Original Article

No significant association between immunosuppression in solid organ transplantation and prostate cancer risk: a meta-analysis of cohort studies

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Background: It is known that organ transplant recipients have a significantly higher risk for developing cancers, but the association between immunosuppression in organ transplantation and the risk for prostate cancer (PCa) remains unclear. We aimed to assess the evidence regarding the association of solid organ transplantation with PCa risk.

Methods: A literature search of the PubMed, Embase, and Web of Science databases was performed up to March 2019. Combined relative risks (RRs) and 95% confidence intervals (CIs) were calculated by using a fixed-effect or random-effect model.

Results: In total, 26 articles including 33 independent population-based cohort studies with 556,812 recipients and 2,438 PCa cases were identified and included in this meta-analysis. PCa risk in the solid organ transplant recipients did not increase compared with the general population (RR=1.04; 95% CI: 0.90–1.18). Independent analysis of different kinds of organ replacements further indicated immune inhibition in the transplantation of kidney, liver, heart, and lung, and was not associated with elevated PCa risk (RR=0.89; 95% CI: 0.83–0.95; RR=0.61, 95% CI: 0.21–1.02; RR=1.70, 95% CI: 0.88–2.52; RR=0.87, 95% CI: 0.57–1.16, respectively).

Conclusions: This study demonstrated that immunosuppression in solid organ transplant recipients was not associated with higher PCa risk.

Keywords: Prostate cancer (PCa); immunosuppression; solid organ transplantation; standardized incidence ratio; meta-analysis

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Introduction

Prostate cancer (PCa) is one of the most common male malignancies in many developed countries globally and accounts for the second most common cause of death in males (1). Aging is a known risk factor of PCa (2), which may be due to the age-related decreased immunosurveillance (3). It is believed that active immunosurveillance in the young body can effectively eliminate neoplastic cells (4,5). Nevertheless, the relationship between PCa risk and either immunodeficiency or immunosuppression remains unclear.

Solid organ transplantation is considered to be the best therapeutic option for patients with end-stage organ failure. Successful outcomes of solid organ transplantation can be achieved by applying strong immunosuppressive drugs that are expected to decrease the incidence of acute graft rejection (6). Notably, solid organ transplant recipients under such treatment are at a higher risk of developing certain malignancies compared with the general population (7). The long duration of immunosuppression in solid organ recipients impairs the immunosurveillance of the body and results in the outgrowth of neoplastic cells (8). To date, organ transplant recipients have a higher risk of developing bladder cancer (9), head and neck cancer (10), thyroid cancer (11), and colorectal carcinoma (12). Based on its 5-years mortality, cancer is now the second, third, and fourth most common cause of death in the transplantation of liver, kidney, and lung recipients, respectively (13).

Although the association between immunosuppression in solid organ transplantation and PCa risk has received much attention lately, the data is still controversial because most studies were carried out from a single center or small sample set; consequently, we were motivated to investigate this association at a meta-analytical level.

Understanding the potential risks of any specific cancer in solid organ transplantation recipients will not only help in fully informing the patient before transplantation, but also allow for a rational approach to monitoring patients during the postoperative period. Currently, there are no conclusive recommendations for the screening of PCa in the solid-organ-transplanted population. Therefore, we conducted the first meta-analysis to investigate the relative risk (RR) of PCa associated with overall and different subsets of solid organ transplant recipients compared with the general male population based on eligible cohort studies.

Methods

Literature search strategy

We performed a systematic search of literature published from 1990 to March 2019 in the PubMed, Embase, and Web of Science databases, using the following keywords: "cancer" or "malignancy" or "neoplasms" or "carcinoma" or "tumor transplantation" or "transplant recipients" or "cohort" and the combination of these phrases. Additional reports were collected from the cross-references within both the original and review articles. No language restrictions were applied.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they met these criteria: (I) it was published between 1990 and March 2019; (II) it was an original cohort study in humans; (III) it examined the association of solid organ transplantation with PCa risk; (IV) it provided enough information to calculate the RR with 95% confidence interval (CI).

