Systematic Review and Meta-Analysis

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Do renin–angiotensin system inhibitors influence the recurrence, metastasis, and survival in cancer patients?

Evidence from a meta-analysis including 55 studies

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Abstract

Background: Renin–angiotensin system inhibitors (RAS inhibitors) are antihypertensive agents with potential antitumor effects. However, various studies have yielded conflicting results on the influence of RAS inhibitors on survival of cancer patients. The aim of this study was to evaluate the effect of RAS inhibitors on recurrence, metastasis, and survival in cancer patients through a meta-analysis.

Methods: PubMed, Web of Science, EMBASE, and Cochrane Library were systematically searched from inception to December 2016. The pooled hazard ratio (HR) with its 95% confidence interval (95% CI) was calculated to evaluate the association between RAS inhibitors and recurrence, metastasis, and survival in cancer patients.

Results: Fifty-five eligible studies were included in the present meta-analysis. Results showed that there were significant improvements in overall survival (OS) (HR = 0.82; 95% CI: 0.77–0.88; $P < 0.001$), progression-free survival (HR = 0.74; 95% CI: 0.66–0.84; $P < 0.001$), and disease-free survival (HR = 0.80; 95% CI: 0.67–0.95; $P = 0.01$) in RAS inhibitor users compared with nonusers. Subgroup analyses revealed that the effect of RAS inhibitors on OS depended on the cancer type or different RAS inhibitors.

Conclusion: This meta-analysis suggests that RAS inhibitors could improve the survival of cancer patients and depend on cancer type and types of RAS inhibitors.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CI = confidence interval, DFS = disease-free survival, DSS = disease-specific survival, HR = hazard ratio, MFS = metastasis-free survival, OS = overall survival, PFS = progression-free survival, RAS = renin–angiotensin system.

Keywords: cancer, meta-analysis, metastasis, recurrence, renin–angiotensin system inhibitors, survival

1. Introduction

Comorbidities are common in cancer patients, and the phenomenon increases in aging populations.[1] Hypertension is one of the most common comorbidities in cancer patients. Therefore, the use of antihypertensive agents in these patients may influence survival outcomes. Renin–angiotensin system (RAS) inhibitors are a diverse group of antihypertensive agents that mainly include angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs).[2] Recently, several studies suggested that treatment with ACEIs and ARBs is not only effective in cardiovascular diseases, but can also improve cancer progression and survival through mechanisms other than antihypertensive activities.[3–7]

The RAS plays a critical role in the maintenance of blood pressure, balance of water and electrolytes, cell growth, and the stability of the cardiovascular microenvironment.[8–11] Overexpressions of angiotensin-converting enzyme (ACE) and angiotensin II type 1 receptor (AT1R), key factors in RAS pathways, have been associated with tumor growth, metastasis, and progression.[12–15] As a growth factor and main effector factor in RAS, angiotensin II can stimulate tumor neovascularization, which is important for tumor growth.[16,17] The antitumor mechanisms of RAS inhibitors seem to be biologically reasonable. ACEIs function to reduce the production of angiotensin II to suppress the RAS, and ARBs can selectively

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block the action of angiotensin II type I receptors[18] to inhibit tumor growth, metastasis, and tumor-associated angiogenesis.[19,20]

Several studies have examined the association between RAS inhibitors and cancer survival. However, the results have remained conflicting even in the same type of cancer. Menter et al[56] and Wilop et al[74] reported that the use of RAS inhibitors was associated with improved survival in patients with nonsmall cell lung cancer. However, Aydiner et al[25] indicated that there was no association between RAS inhibitors and survival in patients with nonsmall cell lung cancer. To help clarify the inconsistent findings, we conducted a meta-analysis of published studies on the association between RAS inhibitors and recurrence, metastasis, and survival in cancer patients.

2. Methods

2.1. Publication search

We performed literature searches in several electronic databases, including PubMed, Web of Science, EMBASE, Cochrane Library, to identify articles on the association between RAS inhibitors and recurrence, metastasis, and survival in cancer patients. We used the following search terms: "Renin–Angiotensin System Inhibitor," or "Angiotensin-Converting Enzyme Inhibitor," or "Angiotensin Receptor Antagonist," or "ARB," or "ACEI," or "RASI," or "ASI," or names of specific RAS inhibitors combined with "neoplasm," or "cancer," or "tumor," or "tumour," or other subtypes/synonyms for cancer and "prognosis," or "prognostic," or "predict," or "predictive," or "prediction," or "morbidity," or "mortality," or "death," or "recurrence," or "recurrent," or "metastasis," or "metastatic," or "survival," or "survive," or "survival analysis." The search terms and strategies are described in detail in Supplementary Table 1, http://links.lww.com/MD/B611. The overall search was limited to human studies and English language publications. Two authors (SH and LT) manually screened the citation lists of retrieved articles independently. All selected studies were checked according to a Newcastle–Ottawa Quality Assessment Scale developed previously.[21] A high-quality study was judged with a score achieved a rating of ≥7 stars.

2.2. Data extraction

Using predefined data summary lists, the information was reviewed and extracted by 2 authors (SH and LT) independently. The detailed information for each study was included as follows: first author, publication year, period of study, country of study, ethnicity, number of patients and cancer types, drug exposure and duration, outcomes, and hazard ratio (HR) estimates method. The survival outcomes, including overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), disease-specific survival (DSS), and metastasis-free survival (MFS), were collected. In addition, the report describing the largest sample size was chosen to be further analyzed when several publications were overlapped. We resolved any discrepancies through discussion.

2.3. Statistical analysis

As a systematic review and meta-analysis, ethical approval of this study is not needed. All statistical analyses were performed using Review Manager 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark). The association between RAS inhibitors and survival in cancer patients was estimated by calculating pooled HRs and related 95% confidence interval (CI). The results are presented in forest plots. The HRs and 95% CIs were extracted according to previously published methods[22,23] if the articles did not include these data. Study heterogeneity was assessed and presented as χ^2 and I^2. The fixed effect model was used to estimate pooled HRs if no study heterogeneity existed; otherwise, the random effects model was used. We used funnel plot to assess potential publication bias. An HR < 1 indicated a better outcome for using RAS inhibitors, while HR > 1 indicated a worse outcome for using RAS inhibitors. We considered a P value less than 0.05 to indicate statistical significance. Subgroup analyses were performed for cancer types, ethnicity, and drug types of RAS inhibitors. To assess the quality and consistency of results, sensitivity analysis was performed by deleting each study in turn. Sensitivity analysis was also performed by the extract methods of HRs and study quality (Newcastle-Ottawa Scale (NOS) score).

3. Results

3.1. Study identification

A total of 13,055 studies were collected in the selected databases after removing duplicates (Fig. 1). Seventy-five potential studies were included for full-text view after reviewing the titles and abstracts. With further screening, a total of 55 studies[24–78] met the inclusion criteria. The main characteristics of the eligible studies are summarized in Table 1. Forty-four studies examined OS, 14 studies examined PFS, 17 studies examined DFS, 9 studies examined DSS, and 4 studies examined MFS. These studies mainly included renal cell carcinoma, lung cancer, colorectal carcinoma, breast cancer, and pancreatic cancer cases. Among the studies that examined OS, 11 studies focused on an Asian population, 33 studies on a Caucasian population, 11 studies examined ARBs, and 12 studies examined ACEIs.

