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REVIEW

The Association of Androgen Receptor Expression with Renal Cell Carcinoma Risk: a Systematic Review and Meta-Analysis

Peng Yuan[1] · Yue Ge[1] · Xiao Liu[1] · Shen Wang[1] · Zhangqun Ye[1] · Hua Xu[1] · Zhiqiang Chen[1]

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Abstract

The relationship between androgen receptor expression and renal cell carcinoma risk remains controversial. This study is aimed to investigate the clinical significance of androgen receptor expression in renal cell carcinoma. A computerized bibliographic search of Embase, the PubMed, and Web of Science combined with manual research between 1977 and 2017 was conducted to explore the association between androgen receptor expression and clinicopathological features of renal cell carcinoma. Data were analyzed by a meta-analysis using RevMan 5.3 analysis software. Eleven retrospective studies with 1839 renal cell carcinoma cases were finally included according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. It was found that there was no significant difference between androgen receptor expression and susceptibility, pathological type, metastatic status, metastatic type (lymph or distant metastasis) and cancer-specific survival of renal cell carcinoma ($P > 0.05$). However, positive androgen receptor expression was demonstrated to be significantly associated with male patients, lower pathological grade, and earlier tumor stage of renal cell carcinoma (OR = 1.69, 95% CI = 1.30–2.19, $P < 0.0001$; OR = 2.06, 95% CI = 1.49–2.85, $P < 0.0001$; OR = 2.81, 95% CI = 1.30–6.12, $P = 0.009$; respectively). In conclusion, higher androgen receptor expression was correlated with male patients, low tumor grade and early stage of renal cell carcinoma. Based on current results, androgen receptor-inhibited target therapy for renal cell carcinoma patients may be of limited benefits and should be taken into more evaluations.

Keywords Renal cell carcinoma · Androgen receptor · Prognosis · Targeted therapy

Background

Kidney and renal pelvis cancer represents 5% and 3% of estimated new cases in male and female respectively, which ranks the 6th and 10th among all cancer [1]. Renal cell carcinoma (RCC) accounts for up to 85% of all kidney cancer and the most common histologic subtype is clear cell RCC (ccRCC). The incidence of RCC has been increasing in recent 20 years [2]. It has been demonstrated that pathological characters of tumor type, stage, and grade are strongly associated with the prognosis of RCC [3, 4]. Studies on oncological biologic pathways involving a variety of potential molecules such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), hypoxia-induced factor (HIF), mammalian target of rapamycin (mTOR), are aimed to seek targeted therapies which may effectively improve the survival of RCC patients [5–9]. Besides, androgen receptor (AR), a member of the nuclear hormone receptor family of transcription factors which plays a vital role in biological mechanisms of the disease emergence and development, is emphasized for its clinical significance in several urological diseases [10, 11]. According to the results of previous in vivo and in vitro researches it was found that AR could modulate the tumorigenesis and metastasis of urogenital cancer including kidney, bladder, and prostate [12–14]. Moreover, AR could also enhance the development of calcium oxalate nephrolithiasis [15, 16].

✉ Zhiqiang Chen
urol_chen@163.com

[1] Department of Urology, Tongji Hospital, Tongji Medical School, Huazhong University of Science and Technology, No.1095 Jie Fang Avenue, Hankou, Wuhan 430030, People's Republic of China

Given the preponderance of males in the incidence of RCC and possible positive response after hormonal treatments on RCC patients, investigators hypothesized that RCC was a hormone-dependent tumor and regulated by the biological function of AR [17, 18]. Increasing studies attempted to evaluate the association of AR and RCC in past years. However, controversial results from previous studies made it hard to identify the true role of AR in RCC. Langner et al. [19] found that AR expression was significantly associated with lower pathological stage and grade as well as better survival outcomes. However, Noh et al. [20] discovered that AR was in relation to poor prognosis with negative overall survival as well as cancer-specific survival (CSS). Additionally, two studies revealed that the role of AR expression differed in distinct metastatic types of RCC. In 2017, Huang et al. [21] found that AR could increase hematogenous metastasis yet reduce lymphatic metastasis; while on the other hand Foersch et al. [22] demonstrated that decreased AR expression accompanied with the presence of distant metastasis but there was no consistent pertinence of AR expression and lymphatic metastasis. On the basis of current results, the association between AR expression and clinicopathologic outcomes in RCC is ambiguous. There has been no meta-analysis which observes the role of AR expression in RC C so far. This study will benefit to a comprehensive evaluation and considerable proofs of the association of AR expression with RCC risk.