Studies were excluded if they met any of the following criteria: (I) they were not cohort studies that evaluated the association between immune inhibition in solid organ transplantation and PCa risk; (II) they were case reports, letters, reviews, editorials, or correspondence articles; (III) they were studies based on incomplete raw data; (IV) the study only contained duplicate data. Also, in cases of multiple publications of the same or overlapping populations, only the most recently published studies or the studies with a large sample size were included.

Data extraction

All data were extracted independently by two investigators (JM Bao and HL Zhu) according to the described selection criteria. Any discrepancy was resolved by the third investigator (GS Yang). The following data were extracted: the name of the first author, publication year, study location, type of transplantation, number of participants and PCa cases, follow-up period, RR and 95% CIs. If one article examined the associations of multiple organ transplantation with PCa risk and provided corresponding independent RR and 95% CIs, we considered this article to contain multiple independent studies.

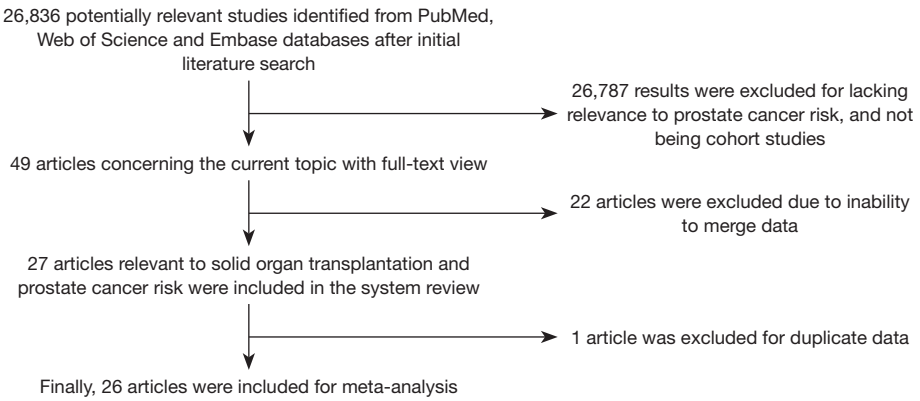

Figure 1 Flow diagram of the study selection process.

Quality assessment

Two investigators (JM Bao and HL Zhu) independently evaluated the quality of all included studies using the criteria adapted from the Cochrane handbook for systematic reviews of interventions (14) and the Newcastle-Ottawa scale (NOS) (15). The NOS ranges from 0 to 9 stars, and study with a score of 7 stars or greater was regarded as high quality. Discrepancies were resolved as described above.

Statistical analysis

RR and 95% CI evaluated the strength of the association between immunosuppression in solid organ transplantation and PCa risk.

The heterogeneity among studies in terms of the degree of association was assessed using the Chi^2 test. The I^2 statistic was used to estimate the percentage of variation between the results occurring because of heterogeneity rather than sampling error (I^2<50% was considered as no significant heterogeneity). When heterogeneity was detected, the RR was pooled according to a random-effect model using inverse variance heterogeneity method (16); otherwise, the fixed-effect model using the inverse variance method (17) was chosen. The Z-test determined the significance of the pooled RR.

Sensitivity analyses were carried out to assess the stability of the results of this study. The impact of each study was evaluated by calculating the combined RRs in the absence of every single study (18).

Potential publication bias was estimated by the Begg's rank correlation (19), Egger's linear regression test (20), and visual inspection of the Begg's funnel plots. For all analyses, a P value <0.05 was considered to represent statistical significance for all comparisons. All statistical analyses were performed using Stata statistical software, version 12.0 (Stata Corp. College Station, TX, USA).

