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Spectrum of Cancer Risk in Renal Transplant Recipients- A Meta-analysis

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ABSTRACT

Introduction: Renal transplant is the main modality of treatment available for end stage renal failure. There is a small risk of various types of cancers associated with renal transplant recipients due to usage of immune suppressive drugs and its consequences. Hence the purpose of this meta- analysisstudy was to determine the spectrum of cancers associatedwith renal transplant recipients.**Methods:**The studies which testified the incidence of cancer after renal transplantation were collected from various search engines such as Google Scholar, PubMed and EMBASE. All studies that evaluated the occurrence of cancer after renal transplantation between the years 1990-2018 were considered to be eligible for this study. Data were collected from 5 National and 5 International studies and analysed. MOOSE guidelines were used to assess the quality of the studies included in this study and reviewed briefly in RevMan version 5.3 review manager software. Statistical analysis of the included data was done using RevMan version 5.3 review manager software designed for meta-analysis and systemic review studies. Quantification of heterogeneity is done by I^2 value. **Result:**This study included 4666 recipients of kidney transplants from National studies and 8189 recipients of kidney transplants from International studies. Incidence of cancer was 61 and Non incidence of cancer was 4605 out of 4666 recipients compared in National studies, Heterogeneity $chi^2 = 32.53$ and $p(<0.0001)$, $I^2 = 88\%$, Test for overall effect Z=33.99 , p(<0.0001).Forest plot comparison for the incidence of cancer after renal transplantation from International studies (figure4) which showed the risk of cancer was low. Total Confidence Interval was 95%, Incidence of cancer was 467 and Non incidence of cancer was 7722 out of 8189 recipients compared in International studies, Heterogeneity tau = 0.04 Chi = 17.24 df= 4 I = 77%(p=0.002), test for overall effect Z=26.17, p (<0.00001).**Conclusion:** There was two fold increase in the occurrence of cancers of stomach, oesophagus, ovary, pancreas, lung, breast, colon, and twenty fold increase in the occurrence of lympho-proliferative cancers.

Key words: Renal transplant, Cancer,Immunosuppressant, Meta-analysis, End stage renal disease

INTRODUCTION

Organ transplantation is considered to be the most effective treatment for patients with end-stage organ failure. Organ transplantation involves removal of organ from the donor's body and transplanting into the

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recipient. It may result in stimulation of immune response against the donated organ by the recipient's body leading to various complication or even death. To reduce the risk of graft rejection immunosuppressant treatments are given to organ transplant recipients. However it may lead to various other complications because of overall reduction of recipient's immune status.Kidney transplantation is by far the most commonly done transplantation all around. Renal transplantation is considered as the most desired option for treatment in patients with irreversible chronic kidney disease. Solid organ transplant patients are at an expanded danger of malignancy when compared with the overall public (about 3– multiple times) with genuine consequences(1).With significantly improved survival due to potent immunosuppressive drugs; better control of infectious complications, and cardiovascular events, there is an increase in incidence (average 5%–6%, range 1%–30%) of malignancies in these patients. Latent viral infection, acquired viral infections and other acquired risk factors are the major cause of post-transplant cancer because of reduced immune response by immunosuppressive drug(2).In a study that included of over 35,000 first time renal transplant recipients, the cancer rates for the commonest tumours , e.g. stomach, oesophagus, ovary, pancreas, lung, breast and colon were roughly twofold higher after kidney transplantation compared with the general population; testicular and bladder cancers were increased about threefold; and kidney cancer was approximately 15 fold more common . Finally, non-Hodgkin's lymphoma, non-melanoma skin cancer, Kaposi's sarcoma were encountered with over 20 fold increased frequency(3).The following factors such as age, previous history of malignancy, male gender, dosage of immune suppression, sun exposure, time period of pre-transplant dialysis concomitant viral infection and lymphocyte-depleting antibodies are said to have a effect on incidence of cancer after transplantation(4,5,7)Hence the purpose of this meta-analysis to find the spectrum of cancers associated with renal transplant patients.

MATERIALS AND METHODS:

Data Source: The studies which testified the incidence of cancer after renal transplantation were collected from various search engines such as Google Scholar, PubMed and EMBASE. Eligible studies were recognized using The Medical Subject Heading (MESH) terms 'Malignancy', 'Cancer' and transplantation. Data from several observational studies have been involved in this meta-analysis.

