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Drugs affecting renin-angiotensin-aldosterone system and the cancer risk: A meta-analysis of nested case-control studies

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Abstract: Multiple studies have discussed the associations between drugs affecting the renin-angiotensin-aldosterone system and the cancer risk, but their consequence s were conflicting. A meta-analysis of nested case-control studies published regarding this subject was conducted in our study, aims to estimate the association between ACEI/ARB and the cancer risk. Pubmed database was searched up to February, 1 2016 to identify eligible nested case-control studies, and we used Newcastle-Ottawa Scale (NOS) to assess quality of the studies. Pooled odds ratio (OR) and 95% confidence intervals (CIs) were calculated (with fixed effect model: Mantel-Haenszel). Publication bias and heterogeneity were evaluated before the calculation. Subgroup analysis and sensitivity analysis were also performed. Seven studies contributed to the analysis. Overall, ACEI/ARB use was not associated with the risk of cancer (OR=0.99, 95% CI 0.97-1.01), nor in long-term use patients (OR=0.97, 95% CI 0.92-1.01). ACEI may decrease cancer risk (OR=0.90, 95% CI 0.82-0.99). We observed no significant publication bias. In conclusion, ACEI/ARB use was not associated with cancer risk, nor in long-term use patients, but ACEI use may decrease cancer risk. More researches are needed to confirm these findings.

Keywords: ACEI, ARB, cancer, meta analysis, nested, case-control studies.

INTRODUCTION

Cancer is the most important cause of death in the world. The global burden of cancer continues increasing. The worldwide burden of cancer could be prevented (Jemal *et al*., 2011).

High blood pressure (BP) is a prevalent disorder, and its complications are a major public health problem. The RAS has a key role to impact blood pressure.

Inappropriate activation of the RAS leads to profound hypertension and cardiovascular morbidity. Angiotensin (AT) II causes hypertension primarily through AT I receptors (Crowley *et al*., 2006). The classical RAS consists of a circulating endocrine system, which included AT II, AT I and AT-converting enzyme etc (Carey *et al*., 2003). The antagonists of RAS, include ACEI and ARB, have gained more and more popularity in the last two decades. However, recent analyses raised the possibility that angiotensin receptor antagonists may increase the risk of cancer (Lonati *et al*., 2015).

In the present study, a meta-analysis of nested case-control studies was conducted to comprehensively evaluate the association between drugs affecting the RAS and cancer risk.

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MATERIALS AND METHODS

Search strategy

We searched PubMed database up to February, 1 2016 for identify potentially relevant publications, reference lists of these relevant publications and review articles were screened. If necessary, correspondent authors were contacted to obtain the original experimental data. All potentially relevant articles (include the titles, abstracts, and/or full texts) were read by two investigators (ZJ and LDM) independently to determine whether they were in accordance with the inclusion and exclusion criteria's, and the divergence resolved through discussion or by another investigator(ZW). Search terms were used as follows: ("angiotensin-converting enzyme inhibitor" OR "ACEI" OR "Angiotensin receptor blockers" OR "ARB") AND ("neoplasms" OR "tumor"). The following information were extracted from all the selected articles: name of first author, publication year, country of the population study period, odds ratio (OR) and the 95% confidence intervals (CIs).

Inclusion and exclusion criteria, and quality assessment

Inclusion and exclusion criteria were as follows: inclusion criteria were 1.nested case-control studies) 2. Evaluated exposure to ACEI/ARB use and risk of cancer. 3. Original article offered ORs. 4. Published in English. Exclusion criteria were 1. Reviews, editorials, letters to the editor without original data, case reports. 2. Not humans. 3. duplicated data (Flow diagram showing in fig. 1). All

nested case-control studies were assessed based on NOS for quality assessment. In this scale, studies were scored across following categories: population selection; comparability of study groups; ascertainment of the outcome/exposure of interest, high-quality study defined as score≥7 (table1) (Wells *et al*., 2011).

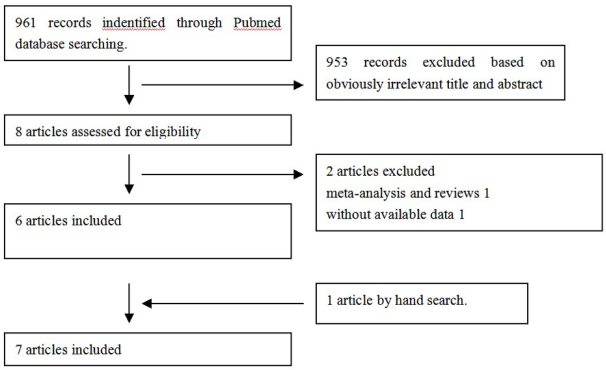

Fig. 1: Flow diagram showing the process of screening references.