Results

Characteristics of eligible studies

We initially identified 26,836 results relevant to the search terms in the selected databases. After reading the titles and abstracts, 49 articles were included for full-text review. Of these, 22 articles were excluded as their data could not be merged. After further screening, 1 article (21) was excluded for duplicate data. Finally, a total of 26 articles totaling 556,812 solid organ transplant recipients, 2,438 PCa cases, and comprising 33 independent cohort studies that examined the association between solid organ transplantation and PCa risk, were selected for meta-analysis. The specific search workflow is shown in *Figure 1*.

Of all the included cohort studies, there were 3 single-center cohort studies (22-24), 2 multicenter cohort study (25,26), and the rest were population-based cohort studies (27-47); 4 cohort studies (37,38,40,46) were conducted with Asians, and the remaining 29 studies were conducted with Europeans. In these studies, the observed number of PCa cases in the solid-organ-transplanted population was compared with the expected number of PCa case based on the standardized incidence rate of PCa, so the control group for each cohort consisted of all the males in a specific country or area. The characteristics of these studies are presented in *Table 1*.

Table 1 Characteristics of included cohort studies

First author [year]	Study location	Type of transplant	No. of patients	No. of PCa cases	Follow-up period	RR (95% CI)	Quality score
Birkeland [1995]	Nordic countries	Kidney	5,692	11	1964–1986	2.10 (1.10–3.80)	7
Kasiske [2004]	USA	Kidney	35,765	NR	1995–2001	0.79 (0.62–1.00)	7
Vajdic [2006]	Australia and New Zealand	Kidney	28,855	41	1982–2003	0.95 (0.68–1.29)	7
Villeneuve [2007]	Canada	Kidney	11,155	37	1981–1998	0.9 (0.6–1.3)	7
Vegso [2007]	Hungary	Kidney	2,535	3	1973–2007	0.65 (0.28–1.59)	7
Webster [2007]	Australia and New Zealand	Kidney	15,183	43	1963–2004	0.9 (0.64–1.2)	7
Aberg [2008]	Finland	Liver	540	2	1982–2005	1.24 (0.15–4.47)	7
Jiang [2008]	Canada	Liver	2,034	5	1983–1998	1.0 (0.3–2.4)	7
Kellerman [2009]	USA	Heart	851	22	1994–2007	1.2 (0.76–1.8)	7
Jiang [2010]	Canada	Heart	1,703	15	1981–1998	1.3 (0.7–2.2)	7
Collett [2010]	UK	Kidney	37,617	112	1980–2007	1.1 (0.9–1.4)	7
Wisgerhof [2011]	Netherlands	Kidney	1,906	8	1966–2006	0.77 (0.38–1.5)	7
Engels [2011]	USA	Kidney/lung/liver/heart	175,732	1039	1987–2008	0.92 (0.87–0.98)	7
Cheung [2012]	China	Kidney	4,674	6	1972–2011	0.88 (0.39–1.95)	7
Li [2012]	China	Kidney	4,716	4	1997–2008	1.79 (0.67–4.76)	7
Sampaio (K) [2012]	USA	Kidney	123,380	446	1999–2008	0.82 (0.75–0.91)	7
Sampaio (L) [2012]	USA	Liver	43,106	155	1999–2008	0.88 (0.75–1.03)	7
Sampaio (H) [2012]	USA	Heart	16,511	235	1999–2008	3.07 (2.7–3.49)	7
Sampaio (Lu) [2012]	USA	Lung	10,908	33	1999–2008	0.88 (0.62–1.24)	7
Kaneko [2013]	Japan	Liver	360	2	NR	2.2 (0.6–8.9)	6
Piselli [2013]	Italy	Kidney	7,217	35	1997–2009	1.7 (1.2–2.3)	7
Krynitz (K) [2013]	Sweden	Kidney	7,952	86	1970–2008	1.1 (0.9–1.3)	7
Krynitz (L) [2013]	Sweden	Liver	1,221	4	1970–2008	0.5 (0.1–1.2)	7
Krynitz (H/Lu) [2013]	Sweden	Heart/Lung	1,012	10	1970–2008	1.3 (0.6–2.3)	7
Tessari [2013]	Italy	Kidney	3,537	19	1980–NR	1.3 (0.8–2.1)	6
Na (L) [2013]	Australia	Liver	1,926	7	1984–2006	0.62 (0.27–1.19)	7
Na (H) [2013]	Australia	Heart	1,518	24	1984–2006	1.10 (0.71–1.60)	7
Na (Lu) [2013]	Australia	Lung	1,200	3	1984–2006	0.73 (0.15–2.14)	7
Maisonneuve [2013]	USA	Lung/Liver	2,749	1	1990–2009	1.8 (0.1–8.7)	7
Secnikova [2015]	Czech	Heart	603	10	1993–2010	2.03 (1.05–3.62)	7
Taborelli [2018]	Italy	Liver	2,832	2	1985–2014	0.1 (0.0–0.5)	7
Heo [2018]	South Korea	Kidney	1,343	3	2010–2014	3.49 (0.70–10.19)	7
Jäämaa-Holmberg [2019]	Finland	Heart	479	15	1985–2014	1.5 (0.8–2.4)	7

