Systematic Review and Meta-Analysis

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.\cite{11} 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).\cite{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.\cite{13–17}

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.\cite{8–11} Over-expressions 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.\cite{12–15} As a growth factor and main effector factor in RAS, angiotensin II can stimulate tumor neovascularization, which is important for tumor growth.\cite{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
block the action of angiotensin II type I receptors to inhibit tumor growth, metastasis, and tumor-associated angiogenesis. 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. and Wilip et al. reported that the use of RAS inhibitors was associated with improved survival in patients with nonsmall cell lung cancer. However, Aydiner et al. 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 “RAS,” or “ASI,” or names of specific RAS inhibitors combined with “neoplasm,” or “cancer,” or “tumor,” or “survive,” or other subtypes/synonyms for cancer and “prognosis,” or “predict,” or “predictive,” or “prediction,” or “mortality,” or “mortality,” or “death,” or “recurrence,” or “recurrent,” or “metastasis,” or “metastatic,” 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 languages and publications. Two authors (SH and LT) independently screened the citation lists of retrieved articles 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. 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 if the articles did not include these data. Study heterogeneity was assessed and presented as $\chi^2$ and $P$. 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 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 =
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 myeloid 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

![Figure 1](image-url)
| 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|
| Aydin et al[25]    | Caucasians | Turkey          | 2003–2011         | 37/117          | Non-small cell lung cancer           | 21 pts ARB/16 pts ACEI. At any time after the diagnosis | OS       | HR and 95% CI|
| Bah癌an et al[26]  | Caucasians | Turkey          | 2005–2012         | 31/218          | Breast cancer                        | ARB/ACEI. ≥ 6mo after the initial diagnosis | OS, DFS  | KM           |
| Bardia et al[27]   | Caucasians | Turkey          | 2003–2011         | 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         | 1515/218        | 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                              | DFS, PFS | KM           |
| Cardwell et al[31] | Caucasians | Northern Ireland | 1998–2006        | 4130/20246      | 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. ≥ 6mo                          | DFS     | HR and 95% CI|
| Chae et al[33]     | Caucasians | USA             | 1999–2005         | 168/703         | Breast cancer                        | ARB/ACEI. Before, or during treatment (during first month) | OS, PFS  | HR and 95% CI|
| Chae et al[34]     | Caucasians | USA             | 1999–2005         | 168/703         | Breast cancer                        | ARB/ACEI. Before, or during treatment (during first month) | OS, PFS  | HR and 95% CI|
| Chen et al[35]     | Asians     | China           | 1996–2011         | 20/141           | Esophageal squamous cell carcinoma   | ARB/ACEI. Before, or during treatment (during first month) | OS, PFS  | HR and 95% CI|
| Chae et al[36]     | Caucasians | USA             | 2000–2009         | 52/193           | Colorectal cancer                    | ARB/ACEI. ≥ 6mo per any year in the observation period | OS       | HR and 95% CI|
| Facciorusso et al[37] | Caucasians | Italy           | 2004–2010         | 80/153           | Hepatocellular carcinoma             | ARB/ACEI                                 | OS, DFS  | HR and 95% CI|
| Fujii et al[38]    | Caucasians | USA             | 2011–2014         | 11/80            | Melanoma                             | ARB/ACEI. ≥ 6mo                          | DFS     | Event and P  |
| Ganz et al[39]     | Caucasians | USA             | 1997–2000         | 76/163           | Breast cancer                        | ARB/ACEI. ≥ 6mo after initial diagnosis | DFS     | Event and P  |
| He et al[40]       | Caucasians | USA             | 1998–2012         | 409/1779        | Breast cancer                        | ARB/ACEI                                 | DFS, DSS | HR and 95% CI|
| Holmes et al[41]   | Caucasians | USA             | 1985–2006         | 143/1043        | Acute myeloid leukemia               | ARB/ACEI                                 | DFS, DSS | HR and 95% CI|
| Izzi et al[42]     | Caucasians | USA             | 2004–2013         | 20/141           | Esophageal squamous cell carcinoma   | ARB/ACEI                                 | OS       | HR, 95% CI   |
| Januel et al[43]   | Caucasians | France          | 2008–2013         | 26/81            | Glioblastoma                         | ARB/ACEI                                 | OS       | PFS KM       |
| Karagiannis et al[44] | Caucasians | USA             | 2003–2011         | 60/8481          | Pancreatic cancer                    | ARB/ACEI                                 | OS       | HR and 95% CI|
| Keizman et al[45]  | Caucasians | USA             | 2004–2010         | 44/127           | Renal cell carcinoma                 | ARB/ACEI                                 | OS, PFS  | HR and 95% CI|
| Keizman et al[46]  | Caucasians | USA, Israel      | 2004–2013         | 106/278          | Renal cell carcinoma                 | ARB/ACEI                                 | OS, PFS  | HR and 95% CI|
| Kim et al[47]      | Caucasians | USA             | 2007–2011         | 30/63            | Gastric cancer                       | ARB/ACEI                                 | OS, PFS  | HR and 95% CI|
| Kumezawa et al[48] | Caucasians | Japan           | 2007–2011         | 18/200           | Gastric cancer                       | ARB/ACEI                                 | OS       | HR and 95% CI|
| Lam et al[49]      | Caucasians | USA             | 2005–2013         | 38/190           | Renal cell carcinoma                 | ARB/ACEI. Beforeafter TKI                | OS       | HR and P      |
| Linden et al[50]   | Caucasians | USA             | 2010              | 10/51            | Head and neck squamous cell carcinoma | ARB/ACEI. During the course of the treatment | OS, PFS  | KM           |
| Magnuson et al[51] | Caucasians | USA             | 1990–2010         | 57/332           | Oncology cancer                      | ARB/ACEI. When RT                        | OS       | OS value      |
| McKay et al[52]    | Caucasians | USA             | 2003–2013         | 148/4736        | Renal cell carcinoma                 | ARB/ACEI. At baseline or within 30 of study treatment initiation | OS, DFS  | HR and 95% CI|
| Melhem-Bertrandt et al[53] | Caucasians | USA             | 1995–2007         | 140/1413         | Breast cancer                        | ARB/ACEI                                 | OS       | HR and 95% CI|
| Memt et al[54]     | Caucasians | USA             | 2005–2011         | 35/1813          | Non-small cell lung cancer           | 86 pts ARB/265 pts ACEIs                 | OS       | HR and 95% CI|
| Miao et al[55]     | Asians     | China           | 2000–2014         | 52/301           | Non-small cell lung cancer           | ARB/ACEI                                 | OS, PFS  | KM           |