3.2. Qualitative assessment

The quality of eligible studies is shown in Supplementary Table 2, http://links.lww.com/MD/B611. The NOS scores ranged from 6 to 8 stars, with an average NOS score of 6.98. Furthermore, 74.5% of the studies were of high quality with a score that achieved a rating of ≥7 stars.

3.3. Meta-analysis results

Fifty-five studies that reported survival outcomes were included in the meta-analysis. The results suggested that RAS inhibitors could significantly improve OS (HR = 0.82; 95% CI: 0.77–0.88; $P < 0.001$; Fig. 2), PFS (HR = 0.74; 95% CI: 0.66–0.84; $P < 0.001$; Fig. 3), and DFS (HR = 0.80; 95% CI: 0.67–0.95; $P = 0.01$; Fig. 4) in cancer patients. Better outcomes in DSS (HR = 0.82; 95% CI: 0.63–1.07; $P = 0.15$; Fig. 5) and MFS (HR = 0.63; 95% CI: 0.40–1.01; $P = 0.05$; Fig. 6) were observed among RAS inhibitor users compared with nonusers.

We also performed subgroup analyses of the association between RAS inhibitors with OS by cancer types, ethnicity, and drug types of RAS inhibitors (Figs. 7–9). Our results revealed a significantly better outcome in OS among RAS inhibitor users with renal cell carcinoma (HR = 0.64; 95% CI: 0.49–0.85; $P = 0.002$), gastric cancer (HR = 0.57; 95% CI: 0.38–0.84; $P = 0.005$), pancreatic cancer (HR = 0.91; 95% CI: 0.87–0.95; $P < 0.001$), hepatocellular carcinoma (HR = 0.59; 95% CI: 0.41–0.86; $P = 0.007$), upper-tract urothelial carcinoma (HR =

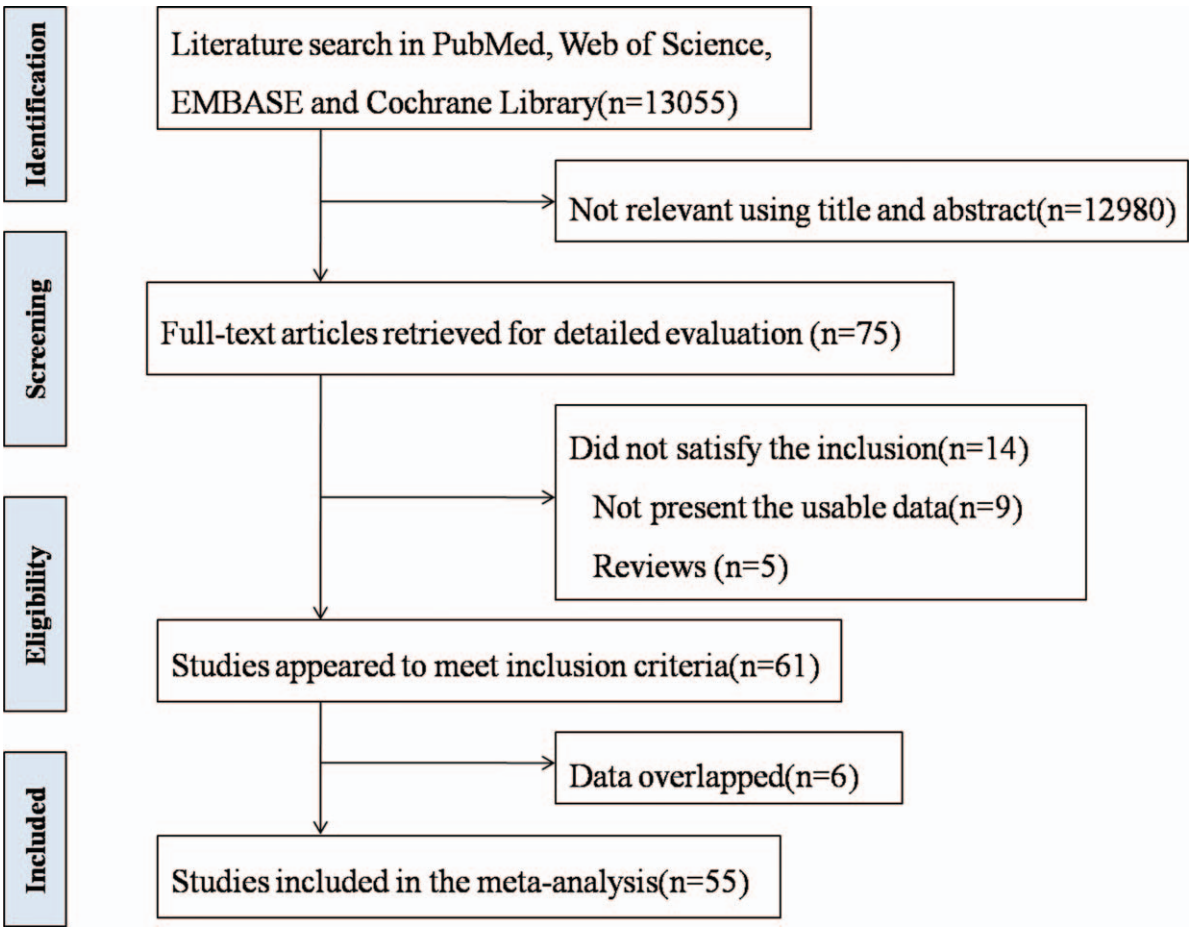

Figure 1. Flow diagram of study searching and selection.

0.53; 95% CI: 0.29–0.97; $P=0.04$), and bladder cancer (HR = 0.36; 95% CI: 0.18–0.72; $P=0.004$). We also observed better outcome in OS among RAS inhibitor users with rectal/colorectal cancer (HR = 0.86; 95% CI: 0.68–1.08; $P=0.19$), lung cancer (HR = 0.89; 95% CI: 0.76–1.05; $P=0.17$), prostate cancer (HR = 0.85; 95% CI: 0.55–1.31; $P=0.45$), glioblastoma (HR = 0.83; 95% CI: 0.47–1.47; $P=0.52$), head and neck squamous cell carcinoma (HR = 0.38; 95% CI: 0.12–1.20; $P=0.10$), oropharynx cancer (HR = 0.63; 95% CI: 0.38–1.04; $P=0.07$), and melanoma (HR = 0.41; 95% CI: 0.10–1.68; $P=0.22$). RAS inhibitors did not seem to influence OS in patients with esophageal carcinoma (HR = 0.98; 95% CI: 0.80–1.19; $P=0.80$), breast cancer (HR = 1.07; 95% CI: 0.91–1.27; $P=0.39$), and biliary tract cancer (HR = 1.00; 95% CI: 0.73–1.37; $P=1.00$). However, there were negative effects on OS in acute myelocytic leukemia (HR = 1.23; 95% CI: 0.94–1.61; $P=0.13$) and multiple myeloma (HR = 2.01; 95% CI: 1.00–4.05; $P=0.05$) in RAS inhibitor users compared with nonusers (Fig. 7).