Methods

Search Strategy

In May 2018, according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [23], a systematic review was performed by a computer search covering January 1977 to December 2017 using electronic databases of Embase, the PubMed, and Web of Science combined with additional manual research of the references of original studies included and reviews on this topic. The search terms included kidney cancer, kidney carcinoma, renal cell carcinoma, RCC, androgen receptor, AR, and hormone receptor.

Inclusion Criteria

All titles, abstracts and articles without abstracts were screened by two independent authors (P Yuan, Y Ge). Eligible studies were included based on the following criteria: full text published in English language; original studies other than reviews, case reports, meeting abstracts, or conference proceedings; studies on RCC patients; evaluation of the association between AR expression and clinicopathological outcomes. Full texts of selected abstracts were further reviewed and two reviewers together decided whether a study should be finally included. If there was any disagreement, a third author (ZQ Chen) made a final consideration after comprehensive discussions.

Data Extraction and Quality Assessment

Data were independently collected and extracted by two authors (P Yuan, Y Ge) using designed forms. Any unavailable data were blanked and defined as 'not available (NA)'. A third author (ZQ Chen) took the responsibility of the judgement whenever there were recording discrepancies. The Newcastle-Ottawa Scale was used to evaluate the quality of studies. A study with the score of 7 or upper was high-quality while a study with the score of <7 was low-quality [24].

Statistical Analysis

Data were presented descriptively as means (range), proportions, or odds ratio (OR) with its 95% confidential interval (CI). Selected data were combined into a meta-analysis using RevMan 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark). Funnel plot visual inspection was performed to evaluate the publication bias only when the analysis included more than 10 studies. Statistical heterogeneity across studies were assessed by the chi-square test and the I^2 statistic. It was indicated that when the heterogeneity existed as I^2 was >50% or $P < 0.05$, data were pooled by the random-effects model; otherwise no heterogeneity was found and then a fixed-effects model was used. All statistical tests were two-sided, and statistical significance was defined as $P < 0.05$.

Results

Literature Search and Study Characteristic

In the final analysis a total of 11 studies [19–22, 25–31] with 1839 RCC cases were eligibly included. The process of study selection was shown by the PRISMA flow diagram (Fig. 1). All studies were in retrospective cohort design and assessed as high-quality by the Newcastle -Ottawa Scale.

General characteristics of study authors, published year, published country, the number of RCC cases, patient age, patient sex, follow-up time, the assay of AR detection, and pathological types of RCC were shown in Table 1. There were 1, 5, and 5 studies designed in American, Asian, and

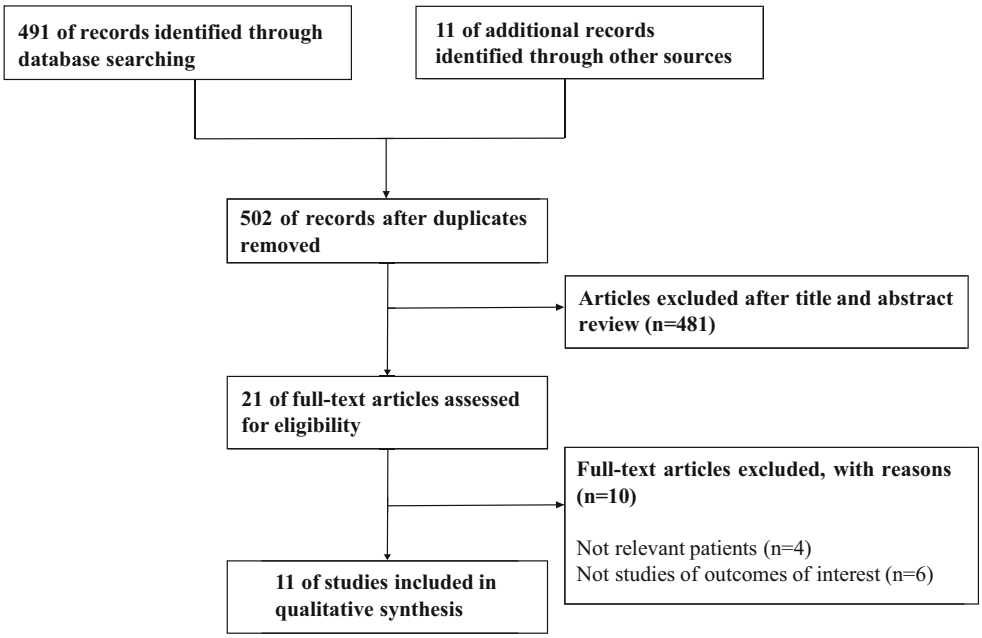

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram detailing the search strategy and identification of studies used in data synthesis

European area, respectively. Patient age in all cases with available data ranged from 18 to 85 years. It was found that the most common pathological type of RCC was ccRCC, followed by papillary and some other types of chromophobe, collecting duct carcinoma, granular cell, spindle cell and mixed cell.