(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% Q |
| 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% Q |
| Nakai et al[60]    | Asians    | Japan       | 2001–2013      | 108/549         | Pancreatic cancer                          | 89 pts ARB/13 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% Q |
| Ole-Petter et al[62]| Caucasians| USA         | NA             | NA/1120        | Renal cell, hepato-cellular, GIST          | ARB/ACEI                                | OS                      | HR and 95% Q |
| Osumi et al[63]    | Asians    | Japan       | 2007–2010      | 104/181         | Colorectal cancer                          | 104 pts ARB                            | OS, PFS                 | HR and 95% Q |
| Renassinghe et al[64]| Caucasians| Australia  | 2003–2007      | 603/1956        | Prostate cancer                            | 603 pts ACEI                            | DSS                      | HR and 95% Q |
| 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, PFS             | 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% Q |
| Holmes et al[68]   | Caucasians| Canada      | 2004–2008      | 42/9/15,582    | Cancer                                     | ARB/ACEI. 1 y before diagnosis          | OS                      | HR and 95% Q |
| Subgroup 1[68]     | Caucasians| Canada      | 2004–2008      | 880/4019       | Breast cancer                              | ARB/ACEI. 1 y before diagnosis          | OS                      | HR and 95% Q |
| Subgroup 2[68]     | Caucasians| Canada      | 2004–2008      | 1187/3697      | Colorectal cancer                          | ARB/ACEI. 1 y before diagnosis          | OS                      | HR and 95% Q |
| Subgroup 3[68]     | Caucasians| Canada      | 2004–2008      | 1256/4241      | Lung cancer                                | ARB/ACEI. 1 y before diagnosis          | OS                      | HR and 95% Q |
| Subgroup 4[68]     | Caucasians| Denmark     | 1996–2003      | 506/18,733     | Breast cancer                              | ARB/ACEI. 0 (no exposure history), 1–5, 6–10, and more than 10 cumulative years of exposure | DFS                     | HR and 95% Q |
| Sonich et al[69]   | 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% Q |
| Tanaka et al[70]   | Asians    | Japan       | 1995–2009      | 48/279          | Upper tract urothelial carcinoma           | 43 pts ARB/5 pts ACEI                  | OS, DSS, MFS             | HR and 95% Q |
| Tuszen et al[71]   | Caucasians| USA         | 2004–2008      | 105/222        | Colorectal cancer                          | ARB/ACEI. ≥3 mo after initial diagnosis and treatment | OS, DFS                 | HR and 95% Q |
| Wang et al[72]     | Caucasians| USA         | 1996–2010      | 142/673        | Non-small cell lung cancer                 | 130 pts ACEI or ARB/4 pts ACEI and ARB  | OS, DSS, MFS             | HR and 95% Q |
| Wilip et al[73]    | Caucasians| Germany     | 1996–2007      | 52/232         | Non-small cell lung cancer                 | 9 pts ARB/43 pts ACEI                 | OS                      | HR and P     |
| Wong et al[74]     | Asians    | China       | 2001–2005      | 22,286/21,7910 | Digestive and respiratory cancer           | 22,286 pts ACEI                         | OS                      | HR and 95% Q |
| Yoshida et al[75]  | Asians    | Japan       | 1995–2013      | 56/269         | Bladder cancer                             | ARB/ACEI                                | OS                      | HR and 95% Q |
| Yoshiji et al[76]  | Asians    | Japan       | 2003–2004      | 19/110         | Hepatocellular carcinoma                   | 19 pts ACEI                            | DFS                     | KM           |
| Yuge et al[77]     | Asians    | Japan       | 1999–2009      | 51/330         | Bladder cancer                             | 46 pts ARB/5 pts ACEI                 | DFS                     | HR and 95% Q |

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.
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, tyrosine kinase, and epidermal growth factor. 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.

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.
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. In addition, therapies that target new blood vessel formation are an emerging and promising area of research in prostate, hepatocellular, gastric, and bladder cancer. 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,
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 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
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. 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. 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.

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 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. 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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