Regarding ethnicity, we observed that ethnicity did not influence the association between RAS inhibitors and survival in cancer patients. With RAS inhibitors use, there was a significant better outcome in OS in cancer patients whether in Asians (HR = 0.82; 95% CI: 0.74–0.91; $P<0.001$) or Caucasians (HR = 0.83; 95% CI: 0.76–0.91; $P<0.001$) (Fig. 8).

We also assessed the effect of drug types of RAS inhibitors on the association between RAS inhibitors and survival in cancer patients. There were 11 studies using ARBs and 12 studies about ACEIs. Results showed that there was a significant improvement in OS among ARB users (HR = 0.80; 95% CI: 0.67–0.95; $P=0.01$), while a little improvement in OS among ACEI users (HR = 0.94; 95% CI: 0.85–1.04; $P=0.27$) (Fig. 9).

3.4. Publication bias

We used Review Manager 5.3 software to analyze the publication bias. The funnel plot was asymmetrical, which suggested that publication bias existed in this meta-analysis (Fig. 10).

3.5. Sensitivity analysis

Sensitivity analysis is shown in Supplementary Table 3, http://links.lww.com/MD/B611. There was no significant alteration in the pooled HRs (HRs ranging from 0.81 to 0.84) when deleting 1 single study from the overall pooled analysis each time in turn. We also assessed the sensitivity analysis according to the differences of the extraction methods of HRs and study quality (NOS score). The results showed that reported HRs had no significant difference compared with recomputed HRs. There was no significant difference between studies with NOS scores ≥7 and those with NOS scores <7.

4. Discussion

This meta-analysis was conducted to clarify the effect of RAS inhibitors on survival of cancer patients. Overall, our results

Table 1

Main characteristics of the studies included in meta-analysis.

Reference	Ethnicity	Country	Study period	No. (cases/all)	Tumors	Exposure (ARB/ACEI user no. and duration)	Outcomes	HR estimates
Abouelezz et al[24]	Caucasians	USA	NA	94/187	Hepatocellular carcinoma	ARB/ACEI	OS	HR and 95% CI
Aydiner et al[25]	Caucasians	Turkey	2003–2011	37/117	Nonsmall cell lung cancer	21 pts ARB/16 pts ACEI. At any time after the diagnosis	OS	HR and 95% CI
Babacan et al[26]	Caucasians	Turkey	2005–2012	31/218	Breast cancer	ARB/ACEI. ≥6 mo after the initial diagnosis	OS, DFS	KM
Bardia et al[27]	Caucasians	USA	Since 1995	2212/6017	Prostate cancer	2212 pts ARB	OS, DSS	HR and 95% CI
Blute et al[28]	Caucasians	USA	NA	143/340	Bladder cancer	ARB/ACEI. The time of the first transurethral resection	DFS	HR and 95% CI
Boudreau et al[29]	Caucasians	USA	1990–2008	1515/4216	Breast cancer	1515 pts ACEI	DFS	HR and 95% CI
Buchler et al[30]	Caucasians	UK	1995–2002	25/168	Multiple myeloma	25 pts ACEI	OS, PFS	KM
Cardwell et al[31]	Caucasians	Northern Ireland	1998–2006	4130/20,246	Prostate, colorectal, breast cancer	ARB/ACEI. From cancer diagnosis until 6 mo before cancer-specific death	DSS	HR and 95% CI
Chae et al[32]	Caucasians	USA	1999–2005	168/703	Breast cancer	ARB/ACEI. ≥6 mo	DFS	HR and 95% CI
Chae et al[33]	Caucasians	USA	1995–2007	159/1449	Breast cancer	54 pts ARB/105 pts ACEI	OS, DFS, DSS	HR and 95% CI
Chae et al[34]	Caucasians	USA	1999–2013	143/1043	Acute myeloid leukemia	35 pts ARB/ 55 pts ACEI/ 88 pts ARB or ACEI/2 pts ARB and ACEI	OS	HR and 95% CI
Chen et al[35]	Asians	China	1996–2011	20/141	Esophageal squamous cell carcinoma	15 pts ARB/5 pts ACEI	OS	KM
Derosa et al[36]	Caucasians	France	2004–2014	102/213	Renal cell carcinoma	ARB/ACEI. Before, or during treatment (during first month)	OS, PFS	HR and 95% CI
Engineer et al[37]	Caucasians	USA	2000–2009	52/193	Colorectal cancer	ARB/ACEI. ≥6 mo per any year in the observation period	OS	HR and 95% CI
Facciorusso et al[38]	Caucasians	Italy	2004–2010	80/153	Hepatocellular carcinoma	31 pts ARB/49 pts ACEI	OS, DFS	HR and 95% CI
Failing et al[39]	Caucasians	USA	2011–2014	11/80	Melanoma	ARB/ACEI	OS, PFS	HR and 95% CI
Fujii et al[40]	Asians	Japan	2004–2006	76/1163	Breast cancer	ARB/ACEI. ≥6 mo after initial diagnosis	DFS	Event and *P*
Ganz et al[41]	Caucasians	USA	1997–2000	409/1779	Breast cancer	409 pts ACEI	OS, DFS, DSS	HR and 95% CI
He et al[42]	Caucasians	USA	1998–2012	350/1174	Esophageal carcinoma	ARB/ACEI	OS, DSS	HR and 95% CI
Holmes et al[43]	Caucasians	USA	1985–2005	478/4661	Breast cancer	478 pts ACEI. After diagnosis	OS	HR, 95% CI
Izzedine et al[44]	Caucasians	France	2004–2013	105/213	Renal cell carcinoma	ARB/ACEI. Before or during sunitinib	OS, PFS	HR and 95% CI
Januel et al[45]	Caucasians	France	2008–2013	26/81	Glioblastoma	19 pts ARB/7 pts ACEI	OS, PFS	KM
Karagiannis et al[46]	Caucasians	USA	2003–2011	NA/8281	Pancreatic cancer	ARB/ACEI	OS	HR and 95% CI
Keizman et al[47]	Caucasians	USA	2004–2010	44/127	Renal cell carcinoma	ARB/ACEI	OS, PFS	HR and *P*
Keizman et al[48]	Caucasians	USA, Israel	2004–2013	106/278	Renal cell carcinoma	ARB/ACEI	OS, PFS	HR and 95% CI
Kim et al[49]	Asians	South Korea	2002–2010	30/63	Gastric cancer	20 pts ARB/10 pts ACEI	OS, PFS	HR and 95% CI
Kumekawa et al[50]	Asians	Japan	2007–2011	18/220	Gastric cancer	ARB/ACEI	OS	HR and 95% CI
Lam et al[51]	Caucasians	USA	2005–2013	38/190	Renal cell carcinoma	ARB/ACEI. Before/after TKI	OS	HR and *P*
Linden et al[52]	Caucasians	USA	2010	10/51	Head and neck squamous cell carcinoma	ARB/ACEI. During the course of the treatment	OS	Event and *P*
Magnuson et al[53]	Caucasians	USA	1990–2010	57/352	Oropharynx cancer	ARB/ACEI. When RT	OS	OS value
McKay et al[54]	Caucasians	USA	2003–2013	1487/4736	Renal cell carcinoma	ARB/ACEI. At baseline or within 30 d of study treatment initiation	OS, DFS	HR and 95% CI
Melhem-Bertrandt et al[55]	Caucasians	USA	1995–2007	140/1413	Breast cancer	ARB/ACEI	OS, DFS	HR and 95% CI
Menter et al[56]	Caucasians	USA	2005–2011	351/1813	Nonsmall cell lung cancer	86 pts ARBs/265 pts ACEIs	OS	HR and 95% CI
Miao et al[57]	Asians	China	2000–2014	52/301	Nonsmall cell lung cancer	ARB/ACEI	OS, PFS	KM

(*continued*)

Table 1

(continued).

