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Review

Risk of renal cancer in liver transplant recipients: A systematic review and meta-analysis

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HIGHLIGHTS

- We performed a meta-analysis based on 8 eligible articles for the risk of renal cancer in liver transplant recipient. These studies were based on several developed countries, which included USA, UK, Finland, Sweden, German, Canada, Japan, Netherlands.
- We also performed sensitivity analyses and publication bias analyses.
- This meta-analysis showed a significantly increased risk of developing renal cancer in LTRs.

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ABSTRACT

Liver transplantation is associated with a significantly increased risk of de novo malignancies, but for renal cancer this risk is less clear. We therefore performed a meta-analysis of published studies to determine whether renal cancer risk in liver transplant recipients (LTRs) was increased. To obtain a more precise conclusion, a systematic search was performed in PubMed and Web of Science databases until June 10, 2015. Standardized incidence ratio (SIR) corresponding 95% confidence interval (CI) were used to estimate risk of renal cancer in LTRs. Heterogeneity test, sensitivity analysis, and publishing bias were also performed. We identified 8 eligible studies and performed a meta-analysis on data of 49,654 LTRs with a total follow-up of 121,514.6 patient-years. The SIR for renal cancer was identified a 3.275-fold higher SIR (95% CI: 1.857–5.777; $P < 0.001$) in LTRs compared with the general population. This systematic review and meta-analysis demonstrated that the LTRs was associated with a significant increase in the incidence of renal cancer. Such association suggests that yearly routine post-transplant surveillance is need for renal cancer in LTRs.

1. Introduction

Liver transplantation is currently considered the only potentially lifesaving treatment for patients with end-stage liver disease or acute/chronic liver disease. Since the first successful human liver transplant was performed in the USA by Thomas Starzl in 1963, the long-term survival of liver transplants have improved considerably over the past five decades, particularly with the highly active immunosuppressants available which significantly reduce the incidence of graft rejection and improve the survival rates of recipients [1,2]. However, the incidence rates of de novo malignancies in organ transplant recipients were reported to range between 3% and 15%, which is at least two times of the incidence observed in the age-matched and sex-matched general population [3,4]. In fact, recurrent and de novo malignancies is currently the third leading cause of death in transplant patients, and is expected to surpass cardiovascular disease and infection as the leading cause of death within the next two decades [5,6]. Previous population-based studies have also demonstrated that de novo malignancies in LTRs at a high risk of developing renal cancer compared with the general population [7]. The most common malignancies were lymphomas and skin cancers (including squamous cell carcinoma and Kaposi's sarcoma), followed by Gastrointestinal, Genitourinary,

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Lung, Oropharyngeal [8,9].

Over the past decade, a number of cohort studies have shown the possible association between liver transplantation and renal cancer risk [10,11]. However, owing to the limitation of small sample volume and not all individual studies shown a similar association, the results were still inconclusive to obtain a reliable conclusion. This meta-analysis, therefore, aimed to determine whether the overall SIR of renal cancer is increased in LTRs compared with the general population.

2. Materials and methods

2.1. Relevant publication search

We performed a comprehensive literature search in public database PubMed and IS Web of Science (the last update in June 10, 2015) for all English-language publications by using following key words: 'liver', 'transplantation', 'renal', 'kidney', and 'cancer'. The relevant search results were restricted to contain the above mentioned keywords in the title or abstract of the publications.

2.2. Inclusion and exclusion criteria

For the selection of eligible studies had to meet the following inclusion criteria: i) studies had to be population-based cohort studies of LTRs; ii) studies had to provide sufficient data on incidence or risk of renal cancer, such as SIR, relative risk (RR), or observed cases of renal cancer in LTRs; iii) SIR with 95% CI were calculated using matched transplant population to standardized population in the studies. Studies were excluded if any of the following criteria were met: i) case-control studies, case series, or case reports; ii) other cancer or organ transplantation studies; iii) studies included only pediatric patients.