Study eligibility: All studies that evaluated the occurrence of cancer after renal transplantation between the years 1990-2018 were considered to be eligible for this study.
Study Selection: Abstract of the potentially suitable studies was read carefully and selected as suitable trials as per inclusion criteria.
Data Collection: Required data from the full-text trials of selected studies were initially tabulated in RevMan 5.3 review software and statistical analyses were performed.
Data Management: Mendeley version 1.91.5 reference manager software is used to download and manage the reference articles used in the study.
Data Items: Data such as the name of the journal, author name, year of article publication, study plan, sample size, Mean age, type of malignancy reported and Immunosuppressant drug used were extracted from the selected eligible studies.
Quality assessment: MOOSE guidelines were used to assess the quality of the studies included in this study and reviewed briefly in RevMan version 5.3 review manager software. Most of the included studies access the incidence of cancer in the renal transplant recipient. The selected studies were well organized and evaluated using funnel plot.
Statistical Analysis: Statistical analysis of the included data was done using RevMan version 5.3 review manager software designed for meta-analysis and systemic review studies. Quantification of heterogeneity is done by I^2 value. The statistical method used was the chi-square test. Funnel plot representation is used to test the publication bias of the studies included.

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FIGURE 1- PRISMA Flow diagram of study selection and search strategy