Reference	Ethnicity	Country	Study period	No. (cases/all)	Tumors	Exposure (ARB/ACEI user no. and duration)	Outcomes	HR estimates
Miyajima et al[58]	Asians	Japan	1996–2009	104/557	Renal cell carcinoma	ARB/ACEI	DSS, MFS	HR and 95% CI
Morris et al[59]	Caucasians	USA	1999–2012, 1995–2010	74/301	Rectal cancer	ARB/ACEI. At the time of the radiation consultation	OS,MFS,DFS	HR and 95% CI
Nakai et al[60]	Asians	Japan	2001–2013	108/349	Pancreatic cancer	89 pts ARB/13 pts ACEI/5 pts ACEI and ARB/1 pts RI	OS, PFS	HR and *P*
Nakai et al[61]	Asians	Japan	2002–2015	74/287	Biliary tract cancer	61 pts ARB/13 pts ACEI	OS	HR and 95% CI
Ole-Petter et al[62]	Caucasians	USA	NA	NA/1120	Renal cell, hepatocellular, GIST	ARB/ACEI	OS	HR and 95% CI
Osumi et al[63]	Asians	Japan	2007–2010	104/181	Colorectal cancer	104 pts ARB	OS, PFS	HR and 95% CI
Ranasinghe et al[64]	Caucasians	Australia	2003–2007	603/1956	Prostate cancer	603 pts ACEI	DSS	HR and 95% CI
Ronquist et al[65]	Caucasians	Sweden	2002–2005	32/62	Prostate cancer	32 pts ACEI. 4–7 d after surgery and continued throughout study	DFS	KM
Sendur et al[66]	Caucasians	Turkey	2004–2011	102/486	Breast cancer	102 pts ARB	OS, DFS	OS and DFS value
Sha et al[67]	Asians	China	2003–2010	11,207/19,592	Lung cancer	ARB/ACEI. Before diagnosis	OS, PFS	HR and 95% CI
Holmes et al[68]	Caucasians	Canada	2004–2008	4279/15,582	Cancer	ARB/ACEI. 1 y before diagnosis	OS	HR and 95% CI
Subgroup1[68]	Caucasians	Canada	2004–2008	880/4019	Breast cancer	ARB/ACEI. 1 y before diagnosis	OS	HR and 95% CI
Subgroup2[68]	Caucasians	Canada	2004–2008	1187/3967	Colorectal cancer	ARB/ACEI. 1 y before diagnosis	OS	HR and 95% CI
Subgroup3[68]	Caucasians	Canada	2004–2008	1256/4241	Lung cancer	ARB/ACEI. 1 y before diagnosis	OS	HR and 95% CI
Subgroup4[68]	Caucasians	Canada	2004–2008	956/3355	Prostate cancer	ARB/ACEI. 1 y before diagnosis	OS	HR and 95% CI
Sorensen et al[69]	Caucasians	Denmark	1996–2003	5064/18,733	Breast cancer	ARB/ACEI. 0 (no exposure history), 1–5, 6–10, and more than 10 cumulative years of exposure	DFS	HR and 95% CI
Sorich et al[70]	Caucasians	Australia	NA	385/1545	Renal cell carcinoma	247 pts ACEI/123 pts ARB/15 pts ACEI and ARB. When conducting clinical study (baseline)	OS,PFS	HR and 95% CI
Tanaka et al[71]	Asians	Japan	1995–2009	48/279	Upper-tract urothelial carcinoma	43 pts ARB/5 pts ACEI	OS, DSS, MFS	HR and 95% CI
Tuazon et al[72]	Caucasians	USA	2004–2008	105/222	Colorectal cancer	ARB/ACEI. ≥3 mo after initial diagnosis and treatment	OS, DFS	HR and 95% CI
Wang et al[73]	Caucasians	USA	1998–2010	142/673	Nonsmall cell lung cancer	138 pts ACEI or ARB/4 pts ACEI and ARB	OS, DFS, MFS	HR and 95% CI
Wilop et al[74]	Caucasians	Germany	1996–2007	52/292	Nonsmall cell lung cancer	9 pts ARB/43 pts ACEI	OS	HR and *P*
Wong et al[75]	Asians	China	2001–2005	22,286/21,7910	Digestive and respiratory cancer	22,286 pts ACEI	OS	HR and 95% CI
Yoshida et al[76]	Asians	Japan	1995–2013	56/269	Bladder cancer	ARB/ACEI	OS, DSS	HR and 95% CI
Yoshiji et al[77]	Asians	Japan	2004–2006	19/110	Hepatocellular carcinoma	19 pts ACEI. Continuously for 48 mo	DFS	KM
Yuge et al[78]	Asians	Japan	1999–2009	51/330	Bladder cancer	46 pts ARB/5 pts ACEI	DFS	HR and 95% CI

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CI = confidence interval, DFS = disease-free survival, DSS = disease-specific survival, GIST = gastrointestinal stromal tumor, HR = hazard ratio, KM = Kaplan–Meier, MFS = metastasis-free survival, NA = not available, OS = overall survival, PFS = progression-free survival.

