ORIGINAL ARTICLE

Hypertension as a Determinant of Kidney Malignancy: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Hypertension becomes a global health burden which is affecting 3 in 10 adults over 20 years old, leading to high morbidity and mortality. Hypertension almost asymptomatically detected when the patient is on a regular check-up. Kidney cancer becomes the 13thmost common type of urinary tract cancer worldwide, approximately accountsforup to 4% of all-cause malignancy.The incidentof urinary tract malignancy diagnosed every year is approximately more than one third of 1 million individuals. The character of which hypertension becomes a determinantof kidney cancer is left tonot fully understoodeven with the proposed mechanismhas been established.
Aim: We performed meta-analysisregarding hypertension as a determinant ofkidney malignancy using materials that were comprehensively taken from a number of databases.
Methods: Studies were obtained by using PubMed and the Cochrane Controlled Trials Register. Keywords were "Hypertension". "Kidney", and "Cancer". Studies published between 2013 and 2020 were included in this review. Inclusion criteria were full-text observational prospective studies andalso the positive cancer patient with hypertension or blood pressure noted in examination (SBP or DBP). Thedata were analysed to measurethe incidence of kidney malignancy as ofRiskRatio (RR), while the confidence intervals (CIs) was 95%. Articles which are retrospective studies and/or not written in English were excluded. From 1,970 studies, a total of 5 studies including 378,488 patients were eligible for this study. The review method was followingPRISMA Review and Metaanalysis. The inputwere then assessed and statistically examined by using RevMan (5.3.0) statistical instrument.
Results: From 5 eligiblearticles included, the statistic suggested a significant association (P<0,05) between hypertension andkidney cancerwith1,79pooledriskratio (95% Confidence Interval, 1,63 – 1,95; P=0,00001) and low heterogeneity (I^2=38%; P=0,17).
Conclusion: Our analysis indicates that hypertension is associated with kidney cancer occurrence.
Keywords: Cancer, Hypertension, Kidney

INTRODUCTION

Carcinoma of renal arises from parenchymal structure. Clear cell RCCs become the commonest form of kidney cases in 70% of adult population[1]. Kidney cancer becomes the 13thmost common type of urinary tract cancer worldwide, approximately accountsfor up to 4% of all-cause cancer.More than 330,000 new cases of urinary tract cancer are diagnosed every year[2].. The incidence is reportedly higher in, Japan, New Zealand, European, and North America[2-3]. The observation of rising kidney cancer incidence is also greatly affected by improved detection with ultrasound and Magnetic Resonance Imaging (MRI) [4].

Hypertension becomes a global health burden which affects 3 in 10 adults over 20 years old, leading to high morbidity and mortality. Hypertension almost asympto-matically detected when the patient is on a regular check-up. Hypertension for this study is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure readings of ≥ 90 mmHg in two different days from office visit. The incidence of obesity and hypertension related kidneycarcinoma is increasing rapidly among Asian. Hypertension itself has been found as an independent risk factor in numerous prospective studies[6-10], yet the true relationship between them are still unknown.

The current reviews suggest thatthe affiliation between high blood pressure and kidney cancer has no longer been mounted comprehensively in terms of quantitative meta-analysis. Thus, we performed meta-analytic evaluation in order to comprehensively evaluate the affiliation among hypertensive patients and the risk itself.

MATERIALS AND METHODS

Quest of Articles: Database of PubMed and the Cochrane Controlled Trials Register were searched to acquire the relevant studies. Keywords were "Hypertension", "Kidney" and "Cancer". Studies published between 2013 and 2020 were included in this review.
Inclusion and Exclusion criteria: Studies above were further assessed on the basis of Population, Intervention, Comparator, Outcome, and Study Design specified by the PRISMA guideline[11]. Inclusion criteria were full-text observational prospective studies, whileinvestigated medical profile of hypertension or measured systolic and/or diastolic blood pressure levels acted as the parameter.The expected result was an incidence of kidney malignancyas for the risk ratioand confidence intervals (CIs) of 95%. Articles that were retrospective studies and/or not written in

English were excluded.The diagram of PRISMA flow for the addition and removal of the studyis showed on Fig 1.

Data Extraction: The following items were recorded for all the studies that fulfill the criteria: Authors name, time of publication, study design, age (mean/age), nationality, follow-up duration, the total number of patients, occurrencesof hypertension which diagnosed within criteria, the other variational related risk evaluated with CIs equivalent of 95%, along with theadjustment of any confounding factor. In the event ofdifferent Risk Ratios of the correlation wasexist,themaximumextentofadjustment would be chosen for potential confounding factorTable 1 [6-10].