No., number; RR, relative risks; 95% CI, 95% confidence interval; NR, not reported; K, kidney; L, liver; H, heart; Lu, lung; PCa, prostate cancer.

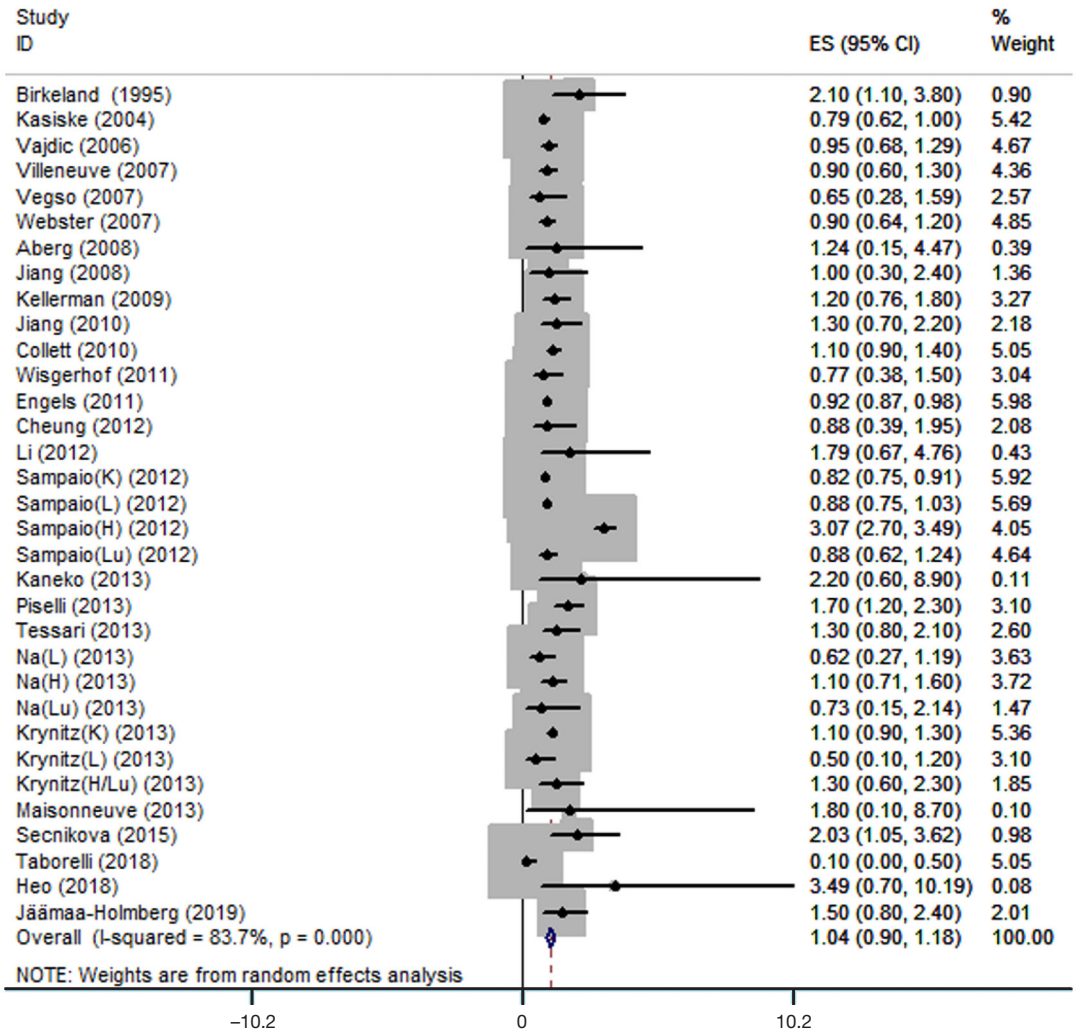

Figure 2 Forest plot of pooled RR with 95% CI for the association between immunosuppression in solid organ transplantation and PCa risk. ES, effect size; 95%CI, 95% confidence interval; K, kidney; L, liver; H, heart; Lu, lung; PCa, prostate cancer.

The methodological quality of the included studies

The scores of the included studies ranged from 6 to 7 (*Table 1*). Thus, the quality of these studies was generally high.

PCa risk in all solid organ transplant recipients

A total of 26 articles reporting associations of immunosuppression in solid organ transplantation with PCa risk were identified and included in this meta-analysis. These comprised 33 independent cohort studies with 556,812 solid organ transplant recipients and 2,438 PCa cases. Significant heterogeneity was detected, and the analysis was therefore conducted using a random-effect model. PCa risk in solid organ transplant recipients did not increase compared with that in the general population (RR=1.04, 95% CI: 0.90–1.18) (*Figure 2*).

PCa risk in different subsets of the transplanted population

PCa risk in the renal-transplanted population

The association of immunosuppression in renal transplantation with the risk of PCa was investigated in 15 independent studies including a total of 291,527 renal transplant recipients. There was no significance between-study heterogeneity by Q-test, and a fixed effect model was used to conduct the analysis. The results showed an absence of a positive association between kidney transplantation and

PCa risk (RR=0.89, 95% CI: 0.83–0.95) (*Figure 3A*).

PCa risk in liver transplanted population