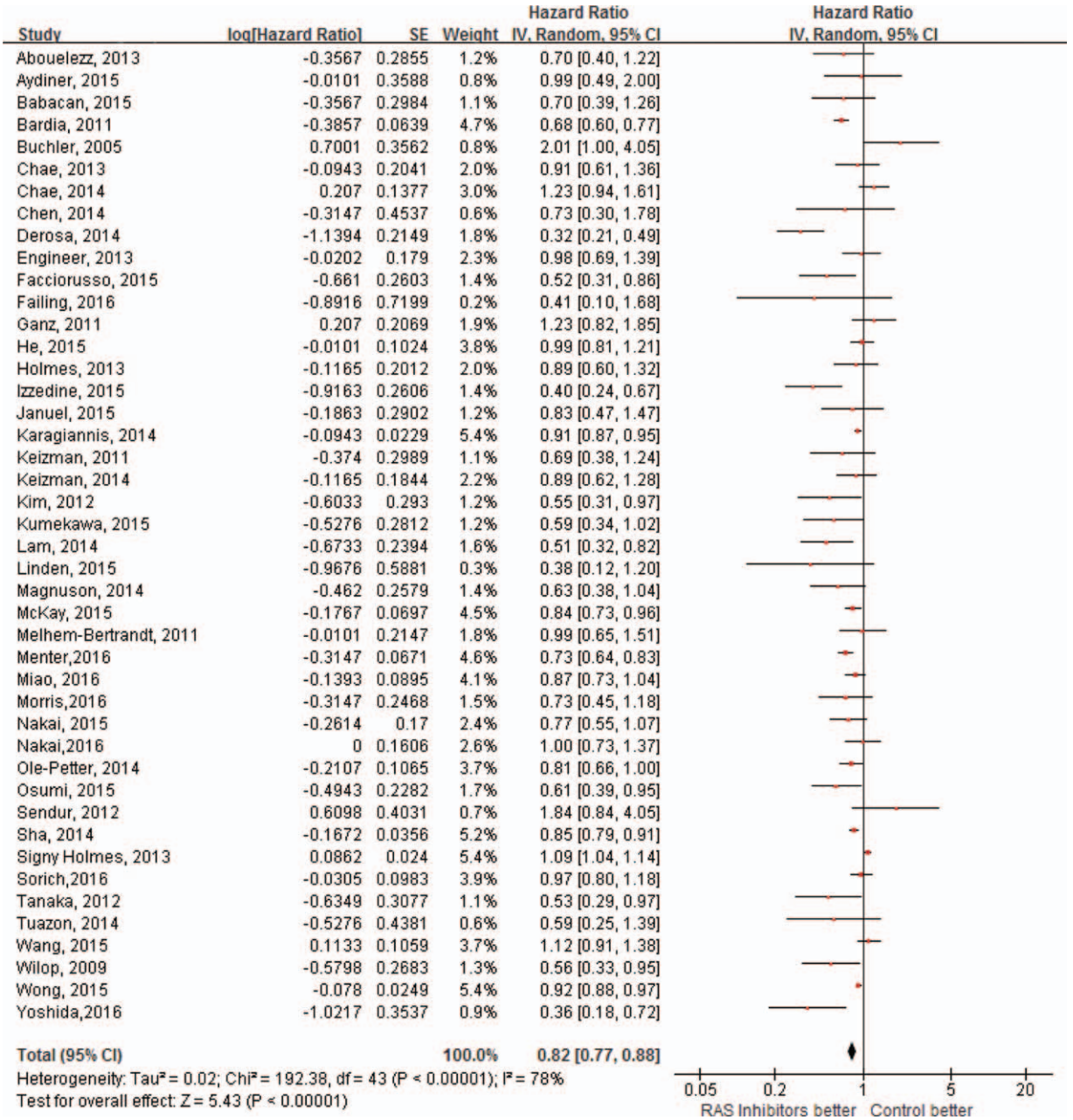

Figure 2. Forest plot for the association between renin–angiotensin system inhibitors and overall survival of cancer patients.

showed that RAS inhibitors could improve survival outcome in cancer patients. For RAS inhibitor users, pooled data showed a significantly better outcome in OS, PFS, and DFS compared with nonusers. In addition, there were better outcomes in DSS and MFS among RAS inhibitor users compared with nonusers.

The mechanisms underlying the effects of RAS inhibitors on the outcome of cancer patients are unclear. Previous studies have established that angiotensin II is involved in promoting the development of cancer. As a powerful mitogen, angiotensin II can promote cell growth and proliferation via transforming growth factor-beta,[79] tyrosine kinase,[80] and epidermal growth factor.[81] Angiotensin II can also regulate cell apoptosis and angiogenesis through upregulating the expression of vascular endothelial growth factor to stimulate neovascularization and Deoxyribonucleic acid synthesis.[82–84] Angiotensin II/AT1R signaling was found to stimulate cell growth, in part through mammalian target of rapamycin activation.[85] Furthermore, angiotensin II receptor expression was strongly correlated with tumor aggressiveness and decreased survival in human clear-cell renal cell carcinoma.[86] Upregulation of ACE enhances cell proliferation and predicts poor prognosis in laryngeal cancer.[87] Studies indicated that RAS inhibitors could suppress the growth of neoplastic cells and inhibit tumor growth in several tumor models.[88–91] In addition, RAS inhibitors were reported to inhibit the signal transduction mediated via growth factors through AT1R antagonism[92] and to suppress cancer cell proliferation through the activation of peroxisome proliferator-activated receptor-γ.[93]

Interestingly, our findings in subgroup analysis showed that the type of cancer can influence the effect of RAS inhibitors on

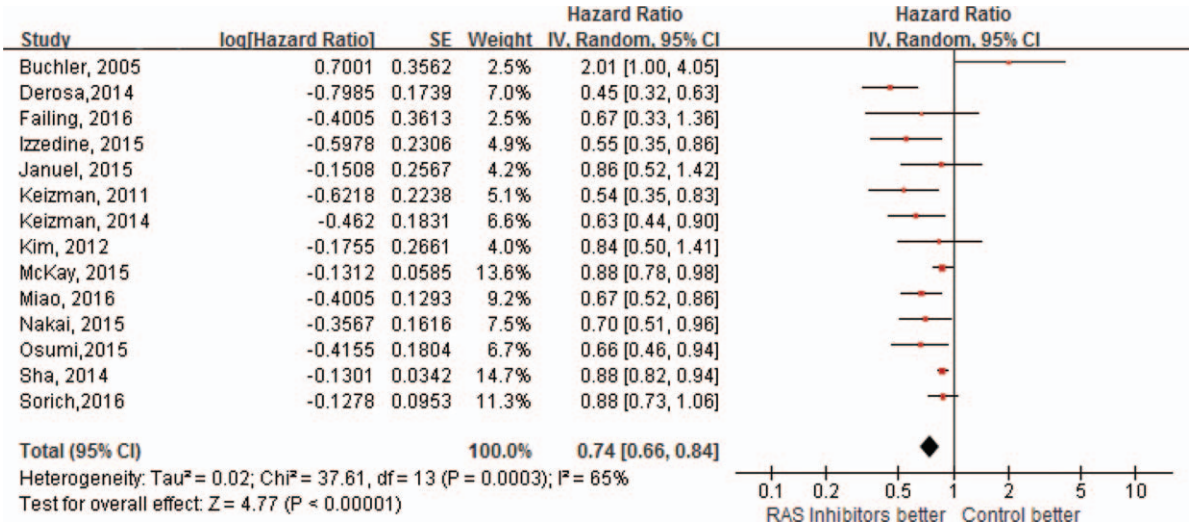

Figure 3. Funnel plot of the association between renin–angiotensin system inhibitors and progression-free survival of cancer patients.