To detect AR expression in RCC and control normal tissues, methods of polymerase chain reaction (PCR), western blot (WB), immunohistochemistry (IHC), and dextran-coated charcoal (DCC) were carried out for the quantitative or qualitative determination of AR protein or messenger RNA (mRNA). Among 6 studies (54.5%) where IHC was used, positive AR expression of RCC was differently defined as the least 10% (4 studies) or 5% (1 study) tumor cells positive for AR nuclear staining. And this information was not mentioned in 1 study. Among 4 studies (36.4%) in which DCC was conducted, the value of AR expression above the lower limit detectable from this method was considered as AR-positive. In the only one study (9.1%) the assay of both PCR and WB were used.

The Association of AR Expression and Clinicopathological Features in RCC

The data of AR expression and clinicopathological features including patient sex, tumor susceptibility, pathological type, pathological grade, pathological T (pT) stage, metastatic status, metastatic type, and survival outcomes were presented in Table 2.

Patient Sex

The association of AR expression and the sex of RCC patients was investigated in 8 studies. No evidence of statistically significant heterogeneity was verified ($I^2 = 23\%$, $P = 0.24$) and then a fixed-effects model was applied to the analysis. Positive AR expression was significantly correlated to the male RCC patients (OR = 1.69; 95%CI = 1.30–2.19; $P < 0.0001$; Fig. 2).

Tumor Susceptibility

In terms of RCC susceptibility, a total of 4 studies compared the difference of AR expression between RCC and normal tissues which were all pathologically identified. Self-matched adjacent normal-appearing kidney tissue specimens were used in 3 studies. But of 8 normal tissue specimens in 1 study, 2 tissue samples were self-matched but other 6 samples were from other RCC patients. A random-effects model served the analysis with the consideration of statistically significant heterogeneity between studies ($I^2 = 87\%$, $P < 0.0001$). Overall, there was no significant association between AR expression and RCC susceptibility (OR = 0.55; 95%CI = 0.06–4.70; $P = 0.58$; Fig. 3).

Tumor Pathological Type, Grade and T Stage

The association of AR expression and pathological types were observed in 3 studies. In this analysis, pathological types were divided into two groups of ccRCC and other types as ccRCC

Table 1 General characteristics of the included studies

ID No	Authors	Year	Country	No. of RCC cases	Age (years)	Sex (M/F),n	RCC Pathological types, n(%)	AR detection assay	Follow-up, mean (months)
1	Ha et al.	2015	Korea	115	57.4(21–83)	86/29	cc: 98(85.2%); p: 13(11.3%); others: 4(3.5%)	PCR, WB	58.2
2	Elizabeth et al.	2014	USA	433	NA	NA	NA	IHC	NA
3	Zhu et al.	2014	China	120	63(35–82)	73/47	cc:96(80%); p:12(10%); others:12(10%)	IHC	NA
4	Nakano et al.	1984	Japan	41	58.8(46–74)	30/11	cc:28(68.3%); others:13(31.7%)	DCC	NA
5	Non et al.	2013	Korea	200	58.1(29–82)	140/60	cc:200 (100%)	IHC	NA
6	Foersch et al.	2017	German	546	NA	338/208	cc:477(87.4%); p:69(12.6%);	IHC	8.14
7	Klotzl et al.	1987	German	21	NA	NA	NA	DCC	NA
8	Langner et al.	2004	Austria	182	62(28–85)	112/76	cc:128(70.3%); p:20(11%); others:34(18.7%)	IHC	24
9	Huang et al.	2017	China	89	NA	70/19	cc:89 (100%)	IHC	NA
10	Ronchi et al.	1984	Italy	78	56(18–70)	55/23	NA	DCC	NA
11	Concolino et al.	1981	Italy	14	55.8 (41–76)	7/7	NA	DCC	NA

M male, *F* female, *AR* androgen receptor, *RCC* renal cell carcinoma, *PCR* polymerase chain reaction, *WB* western blot, *cc* clear cell, *p* papillary, *IHC* immunohistochemistry, *DCC* dextran-coated charcoal, *NA* not available

accounted for most of cases and the number of other types were very low. No statistically significant heterogeneity was testified ($I^2 = 0\%$, $P = 0.57$) and then a fixed-effects model was employed. It was discovered that there was no difference of AR expression between ccRCC and other types of RCC (OR = 0.77; 95% CI = 0.51–1.17; $P = 0.22$; Fig. 4a).