A meta-analysis of the association between immunosuppression in liver transplantation and PCa risk included 7 independent cohort studies with 52,019 liver transplant recipients. The Q-test of between-study heterogeneity was significant, and a random-effect model was used to analyze the data. The results indicated that liver transplantation was not associated with higher PCa risk (RR=0.61, 95% CI: 0.21–1.02) (*Figure 3B*).

PCa risk in heart transplanted population

Six independent cohort studies with a total of 21,665 heart transplant recipients were included in the meta-analysis of heart transplantation. There was significance in the between-study heterogeneity by Q-test, and the data were analyzed using a random-effect model, but no significant association between heart transplantation and PCa risk was detected (RR=1.70, 95% CI: 0.88–2.52) (*Figure 3C*).

PCa risk in lung transplanted population

The association between immunosuppression in lung transplantation and PCa risk was investigated in 2 independent cohort studies with 12,108 lung transplant recipients. The Q-test of heterogeneity was not significant, and a fixed effect model was used to conduct the analysis. No significant association between immunosuppression in lung transplantation and PCa risk was observed (RR=0.87, 95% CI: 0.57–1.16) (*Figure 3D*).

Subgroup analysis by ethnicity

The association between immunosuppression in solid organ transplantation and PCa risk in Asians

Meta-analysis of the association between immune inhibition in solid organ transplantation and PCa risk in Asians included 4 independent cohort studies with a total of 11,093 recipients. A random-effect model was selected to analyze the data. PCa risk did not increase in Asian solid organ transplant recipients (RR=1.09, 95% CI: 0.38–1.80).