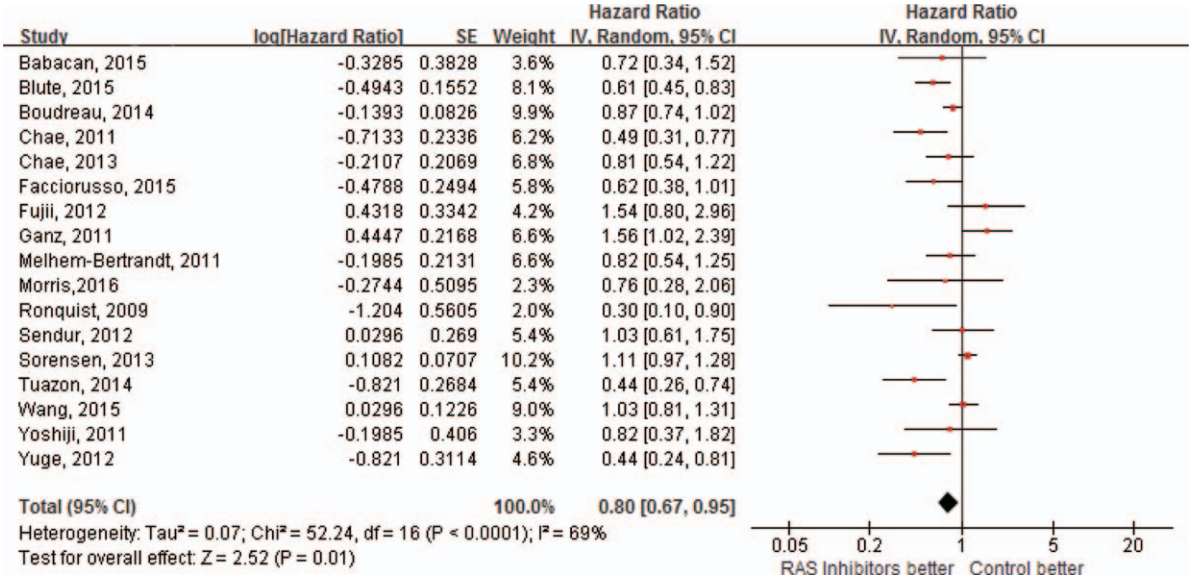

Figure 4. Funnel plot of the association between renin–angiotensin system inhibitors and disease-free survival of cancer patients.

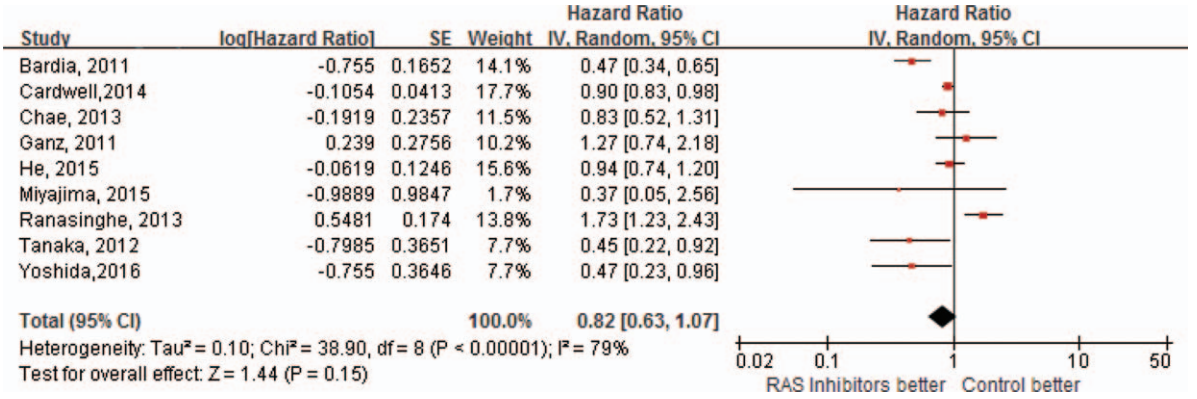

Figure 5. Funnel plot of the association between renin–angiotensin system inhibitors and disease-specific survival of cancer patients.

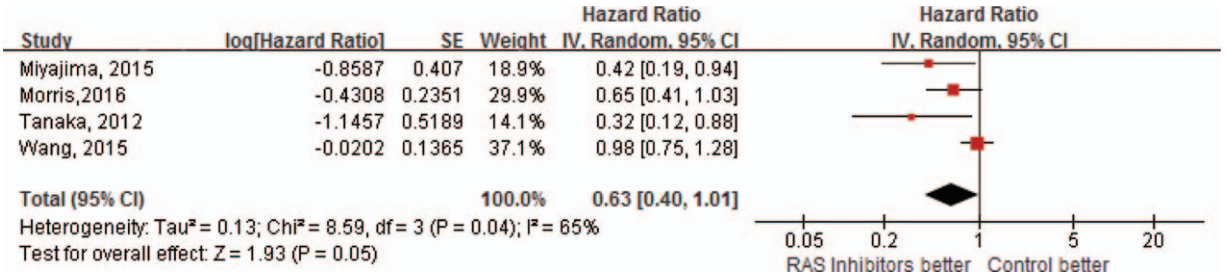

Figure 6. Funnel plot of the association between renin–angiotensin system inhibitors and metastasis-free survival of cancer patients.

survival of patients. Improvement of survival was found in renal cell carcinoma, gastric cancer, pancreatic cancer, hepatocellular carcinoma, upper-tract urothelial carcinoma, and bladder cancer patients in RAS inhibitor users. In addition, a better trend of outcome was observed in rectal/colorectal cancer, lung cancer, prostate cancer, glioblastoma, head and neck squamous cell carcinoma, oropharynx cancer, and melanoma with RAS inhibitor use, although there was no statistical significance. Conversely, the RAS inhibitors showed negative effects in patients with acute myelocytic leukemia or multiple myeloma. The mechanisms underlying the different impacts of RAS inhibitors in various cancer types are poorly understood.

Angiogenesis is a complex physiological process and can be disrupted by several mechanisms: interrupting the signaling pathways, inhibiting endothelial cells, or inhibiting other activators of angiogenesis. This strategy to target angiogenesis has provided therapeutic benefit in several types of cancer and led to the Food and Drug Administration approval of antiangiogenic agents in the treatment of renal, nonsmall cell lung, and colon cancers.[92] In addition, therapies that target new blood vessel formation are an emerging and promising area of research in prostate, hepatocellular, gastric, and bladder cancer.[94–97] We speculate that the different responses to antiangiogenesis therapy in various types of cancer may partly explain our results showing that RAS inhibitors have different influences in different types of tumors.