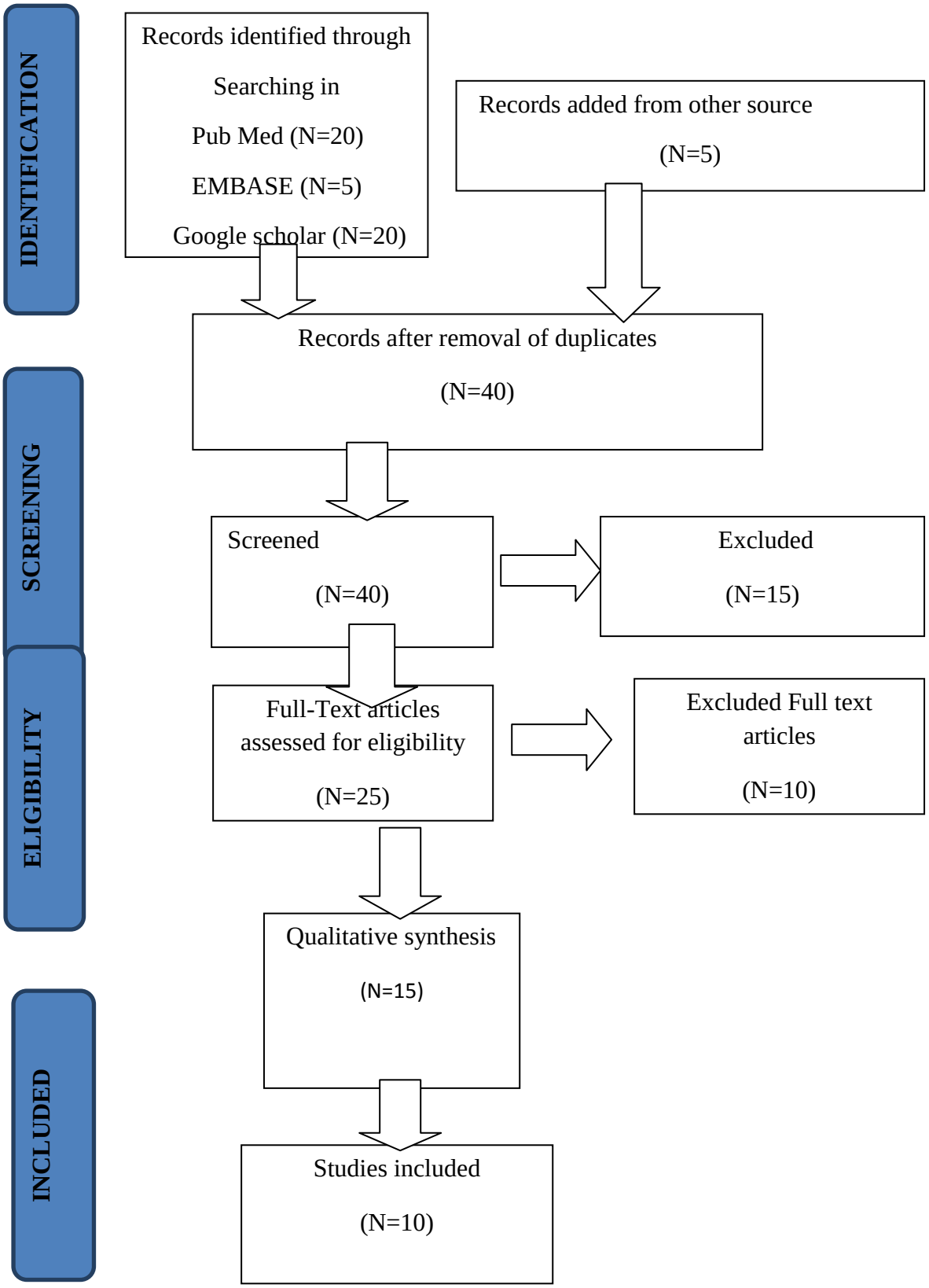

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TABLE 1- Characteristics of National / International studies included in Meta-analysis

Journal	Title	Study Design	Sample Size	Type of Organ Transplant	Reported Malignancy	Immuno - Suppressant Drugs
Indian Journal of Nephrology 2013 Jul-Aug; 23(4);287-291	Spectrum of lympho proliferative disorders following Renal transplantation in North India(5)	Retrospective analysis	2000	Renal	40 malignancy in 29 patients. 72.5% of all malignancy after transplantation	Azathioprine, Prednisolone, Cyclosporine.
Nephrology 1995;1,301-305	Low incidence of malignancies following renal transplantation in India(6)	Retrospective Analysis	334	Renal	6 malignancy in 4 patients	Azathioprine, Prednisolone, Cyclosporine.
Clinical transplantation Clin transplant 2005 :19 :668-673	Post – transplant lymphoproliferative disorder after live donor renal transplantation(7)	Retrospective evaluation	1700	Renal	9 patients	Azathioprine, Cyclosporine, Prednisolone.
Indian Journal of Nephrology Year:2018 Volume: 28	Carcinoma of the tongue in renal transplant recipients: An unusual spectrum of de novo malignancy at a tertiary care centre in India over a period of 26 years (8)	Retrospective Analysis	338	Renal	16 malignancy in 15 patients (average 5%-6%, range 1%-30%) of Malignancy	Azathioprine, Cyclosporine, Prednisolone, Mycophenolate mofetil (MMF) Calcineurin inhibitor or tacrolimus
Journal of Nephrology and Renal Transplantation JNRT2(1)2009: 94-105	Malignancies following kidney transplantation (9)	Retrospective Study	294	Renal	6 malignancy in 4 patients	Azathioprine Prednisolone

Journal	Title	Study Design	Sample Size	Type of Organ Transplant	Reported Malignancy	Immuno-Suppressant Drugs
Indian Journal of Dermatology 2009 Jul-Sep; 54(3);247-250	Benign and Malignant Skin Lesions in Renal Transplant Recipients(10)	Descriptive study	100	Renal	6 (4- cases were skin cancers) (1-Transitional cell carcinoma) (1-non-Hodgkin lymphoma)	Prednisolone, azathioprine and cyclosporine
Transplantation Vol.76,1448-1451, No.10, November 27,2003	Incidence of Cancer after Kidney Transplant Results from the North Italy Transplant	Cohort study	3521	Renal	172 (39-Kaposi's sarcoma) (38-lymphoproliferative diseases) (95-carcinomas	Mycophenolate, Cyclosporine and Tacrolimus

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	program(11)				like kidney,skin,colorectal,breast,gastric, lung,bladder,mesothelioma)	
Department of Dermatology Vol.49,506-509,No.3, March1990	Incidence of Skin cancer after Renal transplantation in the Netherlands(12)	Cohort study	764	Renal	47 (29-squamous cell carcinoma) (18-basal cell carcinoma)	Prednisolone, azathioprine
Supplement to Transplantation November 27,2012,Vol94	Malignancy Incidence after Renal Transplantation (13)	Retrospective study	2461	Renal	138	Not specified
BMC Nephrology (2018)19:311	Cancer risk after Transplantation in South Korea:a nationwide population-based study (14)	Cohort Study	1343	Renal	104	Azathioprine, Cyclosporine, Prednisolone, Mycophenolate mofetil, Tacrolimus, and sirolimus