The association between immunosuppression in solid organ transplantation and PCa risk in Europeans

The association of immunosuppression in solid organ transplantation and PCa risk in Europeans was investigated in 29 independent studies including a total of 545,719 solid organ transplant recipients. The Q-test of heterogeneity was significant, and a random-effect model was used. Immunosuppression in solid organ transplantation showed no significant association with PCa risk in Europeans (RR=1.03, 95% CI: 0.89–1.18). Summary of the results of this meta-analysis is listed in *Table 2*.

Sensitivity analysis and publication bias

Sensitivity analyses were done by removing every included study sequentially to evaluate the influence of every single study on the combined RRs. The results showed the pooled RRs were not significantly changed when any individual study was removed, indicating that no single study showed an excessive impact, and the results were reliable. Other results were also very stable. We conducted Begg's and Egger's tests to assess potential publication bias. No significant publication bias was observed (Begg, P=0.158 and Egger, P=0.437), and Begg's funnel plots also indicated no substantial asymmetry (*Figure 4*). No evidence of publication bias was detected in other results.

Discussion

The goal of this study is to determine the possible elevated risk of PCa in solid organ transplant recipients. This study, to the best of our knowledge, represents the first meta-analysis estimating the PCa risk in the solid-organ-transplanted population. The pooled RRs indicated that immunosuppression in solid organ transplantation did not increase PCa risk. Independent analysis in different subsets of the transplanted population further validated that individual organ transplantation of the kidney, liver, lung or heart is not associated with elevated PCa risk.

The key finding of this study is that there appears to be no significant association between immune inhibition in solid organ transplantation and PCa risk. The exact mechanism behind this surprising phenomenon is still unknown. In general, solid organ transplant recipients are associated with an increased risk of developing cancers, and it is widely believed that immunosuppression is the key reason. However, this simple concept does not explain why a higher frequency is associated with a few specific cancer types (48). Certainly, the relationship between cancer risk and the degree of immunosuppression might not always go hand in hand, and it could be very cancer-specific (49). Despite immunosuppression being a key factor, other risk factors like oncogenic viral infection may also play an important role (50). In an immunosuppressed population