A total of 6 studies reported the relationship between AR expression and tumor pathological grade. In this analysis, tumor grade was divided into grade 1–2 and 3–4 as the corresponding definition of low grade and high grade. No statistically significant heterogeneity was authenticated ($I^2 = 49\%$, $P = 0.08$) and then a fixed-effects model was needed. Compared with RCC without AR expression, those with positive AR expression were associated with a statistically significant lower tumor grade (OR = 2.06; 95%CI = 1.49–2.85; $P < 0.0001$; Fig. 4b).

Four studies reported the relationship between AR expression and tumor pT stage. In this analysis, pT stage was divided into T1–2 and T3–4 as the corresponding definition of early stage and advanced stage. A random-effects model was required in the analysis as there was statistically significant heterogeneity between studies ($I^2 = 64\%$, $P = 0.04$). Similar to the tumor grade, positive AR expression was significantly associated with lower tumor stage (OR = 2.81; 95%CI = 1.30–6.12; $P = 0.009$; Fig. 4c).

Metastatic Status

Of the 5 studies evaluating the association of AR expression and metastatic status, there was statistically significant heterogeneity ($I^2 = 77\%$, $P = 0.002$) and the analysis was performed by a random-effects model. There was no difference of AR expression between metastatic and non-metastatic status (OR = 0.77; 95%CI = 0.37–1.62; $P = 0.49$; Fig. 5a). In addition, of the 3 studies evaluating the association of AR expression and metastatic type, there was also statistically significant heterogeneity ($I^2 = 61\%$, $P = 0.07$) and a random-effects model was wielded. And no difference of AR expression between lymph and distant metastasis was observed (OR = 0.54; 95%CI = 0.09–3.24; $P = 0.50$; Fig. 5b).

Survival Outcomes

Three studies explored the relevance of AR expression and the survival. CSS was chosen as the only indicator for the survival, and in a study CSS was respectively evaluated in two subgroups of ccRCC patients and non-ccRCC patients. Statistically significant heterogeneity existed ($I^2 = 85\%$, $P = 0.0002$) and a random-effects model was finally utilized. The difference between AR expression and CSS was not statistically significant (OR = 1.14; 95%CI = 0.21–6.26; $P = 0.88$; Fig. 6).

Table 2 AR expression and clinicopathological features of the patients included

ID No	Sex*		Tissue*		Pathological type*		Tumor grade*	
	M	F	Tumor	Normal	cc	others	1–2	3–4
1	NA		NA	NA	NA	NA	NA	NA
2	NA		NA	NA	NA	NA	NA	NA
3	73/24 (32.9%)		47/12 (25.5%)	44/40 (90.1%)	NA	NA	89/32 (36.0%)	31/4 (12.9%)
4	30/10 (33.3%)		11/3 (27.3%)	NA	27/9 (33.3%)	14/4 (28.6%)	20/6 (30.0%)	21/7 (33.3%)
5	140/93 (66.4%)		60/33 (55%)	NA	NA	NA	158/101 (63.9%)	42/25 (59.5%)
6	338/126 (37.3%)		208/61 (29.3%)	NA	477/187 (39.2%)	69/34 (49.3%)	400/165 (41.3%)	77/22 (28.6%)
7	NA		NA	5/0	NA	NA	NA	NA
8	112/24 (21.4%)		182/27 (14.8%)	8/0	128/19 (14.8%)	54/8 (14.8%)	99/21 (21.2%)	83/6 (7.2%)
9	70/42 (60%)		89/49 (55.1%)	NA	NA	NA	59/40 (67.8%)	30/9 (30.0%)
10	55/12 (21.8%)		78/14 (17.9%)	77/15 (19.5%)	NA	NA	NA	NA
11	7/3 (42.9%)		14/8 (57.1%)	NA	NA	NA	NA	NA