Why may the types of RAS inhibitors influence the association between RAS inhibitors and survival in cancer patients? There was significant improvement in OS among ARB users, while there was little improvement in OS among ACEI users. However, only 11 and 12 studies focused on ARBs and ACEIs, respectively, and the different cancer types may influence the results. Therefore,

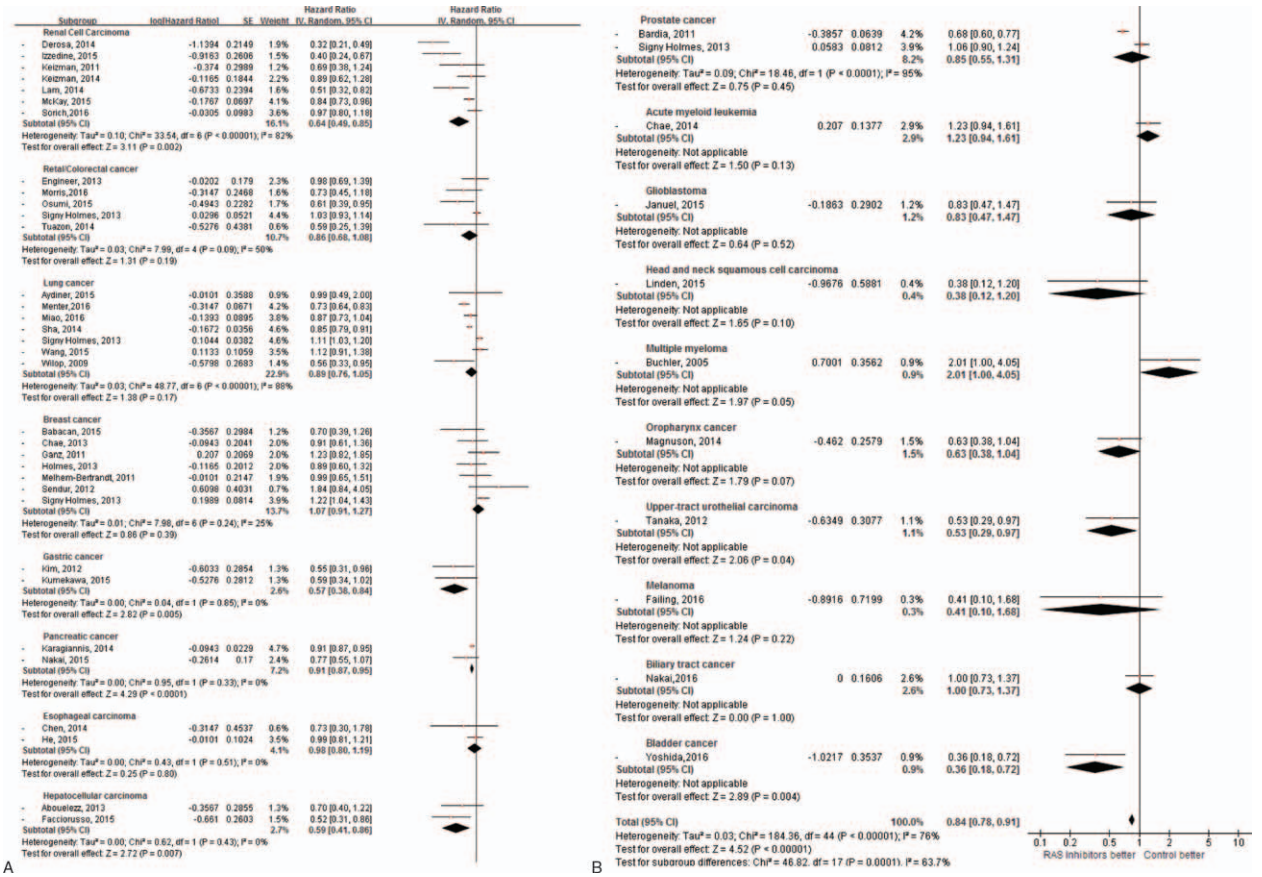

Figure 7. Forest plot for the subgroup analysis of cancer types.

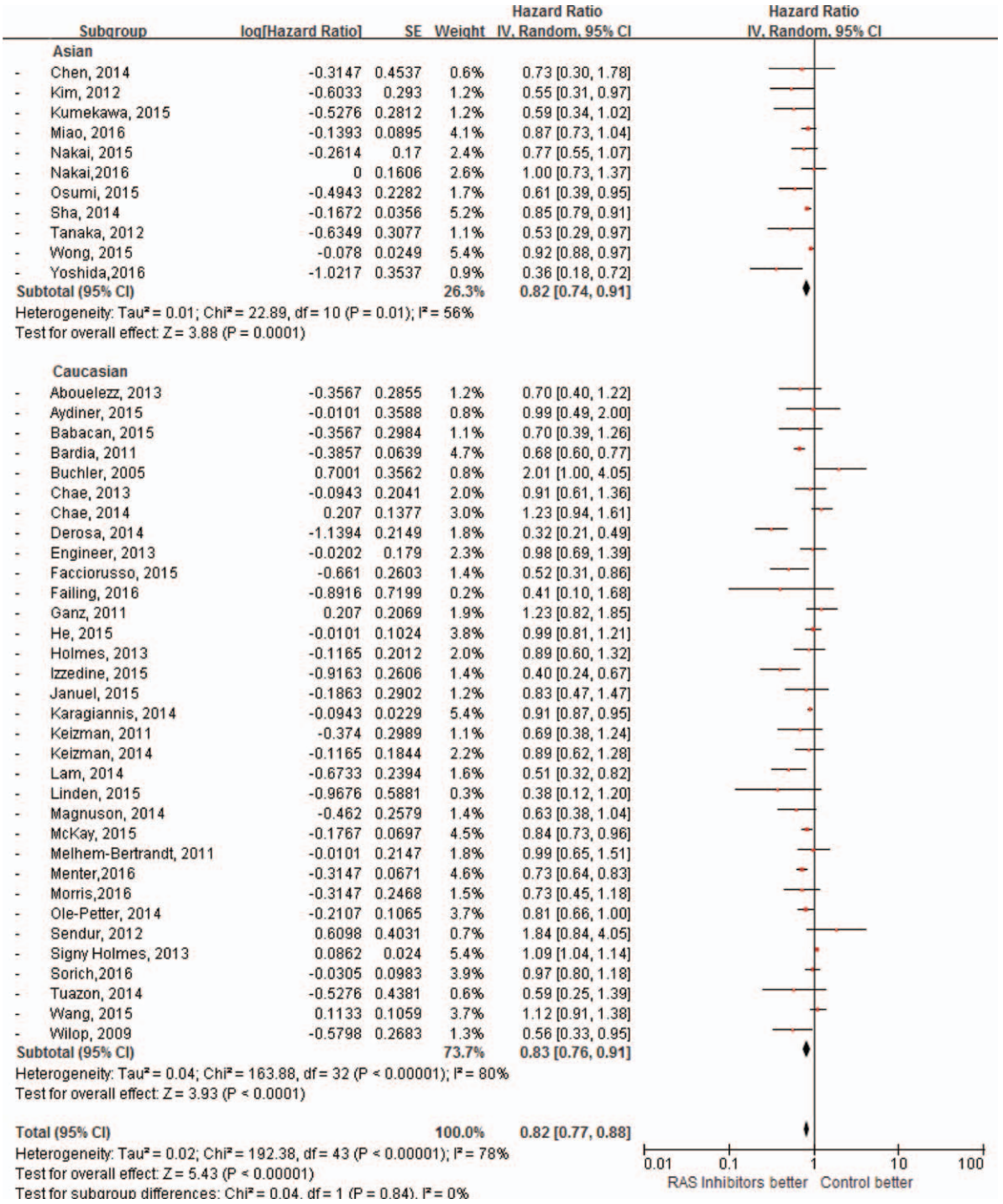

Figure 8. Forest plot for the subgroup analysis of ethnicity.

more studies are needed to investigate the impact of different drug types of RAS inhibitors on cancer survival.