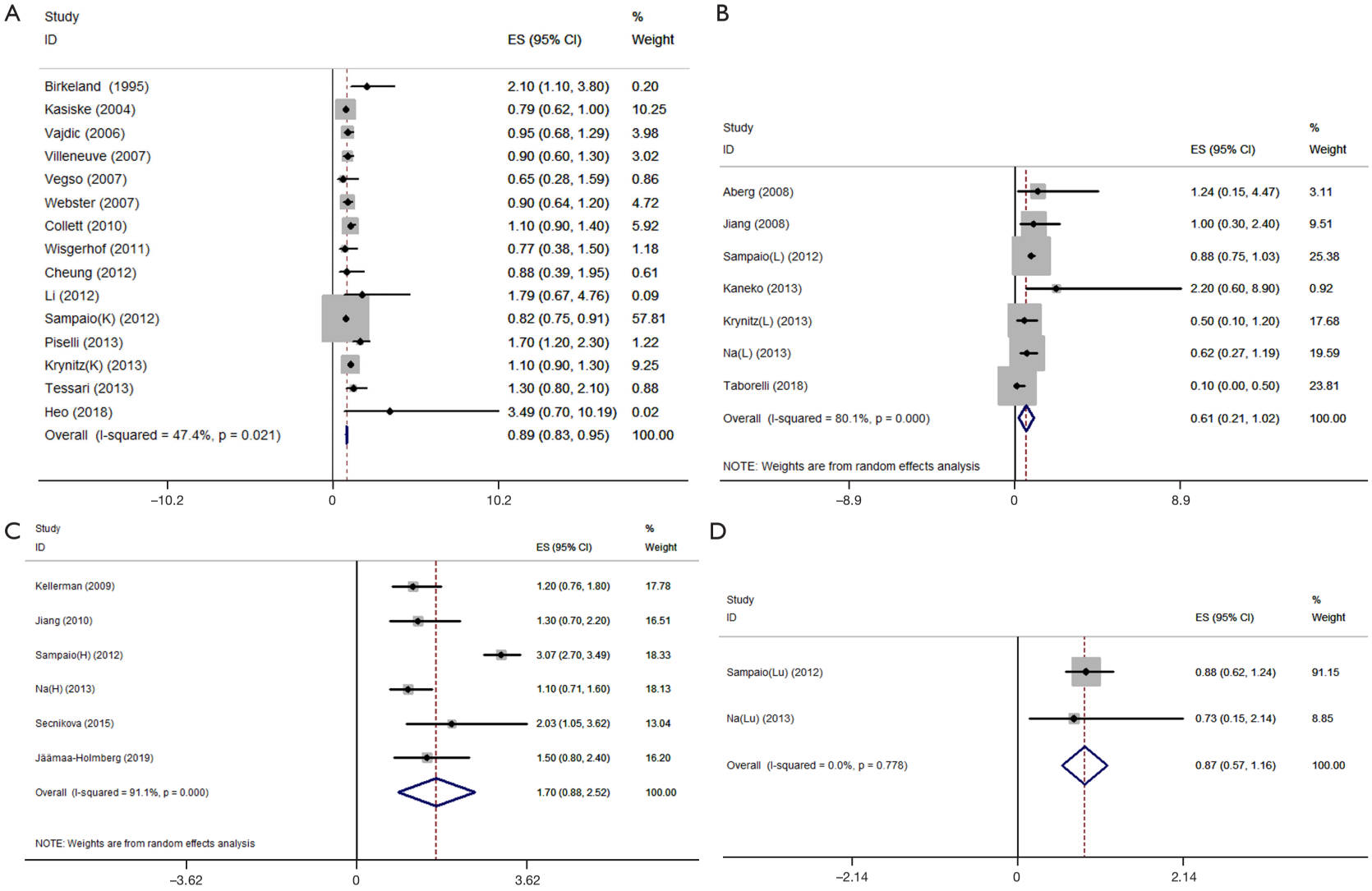

Figure 3 Forest plot of pooled RR with 95% CI for the association between PCa risk and immune inhibition in the transplantation of the kidney (A), liver (B), heart (C), and lung (D). RR, relative risks; ES, effect size; 95%CI, 95% confidence interval; K, kidney; L, liver; H, heart; Lu, lung; PCa, prostate cancer.

Table 2 Meta-analysis results of the association between immunosuppression in solid organ transplantation and prostate cancer risk

Group	No. of studies	Total patients	Total cases	Test of association			Test of heterogeneity	
				Pooled RR	95% CI	Model	P	I^2
Overall	33	556,812	2,438	1.04	0.90–1.18	R	0.0	83.7%
Type of transplantation								
Kidney transplantation	15	291,527	854	0.89	0.83–0.95	F	0.02	47.4%
Liver transplantation	7	52,019	177	0.61	0.21–1.02	R	0.0	80.1%
Heart transplantation	6	21,665	321	1.70	0.88–2.52	R	0.0	91.1%
Lung transplantation	2	12,108	36	0.87	0.57–1.16	F	0.78	0.0%
Ethnicity								
Asians	4	11,093	15	1.09	0.38–1.80	R	0.58	0.0%
Europeans	29	545,719	2,423	1.03	0.89–1.18	R	0.0	85.5%

No., number; RR, relative risks; 95%CI, 95% confidence interval; R, random effect; F, fixed effect.