ID No	pT stage*		Metastasis*		Metastasis type*		CSS, HR(95%CI)
	1–2	3–4	Yes	No	lymph	distant	
1	NA	NA	NA	NA	NA	NA	15.546 (1.320–183.131)
2	NA	NA	126/35 (27.8%)	307/57 (18.6%)	NA	NA	NA
3	95/34 (35.8%)	25/2 (8%)	16/2 (12.5%)	104/34 (32.7%)	10/2 (20%)	6/0	NA
4	NA	NA	NA	NA	NA	NA	NA
5	NA	NA	NA	NA	2/1 (50%)	NA	5.105 (0.918–28.399)
6	294/136 (54.6%)	183/51 (27.9%)	111/28 (25.2%)	366/159 (43.4%)	31/7 (22.6%)	80/21 (26.3%)	0.65 (0.46–0.92)# 0.083 (0.02–0.43) ##
7	NA	NA	NA	NA	NA	NA	NA
8	102/24 (23.5%)	80/3 (3.8%)	NA	NA	NA	NA	NA
9	63/35 (55.6%)	26/14 (53.8%)	22/12 (54.5%)	67/37 (55.2%)	9/2 (22.2%)	13/10 (76.9%)	NA
10	NA	NA	18/3 (16.7%)	60/11 (18.3%)	NA	NA	NA
11	NA	NA	NA	NA	NA	NA	NA

M male, *F* female, *cc* clear cell, *pT stage* pathological T stage, *CSS* cancer-specific survival, *HR* hazard ratio, *CI* confidence interval, *NA* not available

Data of subgroup of clear cell renal cell carcinoma patients; ## Data of subgroup of papillary renal cell carcinoma patients;

*Data are presented as the number of total patients / the number of androgen receptor-positive patients in this cohort, (proportion);

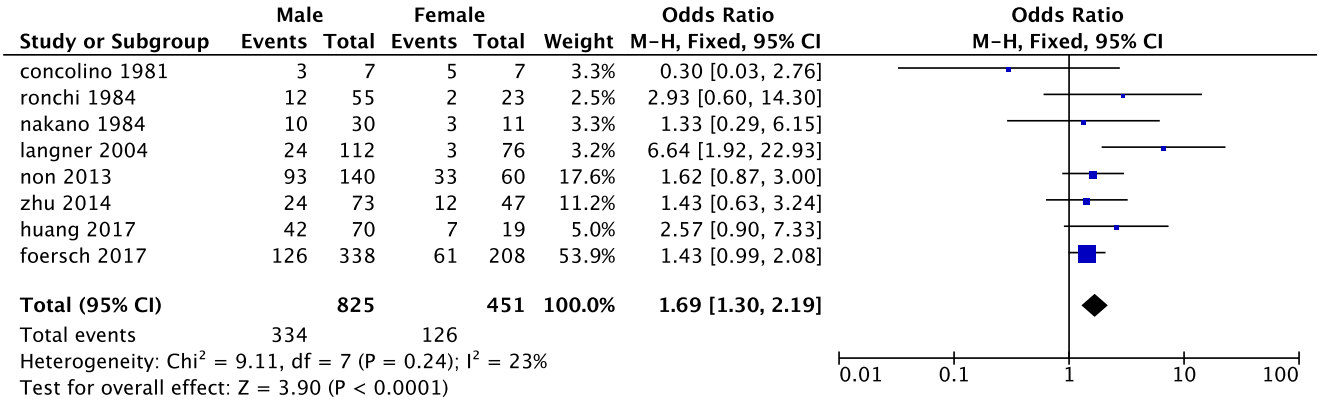

Fig. 2 Forest plots for association between androgen receptor expression and the sex of renal cell carcinoma patients (CI: confidence interval)

Discussion

AR signaling, which involves nucleus translocation after the combination of AR and hormones and the transcription of AR target genes, has much influence in human malignances as well as other hormone-dependent aliments [32]. Disease processes such as cell proliferation, migration, angiogenesis, epithelial-mesenchymal transition, oxidative stress, and inflammatory, are ascribed to the biological function of AR signaling by the interaction of other signaling pathways and targeted genes [33, 34]. Study of AR in prostate cancer has remained for several decades, which promoted to the development of AR-targeted therapy and the renewal of anti-androgen drugs [35]. In bladder cancer, high AR expression implicates low tumor grade and stage and benefits to the survival time [36].

Besides that, it has been found that AR expression was associated with breast cancer, pancreatic cancer, liver cancer, ovarian cancer, endometrial cancer and so on [37, 38]. A meta-analysis found that breast cancer expressing both ER and AR indicated better survival compared with those expressing only ER [39]. Based on the significant association of AR and breast cancer, some studies have focused on the antiandrogens for the treatment of breast cancer, which aimed to provide a promising therapeutic choice which might improve the survival outcomes in AR-positive but ER/PR-negative cancers [40, 41]. And AR expression is also associated with the development and prognosis of liver cancer, which promoted to tumor growth and invasion [42].