Study Quality: Newcastle-Ottawa Quality Assessment Scale (NOS) [12] is deemed fundamental to establish the outcome of the study. NOS is consisted of three domains: Selection, Comparability and Exposure. Selection domain has a highest score of 4, Comparabilityhas 2, while Exposurehas 3. The score here is denoted by stars. The total score of≥ 6 are considered to be high quality study (Table 2).

Publication Bias: Egger's Test was used because the number ofstudies was less than 20. No significant publication bias was detected for overall outcomes, (P = 0.393) . Egger's regression test (P > 0.5) showed no publication bias evidence.(Fig S1)

Statistical Analysis: The data that have been obtained from the screening results was based on study criteria, processed using software application (Review Manager version 5.3).Forest plots were used as output of research results to describe the pooled risk ratio (RR). Authors would use random effect models (REM) if heterogeneity was obtained in the study, whereas a fixed-effect model (FEM) was used if homogeneity was obtained in the study. Heterogeneity is statistically defined by I^2. The assessment ofpublication bias required funnel plot analysis and Egger's regression test.

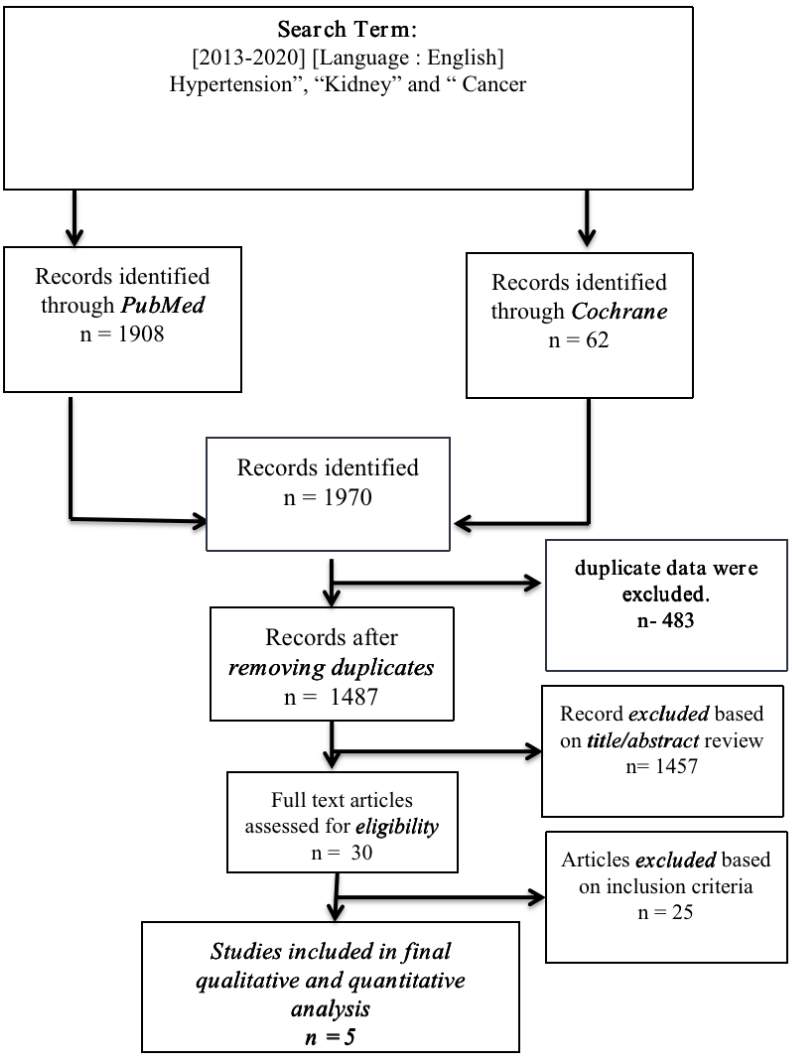

Fig 1. The diagram of literature selectionand eligible criteria

Table 1. Baseline characteristics of included study

Author	Study design	Age : mean/range (years)	country	Duration of follow up	Sample size (cases)	Exposure variables	Adjusted RR (95%CI)
Hofmann et al, 2015. (6)	cohort prospective	18–99	USA	10	31.167(3136)	Hypertension (yes vs no)	1.90 (1.70 , 2.00)
Shen et al, 2015. (7)	cohort prospective	40-70	China	12	2.693 (271)	Hypertension (yes vs no)	1.40 (1.10 , 1.90)
Sanfilipo et al, 2014. (8)	cohort prospective	50–79	USA	5	156.774 (407)	SBP > 140 vs <140	1.93 (1.42 , 2.63)
Washio et al, 2014. (9)	cohort prospective	40-79	Japan	2	110,585	Hypertension (yes vs no)	1.40 (0.85 , 2.30)
Macleod et al, 2013. (10)	cohort prospective	50-76	USA	8	77.269(249)	Hypertension (yes vs no)	1.70 (1.30 , 2.22)