STATISTICAL ANALYSIS

The pooled OR of ACEI/ARB therapy group versus control group were calculated, all statistical analysis were conducted using STATA version 12.0 (Stata Corporation, College Station, TX, USA). Dichotomous data results were summarized using OR and 95% CIs as the effect size. Heterogeneity was assessed by the Cochrane Chi-square Q test and I^2 test, I^2> 50% and P<0.1 was considered statistically significant, a fixed effect model (with Mantel-Haenszel) was used to pool the data when no significant heterogeneity was found. Otherwise, the random effect model (with Der Simonian-Laird) was used. The significance of the pooled OR was determined with Z-test, P<0.05 was considered to be statistically significant. This meta-analysis was performed in accordance with the PRISMA guidelines (Moher *et al*., 2009).

RESULTS

Meta-analysis result

Seven nested case-control studies contributed to the meta-analysis. All studies reported OR. The OR of cancer risk for ACEI/ARB use was 0.99(95% CI 0.97-1.01) for all studies combined (fig. 2). No significant heterogeneity (I^2=0%) was observed (table 2).

Long term ACEI/ARB use and the cancer risk

Four studies reported OR estimates of the association in long term ACEI/ARB use and the cancer risk, the overall OR was 0.97(95% CI 0.92-1.01). No significant heterogeneity (I^2=0%) was observed (table 3).

Sensitivity analysis and publication bias

Sensitivity analysis were conducted to evaluate the stability of the combined results, Single study was excluded at once and the main summary estimate OR and Cochran's Q-test for heterogeneity was evaluated. No significant variation in combined OR were observed by excluding any of the study. Visual inspection of funnel plots and Begg's test were applied to screen for the potential publication bias, and funnel plot of meta analysis was symmetric, Begg's test: P>0.133 (fig. 3).

DISCUSSION

The global burden of cancer continues increasing，the mechanism of carcinogenesis is complex. The antagonists of RAS have gained more and more popularity in the last years, and the drug carcinogenesis was wildly followed. Understanding of the role of ACEI/ARB in the development of cancer has been increased in the past few decades. Accumulated *in vitro* and *in vivo* clinical evidence point out that ACEI/ARB was a variety of human malignancies, and the results were controversial.

As *in vivo*, Okazaki *et al* reported that candesartan can significantly reduced epithelial-to-mesenchymal transition-like change and TGF-β1 expression in human peritoneal mesothelial cells and gastric cancer cell line (MKN45) cells. According to this, AT II signaling pathway may be a target for treatment of fibrosis and tumor proliferation (Okazaki *et al*., 2014). Also, de Araújo *et al* reported that telmisartan can induce apoptosis in human renal cancer cells (de Araujo Junior *et al*., 2015). Treatment of AGTR2 agonist, CGP42112A and/or AT II type 1 receptor (AGTR1) antagonist, losartan mediated anti-cancer effects ,as down-regulation of vascular endothelial growth factor (VEGF) and decrease of cell survival (Park *et al*., 2014).

Table 1: Quality assessment of included studies by Newcastle–Ottawa scale

Study	Selection	Comparability	Exposure	Total score
Makar *et al*. (2014)	★★★★	★	★★	7
Azoulay *et al*. (2012)	★★★★	★	★	6
(Sjoberg *et al*. (2007)	★★★★	★	★	6
Houben *et al*. (2006)	★★★★	★	★★	7
Assimes *et al*. (2008)	★★★★	★	★★	7
Perez *et al*. (2004)	★★★	★	★★	6
Jick *et al*. (1997)	★★★★	★	★★	7

Table 2: Characteristics of included studies in the meta-analysis

Study	Year	Location	OR	95% CI	Drug	Cancer site	Adjustment
Makar	2014	USA	0.98	0.90,1.06	ACEI/ARB	Colon	Average number of doctor visits during follow-up
Azoulay	2012	Canada	0.99	0.98,1.01	ACEI/ARB	Lung, colon, breast, and prostate	Excessive alcohol use, body mass index, smoking, diabetes, previous cancer, and ever of aspirin, statins, and NSAIDs.
Sjoberg	2007	UK	0.90	0.77,1.05	ACEI	Esophagus, stomach	Age, sex, BMI, calendar year, tobacco smoking, alcohol consumption, upper gastrointestinal disorder, concurrent drug use
Houben	2006	Netherland	1.03	0.84,1.25	ACEI/ARB	Head	Age, sex, duration of follow-up, use of other types of antihypertensive drugs, lag time of 3 yr
Assimes	2008	Canada	1.01	0.91,1.02	ACEI/ARB	Breast, colon, lung, prostate, kidney, hepatologic, head and neck	Age, all measured comorbid conditions, exposure to all other classes of antihypertensive medication
Perez	2004	UK	0.93	0.81,1.07	ACEI	Breast	Age, calendar year, BMI, alcohol intake, smoking status, HRT use, prior breast lump or biopsy, hypertension, use of other antihypertensive medication

Table 3: Studies evaluating the association between long-term ACEI/ARB use and cancer risk