Despite a relatively low incidence of RCC compared with the prostate cancer in males and the breast cancer in females, some cases were initially diagnosed with advanced even metastatic RCC because of atypical syndromes in the early stage [43]. RCC patients with high tumor grade and stage are inclined to increased risks of tumor recurrence and metastasis [44]. Poor survival outcomes were observed in metastatic RCC patients. Adjuvant targeted therapies of VEGF-R inhibitors have been applied to advanced or metastatic RCC patients to repress the pathogenesis and to improve the survival [45]. So researchers are attempting to seek more considerable molecules associated with RCC so that the disease can be better understood to achieve explicit assessment and precise treatment of RCC.

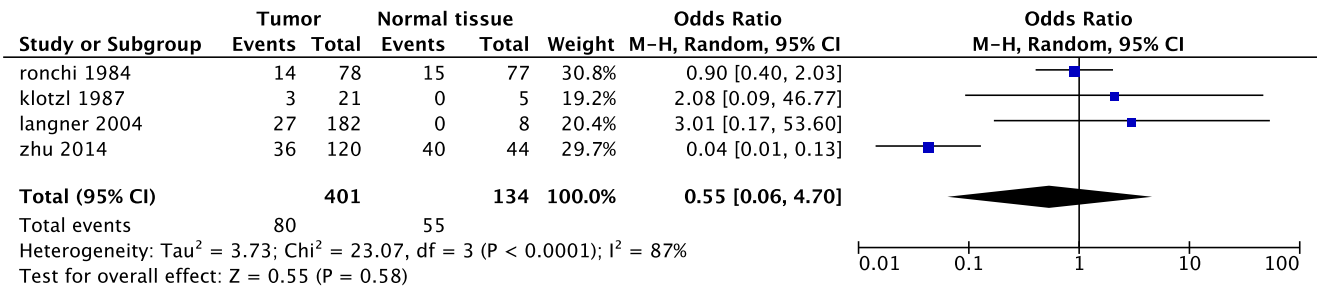

Fig. 3 Forest plots for association between androgen receptor expression and renal cell carcinoma susceptibility (CI: confidence interval)