Some limitations of our meta-analysis should be considered. For example, we only included the published studies. Therefore, the publication bias may influence the results of our meta-analysis. We only searched specific databases, which may have left out some studies in other databases. In addition, some relevant studies could not be included in our meta-analysis due to publication limitations or incomplete raw data. Furthermore, the search strategies were limited to English language publications; therefore, some studies were not be included in our meta-analysis.

Nevertheless, the meta-analysis was carried out at an appropriate time to clarify the association between RAS inhibitors and recurrence, metastasis, and survival of cancer patients. Multiple strategies and strict criteria were applied to identify and include the studies and subgroup analyses to reveal the factors that may influence the association between RAS inhibitors and cancer survival. To our knowledge, only 2 published meta-analyses have reported the association between

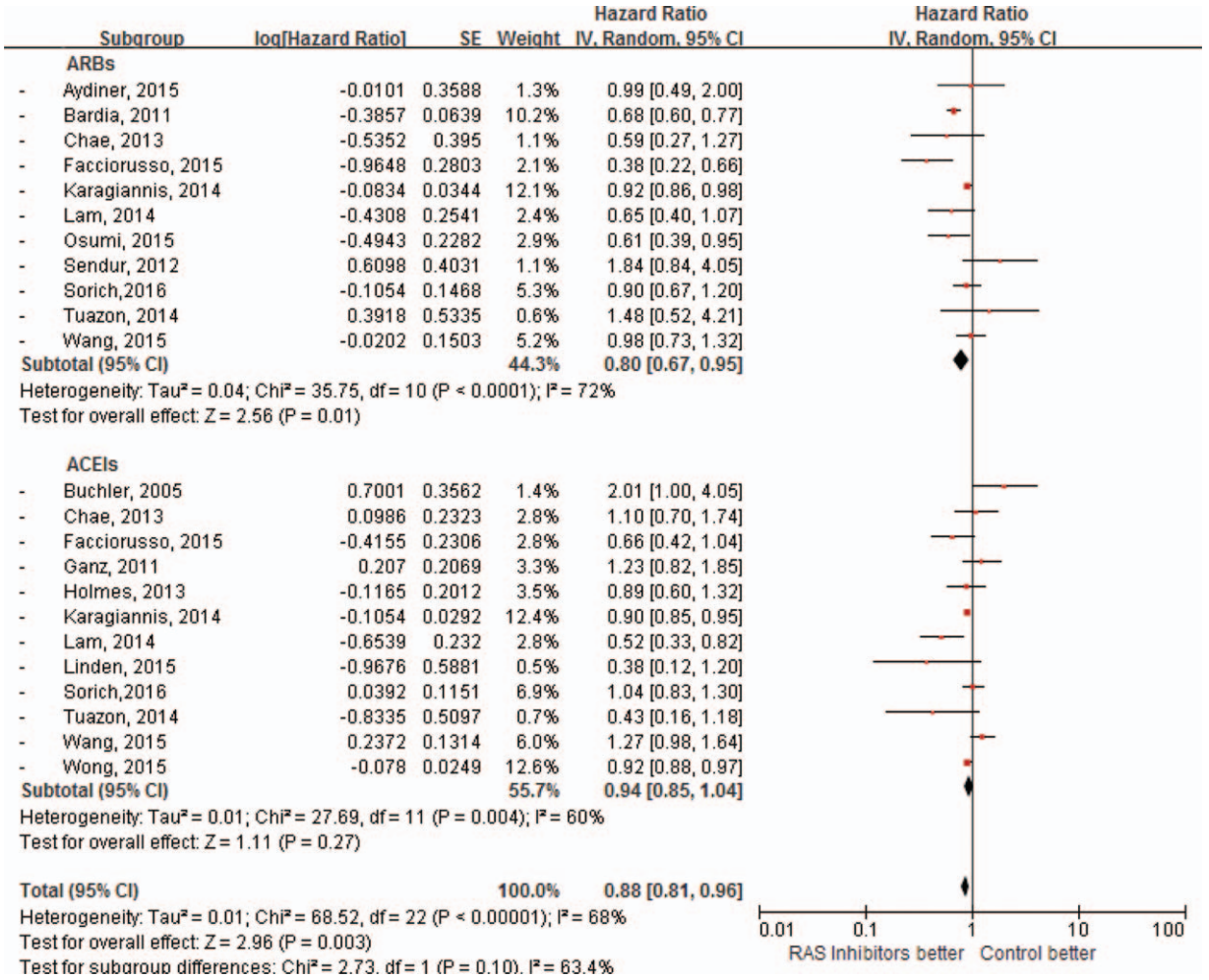

Figure 9. Forest plot for the subgroup analysis of drug types of renin–angiotensin system inhibitors.

ACEI or ARB use and cancer survival. One published meta-analysis including 11 studies indicated that ACEI or ARB use may be associated with cancer recurrence and survival.[98] Our results are consistent with this meta-analysis. However, a number of studies published in recent years have not been included in this meta-analysis, which may obscure a true association. Another published meta-analysis only focused on breast cancer.[99] Our subgroup analysis by cancer types is consistent with this meta-analysis, showing no association between RAS inhibitors and survival outcomes in patients with breast cancer.

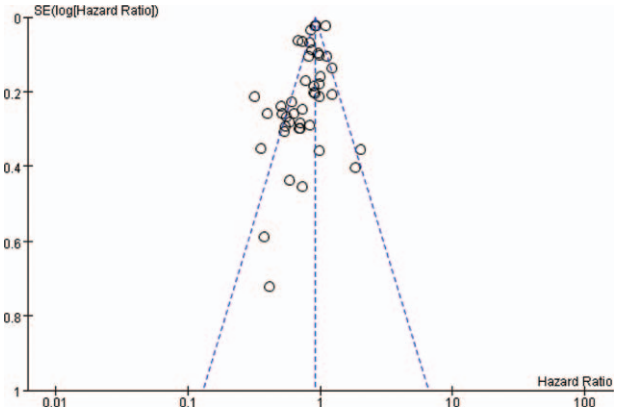

Figure 10. Funnel plot for publication bias test.

It is worth noting that RAS inhibitors are nontoxic and usually are active only in hypertensive patients while producing no adverse effects in healthy individuals. Although limited studies focused on the side effects of RAS inhibitors in cancer patients, Keizman et al[47] reported that no inadvertent interactions were observed in patients receiving RAS inhibitors concurrently with sunitinib. In addition, there is an overwhelming body of evidence for the cardioprotection afforded by RAS inhibitor treatment.[100] Considering the minimal side effects, relatively low costs and organ protection, more large-scale, and well designed future studies may be warranted to confirm our results, to investigate the underlying molecular mechanisms, and to define the target population that can benefit from the use of RAS inhibitors.

In conclusion, our findings showed that RAS inhibitor use was associated with cancer progression and survival. Cancer type and type of RAS inhibitor can influence the association between RAS inhibitor use and OS in cancer patients, while ethnicity had no influence. We believe that our results have great significance to guide clinical rational drug use of antihypertensive agents in cancer patients with hypertension. For further verification of our results, more large-scale and well designed studies are warranted.

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