2.3. Data extraction

Two investigators (Zhu and Wang) independently reviewed and extracted the data, any potential conflict was resolved by discussion. The following information were extracted from each eligible study: the first author's name, year of publication, type of transplant, data source, geographic origin, number of patients, number of liver transplant cases, length of follow-up time, number of all cancers in liver transplant cases, mean follow-up time (years), patient-years (years), mean age at transplantation (years), number of expected cases of renal cancer, number of identified cases of renal cancers, the SIRs of renal cancer. All required data were collected into a data extraction table.

2.4. Statistical analysis

In this meta-analysis, each study of the unadjusted RR with 95% CI was estimated. A random-effects model was used to account for possible heterogeneity between studies and calculated pooled effects (95% CIs) for RR by using the inverse variance method. When a P value for the Qstatistic less than 0.05 indicated statistical heterogeneity to be significant, the random-effects model (the DerSimonian and Laird method) was used to analyze the pooled ORs [12]. Otherwise, a fixed-effects model (the Mantel–Haenszel method) was applied if the P-value greater than 0.05 [13]. The inconsistency index (I^2) was defined as the percentage of the observed between-study variability caused by heterogeneity rather than random error or chance, I^2<25%, 25–75%, and>75% indicating low, moderate and high inconsistency, respectively [14]. Additionally, one-way sensitivity analysis were conducted to assess the effects of each study by sequential removal of each individual study data on the pooled RR. The Begg's funnel plot and Egger's test were conducted to assess the potential publication bias [15]. All statistical analysis were carried out using the STATA software (version 11.0; Stata Corporation, College Station, Texas, USA).

3. Results

3.1. Study characteristics

In this meta-analysis, 8 eligible articles were identified under the selection criteria [10,11,16–21], comprising a total of 49,654 LTRs performed on 228,933 patients. The outline diagram for searching and selecting articles is illustrated in Fig. 1. The studies and their important characteristics are extracted and listed in Table 1. All the studies were retrospective and had sufficient sample size. Among them, the largest study included 37,888 LTRs. These studies were based on several developed countries, which included USA, UK, Finland, Sweden, German, Canada, Japan, Netherlands.

Table 2 shows a summary of the included studies with their demographic details. As can be noted, a liver transplant population of 49,654 patients were followed-up for a total of 121514.6 person-years. The overall mean age in transplantation patients was 48 years old (range: 43–56 years old) with a mean follow-up duration of 7.8 years (range: 5.1–16.0 years). A total number of 472 cancers and haematological malignancies in liver transplant cases were observed, and a total of 87 renal cancer patients were identified compared with 41.72 expected cases.

3.2. Evidence synthesis

Meta-analysis for the SIR indicated LTRs were associated with a significantly increased risk of renal cancer (SIR = 3.275, 95% CI: 1.857–5.777; P < 0.001, Table 3). The forest plot for individual and overall RR measures is shown in Fig. 2. Significant heterogeneity was observed (I^2 = 66.4%, Pheterogeneity = 0.004) in the pooled analysis. Due to the limitations of existing data, our meta-analysis could not detect any sources contributing to the substantial heterogeneity.

However, we performed a sensitivity analysis to assess the effect of each study on the pooled ORs by sequentially removing individual eligible study, respectively. Sensitivity analysis indicated that no individual study altered the overall significance of the RRs, the omission of any one study resulted in SIRs between 2.003 (95% CI: 0.822–4.880) and 2.795 (95% CI: 0.849–9.207; Table 4), which implied the results of this meta-analysis were stable and reliable (Fig. 3). Furthermore, there was no evidence of publication bias found by using Begg's test (P = 0.174) or Egger's test (P = 0.068) (Fig. 4).

4. Discussion

The main objective of this meta-analysis was to determine whether the risk of renal cancer among LTRs is increased to a certain extent that separate surveillance recommendations would be warranted. Interestingly, our data shown a significantly elevated risk of renal cancer in allogenic liver transplantations compared with the general population (SIR = 3.275, 95% CI: 1.857–5.777; P < 0.001).

Numerous publications and research papers have been well described the incidence of renal cancer after liver transplantation [22,23]. For Haagsma et al. [17] the results shown an overall 30-fold increased risk of renal cell carcinomas in LTRs compared with the general population. However, it is still uncertain whether the increased risk of de novo renal cancer post transplantation is related to long-term administration of immunosuppressive agents