RESULT

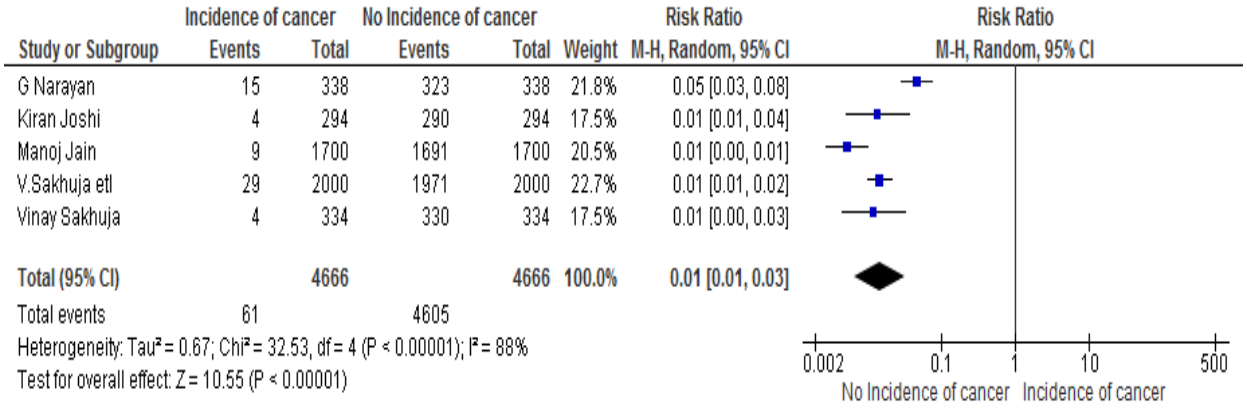

Figure 2: Forest plot comparison of Incidence of cancer after renal transplantation from National studies Analysis model = random effects. Effect measure = risk ratio; Statistical method = I^2 Heterogeneity. 95% CI is represented by the diamond at the bottom.

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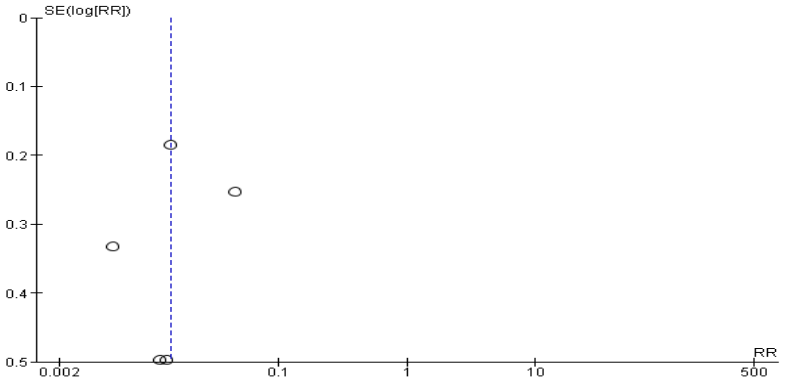

Figure 3: Funnel plot comparison of National studies for Incidence of cancer and Non-incidence of cancer.