SBP Systoilic blood pressure, *RR* risk ratio

Table 2. Newcastle-Ottawa Scale

	Selection				Comparation	Exposure			Total stars
Study	Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Shen, 2015	1	1	1	1	2	0	1	1	8
Hofmann, 2015	1	1	1	1	1	0	1	1	7
Washio, 2014	1	1	1	1	1	1	1	0	7
Macleod, 2013	1	1	1	1	2	1	1	0	8
Sanfillipo, 2014	1	1	1	1	2	1	1	0	8

RESULT

Characteristics of eligible studies: We found 1970 total articles from PubMed and the Cochrane Controlled trials Register. 483 duplicate data were excluded. Titles and abstracts of these studies were evaluated. The remaining 30 articles were screened and 1,457 were excludedafter title and abstract evaluation. Full texts were read carefully and 25 morewere studies excluded due to inclusion criteria. Anamount of 5articles were ultimately selected for the meta-analysis. These studies consisted a total of 378.488 patients [6-10].

Three studies were conducted in the USA, one in Japan, and another in China. All the eligible studies were published between 2013-2020. The cohort prospective studied had a sample size ranged from 2.693-156.774 patients. The range of follow-up was 2 to 10 years. The details of quality assessment are presented in Table 2. All of these studies were given scores of at least 7.

Hypertension and Carcinoma Kidney risk Assessment: From five studies [6-10], hypertension is associated with kidney cancer. Data pooling showed RR 1.79 (95% CI 1.63–1.95; P<0.05) for a fixed effect model, with low heterogeneity (I2=38%, P=0.17). Every patient with hypertension was 1.79 more prone to have kidney cancer in the future (Fig 2).

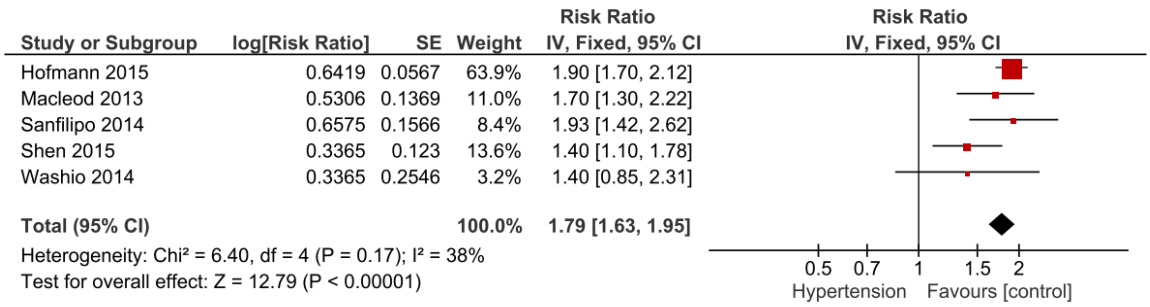

Fig. 2: Forest plotsshowa relative risk ofhypertensionagainst kidney cancer

DISCUSSION

The prevalence of hypertension is expanding rapidly in worldwide population. The mechanism of hypertension and kidney cancerconnection were not fully understood nor part of explicit antihypertensive medication treatment in reducing the possibilityof kidney malignancy[8]. Not many investigations have already demonstrated a correlation connecting raised BP with the developedpossibilityof renal disease and raised kidney malignant growth risk[14]. Sufficient BP maintenance commonly identified as a decreased susceptibility of kidney disease[15,16].However, the fundamental clarityrelatingto hypertensive patients or moreover the use of antihypertensive drugs again strenal malignant growth continue to be generally obscure.

Moreover, hypertensive people may undergolong-standing depleted renal oxygenationsince the production of hypoxia-prompting constituents could advance neoplasm expansion, angiogenesis, and up-regulation of similar factors as part of an oncogenesis process [19]. Hypertension has likewise been related toformed radicals such as oxidative deterioration of lipids, thus estimated asa contributing statefor renal malignancy patho-mechanism. The unpredictableclear-cell kidney malignancy generally includes transformations of von Hippel-Lindau (VHL) gene; withmore than 90% ofclear-cellRCC consisting of an altered tumor suppressor gene.This gene is a significant controller of hypoxia-prompting constituents, recruitment of fibronectin, and complete sequence of cellmodulation[8]. The organic components hiding the correlation connecting hypertension with kidney malignancy remains not fully understood,nonetheless, it is estimated to involve long-standing depleted renal oxygenation along with oxidative deterioration of lipids and the forming of ROS[17,18]. Correspondingly, many non-experimental researches continually stated that people with hypertensionare more vulnerable to kidney problems[20]. We conduct this meta-examination to thoroughly survey a relationship among hypertension and kidney disease susceptibility.