Study(year)	OR	95% CI	Study period (years)
Makar *et al*. (2014)	0.94	0.81-1.09	3
Azoulay *et al*. (2012)	0.97	0.93-1.02	3.48
Sjoberg *et al*. (2007)	0.96	0.71-1.29	3
Perez *et al*. (2004)	0.93	0.74-1.18	3
Overall (I2=0.0%,P=0.961)	0.97	0.92-1.01	

OR, Odds ratio; CI, Confidence interval

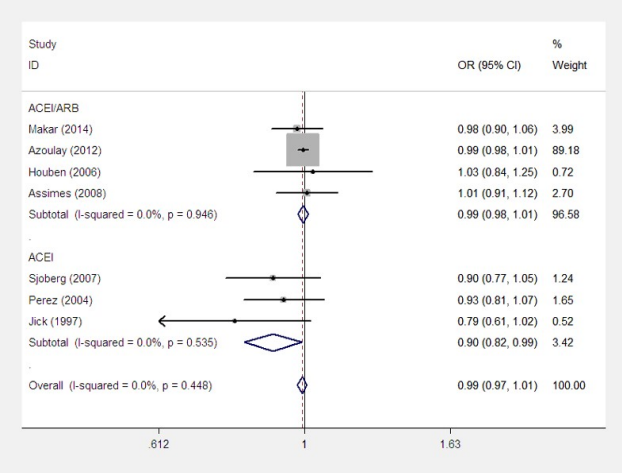

Fig. 2: Subgroup meta-analysis of ACEI/ARB use and the risk of cancer (Abbreviations as in table 3).

As *in vitro*, animal studies suggest the key to carcinogenesis is modulation of angiogenesis via the RAS and AT II receptors (Escobar *et al*., 2004; Walther *et al*., 2003). AT II-inoculated animals to develop renal tumors. Animals treated with ACEI/ARB presented smaller tumors. The expression of CD34 and VEGF were significantly decreased. RAS blockade decreases tumor metastatic capacity and proliferation of renal cell carcinoma (Ararjo *et al*., 2015). The effects of Enalapril were assessed in a transgenic mouse model of pancreatic neuroendocrine neoplasms (pNENs). Proliferation of neuroendocrine cell line BON1 was significantly inhibited by enalapril, Target genes Vegf and Rela were significant down regulation at RNA level. Enalapril significantly inhibited Tumor growth (Fendrich *et al*., 2014). Candesartan significantly inhibited growth of PC3 cell tumor in mice (Alhusban *et al*., 2014). Combined treatment with losartan and gemcitabine can significantly improve the survival of rats with orthotopic pancreatic cancer (Kim *et al*., 2014).

In human studies, results by Devore *et al* indicated that current use of ACEI was not associated with breast cancer risk compared with past/never use (Devore *et al*., 2015), and Schmidt *et al* reported that Long-term ARB use was associated with risk of malignant melanoma (MM) (Schmidt *et al*., 2015). In recent decades, data from randomized controlled trials (RCTs) supported evidence that ARB may decrease cancer risk (Pfeffer *et al*., 2003; Dahlof *et al*., 2002; Investigators *et al*., 2008; Teo *et al*., 2008). Meta-analysis of observational studies by Yoon *et*

al. showed no significant association between the use of ACEI or ARB and overall risk of cancer (Yoon *et al*., 2011).

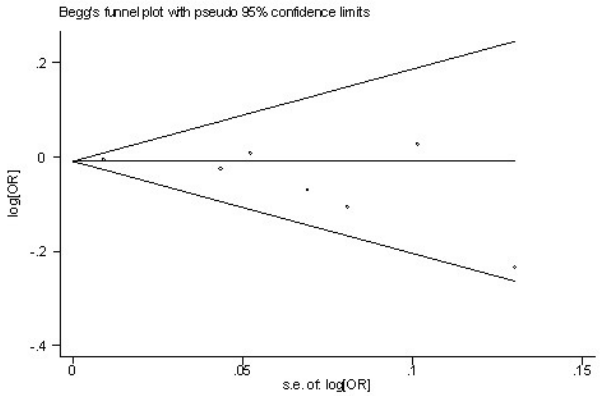

Fig. 3: Funnel plot (publication bias assessment plot) of the odds ratio, by the standard error, for all studies. Circles- studies included in the meta-analysis. Begg's test: P>0.133

Overall, in the present meta-analysis, there was no evidence of association between cancer risks and ACEI/ARB use, even in long-term use patients. But subgroup meta-analysis indicated that ACEI use may decrease cancer risk. Further studies are needed to confirm these findings.

In the present meta-analysis, there are following limitations to be concerned. First, neither unpublished studies nor original data were obtained. Moreover, literature search was restricted to the English articles, which may cause bias. However, the funnel plots were symmetric. Finally, literature search was restricted to nested case-control studies, which designed for the least bias, yet no significant heterogeneity was observed in the meta-analysis.

CONCLUSION

In conclusion, ACEI/ARB use was not associated with cancer risk, but ACEI use may decrease cancer risk. More researches are needed to confirm these findings.

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