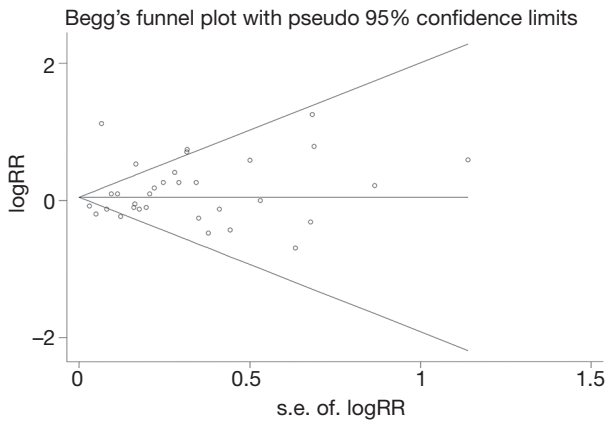

Figure 4 Forest plot of pooled RR with 95% CI for the association between immunosuppression in solid organ transplantation and PCa risk. RR, relative risks; 95%CI, 95% confidence interval; PCa, prostate cancer.

with impaired immunosurveillance, the implicit ability of several viruses to immortalize infected cells by disrupting the cell-cycle control could lead to tumorigenesis; meanwhile, immunosuppressive drugs damaging the immune function controlling the oncogenic viral infections may be involved in the initial effect on carcinogenesis by transforming cells and then evading immune recognition (51). Virus-related cancers consistently associated with an elevated risk in transplant recipients include hepatocellular carcinoma (52), squamous cell carcinoma of the cervix, Kaposi's sarcoma (53), and Merkel cell carcinoma (54,55). However, to date, there is no conclusive evidence to support that infection is likely to be involved in prostate carcinogenesis (56). Therefore, a possible explanation is that most of the cancers occurring at increased rates in solid organ transplant recipients are infection-related, but PCa is not related to infection (56,57); hence, PCa risk does not increase in solid organ transplanted population.

One previous study indicated that PCa risk differs across race and ethnicity in renal transplanted population, and the black population had an elevated PCa risk following kidney transplantation (58). In our study, we also conducted a subgroup analysis to evaluate the ethnic differences in PCa risk after solid organ transplantation. However, the results indicated that PCa risk did not increase after solid organ transplantation both in Asians and Europeans.

Heterogeneity is considered to be a significant issue in meta-analytical studies. We detected significant between-study heterogeneity in some analyses. Sensitivity analyses showed that no individual study exhibited excessive impact on the pooled RRs, indicating these findings were relatively stable. Also, no evidence of publication bias was detected in Begg's funnel plots and Begg's tests, so the results were unbiased.

We believe our study has several strengths to support the conclusion. This is the first systematic quantitative assessment of the association between immune inhibition in solid organ transplantation and PCa risk. Our study included 33 independent population-based cohort studies with a large sample size of 556,812 recipients that enhanced the power of statistical analysis to lead to a more reliable outcome; this study surpasses the insufficient statistical power of individual studies. Four kinds of regular solid organ transplantation were involved in our included studies, and we further

evaluated the association between immunosuppression and PCa risk in four subsets of recipients; the results indicated that none of the four kinds of solid organ replacement were associated with elevated PCa risk, which allows us to draw a comprehensive conclusion. We were able to conduct subgroup analysis to explore the racial differences in PCa risk following solid organ transplantation, and we demonstrated that neither Asians nor Europeans were associated with an elevated risk of PCa after solid organ transplantation.

Nevertheless, this study has some limitations that should be taken into consideration. First, we were not able to conduct a stratified analysis by different age groups to evaluate the impact of immunosuppression in solid organ transplantation on PCa risk because of a lack of data. Second, other confounders like dietary factors (59-62) and smoking (63) may play a role in prostatic carcinogenesis in solid organ recipients which may affect the association between immunosuppression in solid organ transplantation and risk of PCa, but we could not rule out the impact of these factors due to insufficient data. Third, heterogeneity among studies existed in some analyses.

Conclusions

Taken together, immunosuppression in solid organ transplantation is not associated with increased PCa risk. Organ-transplantation-related immunosuppression may not be a risk factor of PCa. Large prospective cohort studies are needed to confirm our findings.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.06.03). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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