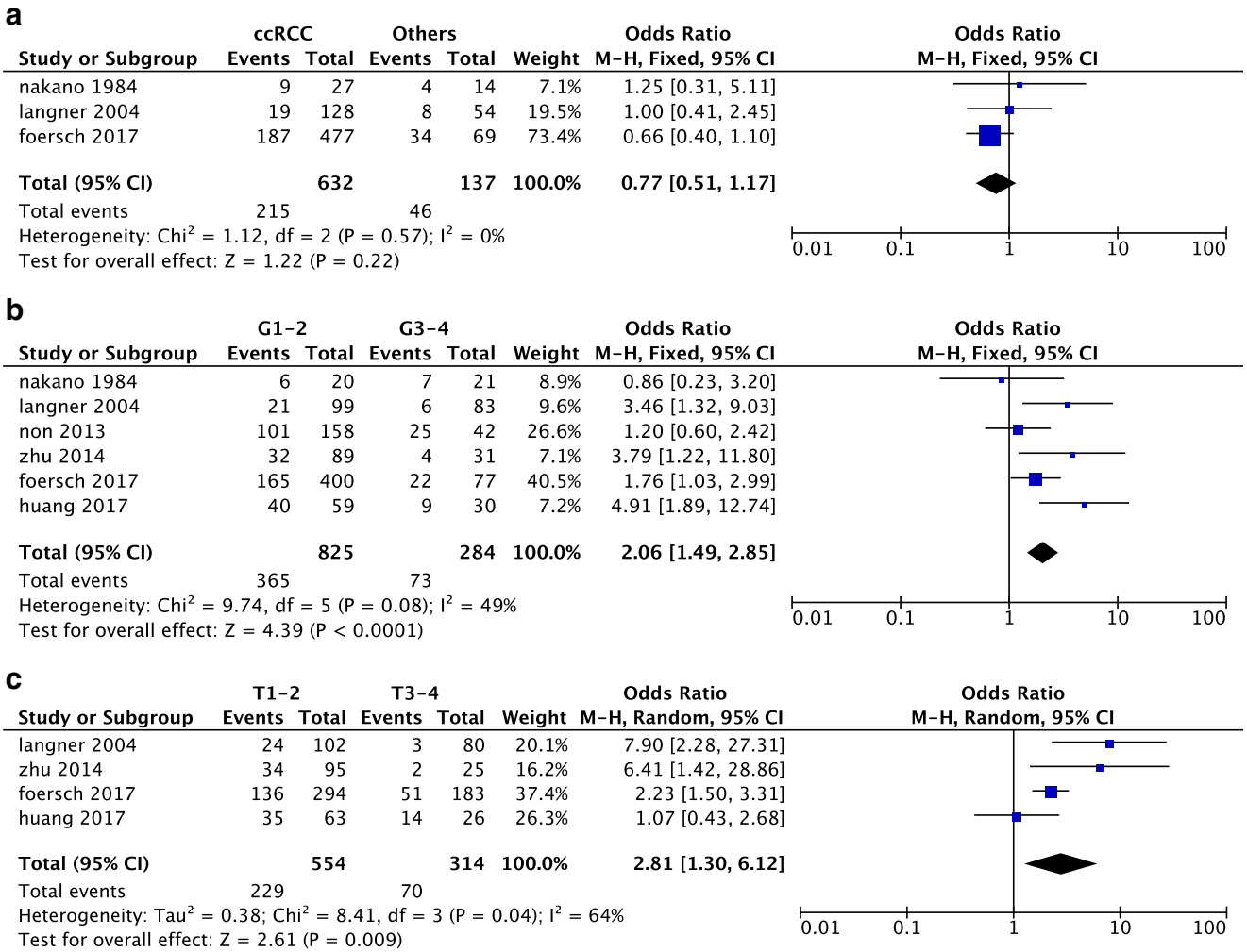

Fig. 4 Forest plots for association between androgen receptor expression and pathological features of RCC including (**a**) pathological types, **b** pathological grade, and (**c**) pathological T stage (ccRCC: clear cell renal cell carcinoma; CI: confidence interval; G: grade)

When it comes to the association of AR with RCC, it is of essence that RCC is hormone-related based on integrated analyses of epidemiological, clinical, molecular-biological, and genetic findings. Abnormal expression of AR in RCC is linked with specific pathophysiology. In vitro experiments have demonstrated the role of AR in RCC progression through possible signaling pathways such as HIF2α/VEGF, circHIAT1/miR-195-5p/29a-3p/29c-3p/CDC42, and LncRNA-SARCC/miRNA-143- 3p [5, 46, 47]. Generally, proliferation, migration and invasion of RCC cell were enhanced after the exposure of moderate ADT, which consequently could be well inhibited by the antiandrogens or suppressing AR expression [48]. These in vitro results showed that AR might be the potential therapeutic target of RCC in favor of restraining the tumorigenesis and metastasis. But unfortunately, consensus could be hardly reached on the linkage between AR expression and RCC in patients. It seems equivocal that whether AR expression correlates to RCC susceptibility. What's more, it still remains unclear that whether enhancive AR expression is indicated for a low or high tumor grade and stage, and good or bad survival. Consequently, it can't be easily concluded that degradation of AR benefited to RCC patients. If a loss of AR expression was noted in advanced or metastatic RCC, inversely, supplementary AR with testosterone was vital in therapeutic strategies.

It is imperative to explore the clinical significance of AR expression in RCC. In this work, evaluation of the association between AR expression and clinicopathological features of RCC was evaluated, which revealed that higher expression was relative to male patients and lower pathological grade