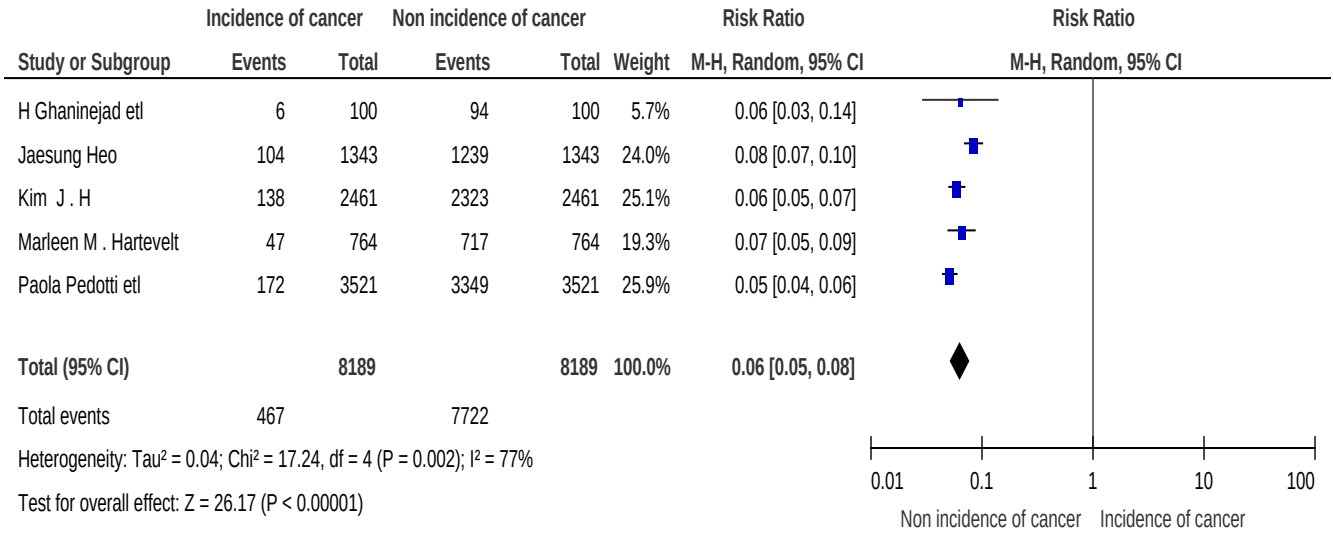

Figure 4: Forest plot comparison for Incidence of cancer after renal transplantation from International studies. ; Analysis model = random effects, Effect measure = risk ratio; Statistical method = I^2 Heterogeneity. 95% CI is represented by the diamond at the bottom.

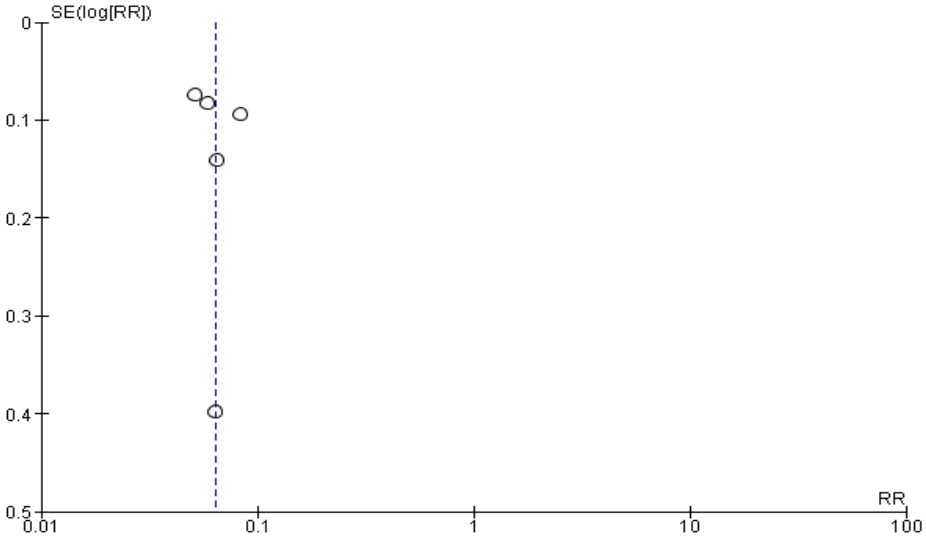

Figure 5: Funnel plot comparison of International studies for Incidence of cancer and Non Incidence of cancer

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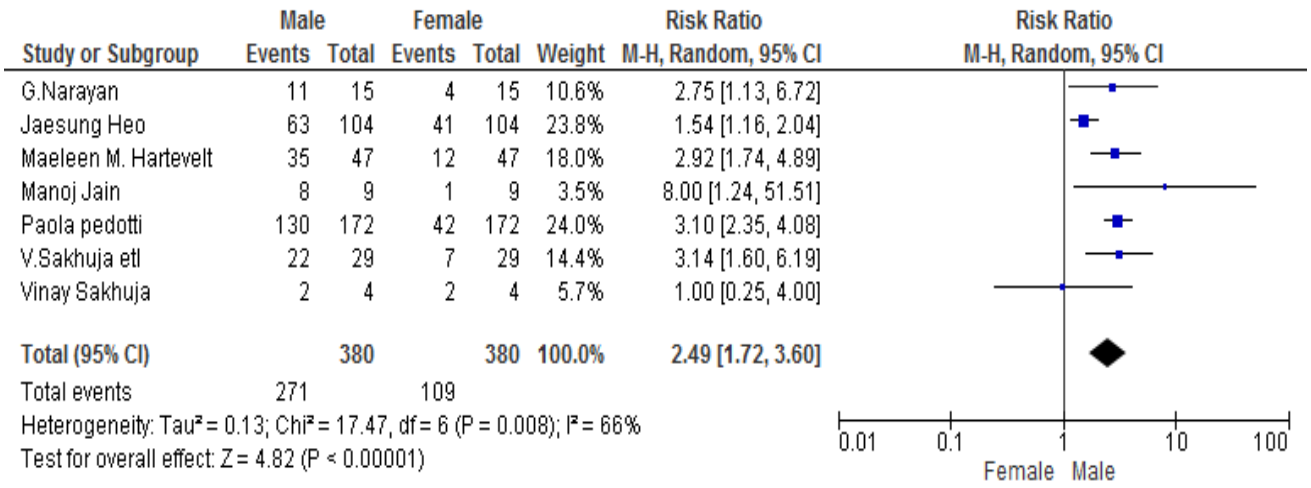