Hoffman *et al*., mention hypertension was related to expanded kidney malignancy hazard; these affiliations largely did not varied by race/identity, as they watched a solid relationship between the long haul of hypertension (≥5 years) and kidney malignancy hazard with 1.90 adjusted risk ratio[6]. Shen *et al*., showed a high ambulatory blood pressure report was related with a significantor about 40% higher chance of kidney disease among women and men with 1.40 adjusted risk ratio[7].

Sanfilipo *et al*., found that hypertension alone wasrelated to the growth of most renal cancers, furthermore high blood pressure indicates a potent relationship with renal malignancy in lengthy observation among the USA population. It is exceptional that interior blood strain layers, shows that there is an increasing prevalence of kidney malignancy among hypertensive who receive pharmacological treatment versus untreated population. These discoveries possibly recommend that antihypertensive drugs may add to kidney malignancy hazard[8].

Washio *et al.*,mentiona history of hypertension that demonstrated high levels of harm. Theseharms would in general increment with SBP. In contrast of SBP that isless than 129 mmHg, escalated levels ofharm was recognized for SBP of 130 mmHg or more. Then again, little to none study has the explanation of any important relationship regarding the risk of malignant renal disease withhighDBP. The escalated harm was distinguished solely at above 80 mmHg,in comparison to less than80 mmHg. As a result, it is proposed that SBP might be more significant as a determinant of renal cancer related mortality than DBP[9].

Macleod *et al.*, said the most reliably observed relationship in the writing of constant morbidity is related to hypertension. We comparatively found positive affiliation. In our investigation a measurably expanded risk of kidney malignancy was recognized with hypertension alongside 1.70 adjusted risk ratio[10].

All studies agreed to suggest that hypertension is positively associated with kidney cancer[6-10]. Under this analysis, we take a pooled RR for 5 studies comparing hypertension and kidney cancer risks. The RR was 1.79 which means patients with hypertension are 1.79 more prone to have kidney cancer in the future. In this manner, we should highlight the need and significance of genuine general wellbeing methodologies pointed toward strategies and adequately controlling hypertension to diminish the rate of various ailments identified with raised circulatory strain including kidney malignancy.

We found low heterogeneity and no significant bias has been observed in this study. Low heterogeneity has been found means the data was consistent or stable and homogenous. Non significant publication bias was observed with egger test in this meta-analysis.

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Fig. S2. Egger test

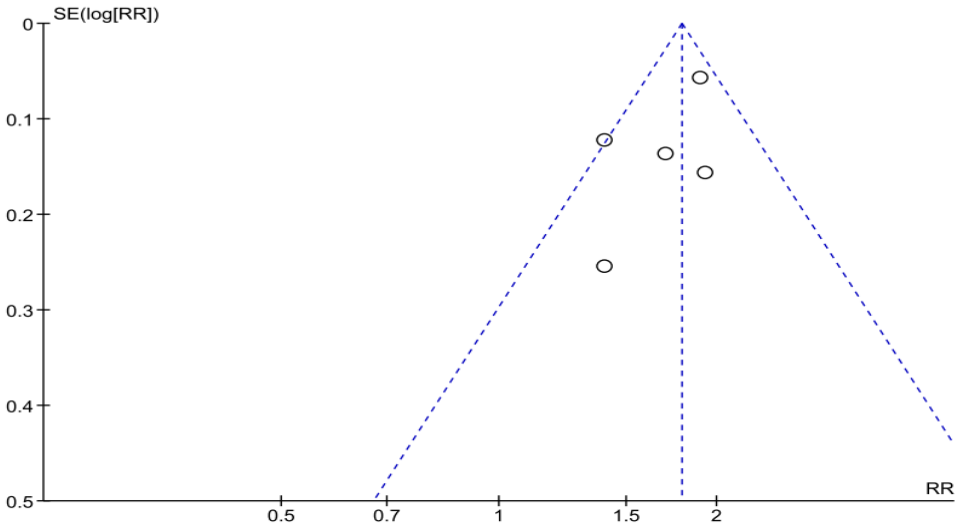

Fig. S2. Funnel Plot CSS

CONCLUSION

This studyindicates that hypertension is a positive determinant of kidney cancer.

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Conflict of interest There is no conflict of interest in our study

Informed consent No informed consent needed.

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