysis, we showed an increased risk of developing bladder cancer in transplant populations. Such an association suggests that physicians should be more vigilant in checking for bladder cancer in the transplantation population.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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