Figure 6: Forest plot comparison of Gender representation for National and International Studies. Analysis model = random effects, Effect measure = risk ratio; Statistical method = I^2 Heterogeneity. 95% CI is represented by the diamond at the bottom.

DISCUSSION

This meta-analysis aims todescribe the risk of cancer in renal transplant recipients. Renal transplantation has progressively become a routine medical treatment. The overall occurrence of malignancies in Indian transplant recipients is low (6). The absence of registry prevents an accurate estimation of cancer risk. Data werecollected from 5 National and 5 International studies from the 1990s and analysed. The most common cancer noticed from the observed general population are kaposi sarcoma , non-melanoma skin cancers, myeloma, thyroid cancer, lymphoproliferative disorders, oral cancer, non-hodgkin lymphoma, cervical cancer, breast cancer, lung cancer, kidney cancer and stomach cancer (8,9,10).

This study included 4666 recipients of kidney transplants from National studies and 8189 recipients of kidney transplants from International studies. The mean age for cancer risk observed from the National studies was 43.35 year and for International studies was 45.75 year. The data collected from different studies were analyzed using RevMan software 5.3 version. Forest plot comparison for incidence of cancer after renal transplantation from National studies (figure2) which showed the risk of cancer was low and total Confidence Interval was 95%, Incidence of cancer was 61 and Non incidence of cancer was 4605 out of 4666 recipients compared in National studies, Heterogeneity chi^2 = 32.53 and p(<0.0001), I^2 =88% , Test for overall effect Z=33.99 , p(<0.0001).Forest plot comparison for the incidence of cancer after renal transplantation from International studies (figure4) which showed the risk of cancer was low. Total Confidence Interval was 95%, Incidence of cancer was 467 and Non incidence of cancer was 7722 out of 8189 recipients compared in International studies, Heterogeneity tau = 0.04 Chi = 17.24 df= 4 I = 77%(p=0.002), test for overall effect Z=26.17, p (<0.00001).Forest plot for comparison of Gender representation of National and International studies (figure 6) which showed that risk of cancer after renal transplantation was more common in males than

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in female. Total confidence interval was 95%, Heterogeneity tau^2 =0.13 Chi ^{2}=17.47, df=6(p=0.008) I^2=66%. Test for overall effect Z=4.82(p<0.00001).

STRENGTH AND LIMITATIONS

The study has several strengths. It is one of the few meta-analysis studies which described the cancer risk in renal transplantation. We used data from valuable studies with huge number of sample size. This study summarizing all available data on the risk of cancer after renal transplantation providing pooled risk estimate separately from National and International studies for Incidence of cancer, Non-incidence of cancer, Mean age and Gender representation. The year of transplantation ranged from 1990 to 2018 in the included studies. We limited the study to a single organ type**.** We observed an asymmetrical funnel plot due to the inclusion of studies in small number with different sample sizes and hence the possibility of publication bias needs to be addressed.

CONCLUSION

From this meta-analysis of 12,855 patients with renal transplant recipients, it can be concluded that there was twofold increase in the occurrence of cancers of stomach, oesophagus, ovary, pancreas, lung, breast, colon, and twenty fold increase in the occurrence of lympho-proliferative cancers. Association of various above cancers in other organ transplant recipients can be taken as further scope of this study and can be compared.

Declaration of interest:
I declare that there is no conflict of Interest that could be perceived as prejudicing the impartiality of the research reported.

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