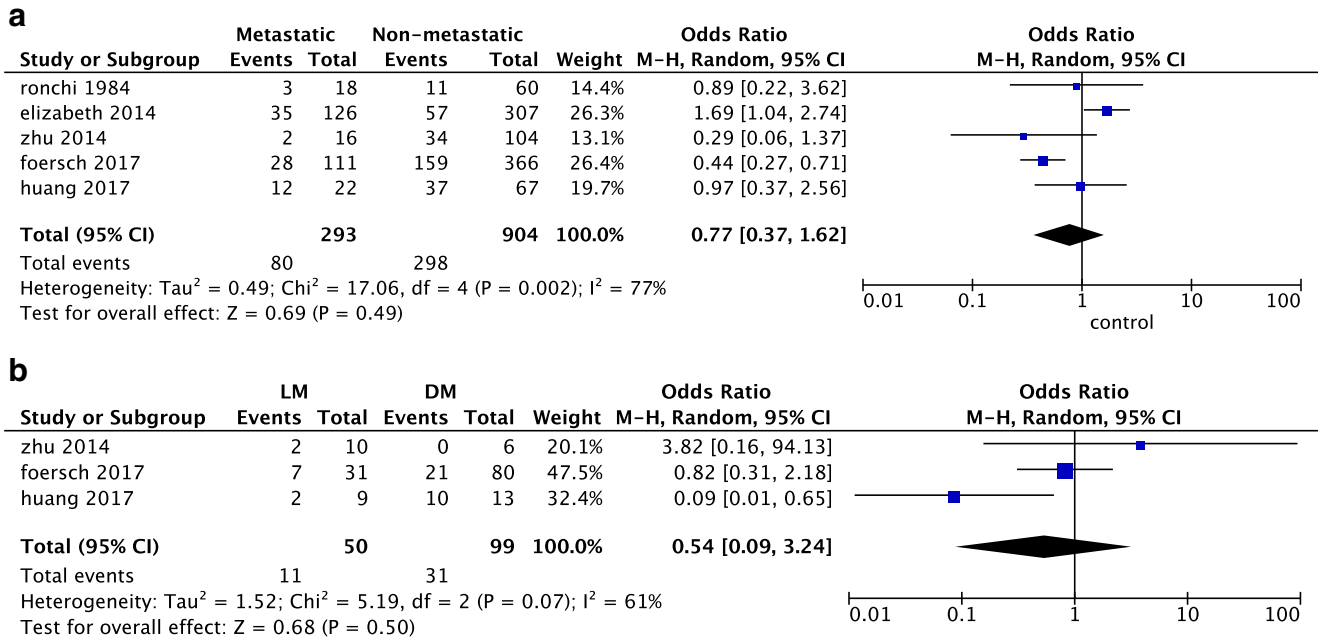

Fig. 5 Forest plots for association between androgen receptor expression and metastasis of renal cell carcinoma including (**a**) metastatic status and (**b**) metastatic type (CI: confidence interval; LM: lymphatic metastasis; DM: distant metastasis)

and earlier stage rather than the factors of RCC susceptibility, pathological type, metastatic status, metastatic type and the survival. It was found that increasing AR expression may not lead to worse survival results. These results contradicted what had been found in several studies in which AR was thought to be stimulative to the tumor progression. Based on these results in our study, target therapy of AR inhibitors for RCC may be not reliable. Moreover, studies of AR inhibitors for RCC patients should be taken into more consideration. It is crucial to explore more detailed and convincing proof on the direction and magnitude of the effect of AR expression on RCC.

However, it is regrettable that some reasons may be responsible for the divergence of results among studies and possible bias, which included district and ethnicity imparity, disparate methods for detecting AR, as well as the diversity of AR expression in various pathological subtypes of RCC. This meta-analysis includes the methods of PCR, IHC, and DCC for the detection of IHC. The difference in the definition of positive AR expression may confine the accuracies of results. Several other limitations in present meta-analysis should be also noted. It is a retrospective study which reduced the credibility of associations between AR and RCC. So in future, high-quality and large-sample prospective studies are in urge need for comprehensive evaluations in the association of AR with RCC risk.

Conclusions

In conclusion, it can be found that AR expression is significantly associated with male patients, lower tumor grade, and

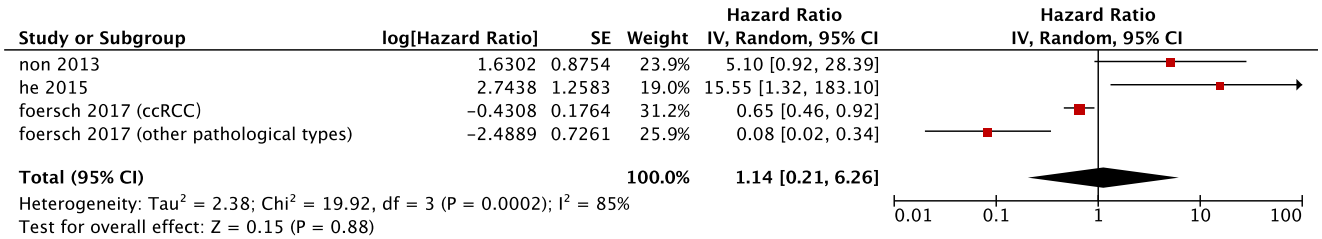

Fig. 6 Forest plots for association between androgen receptor expression and survival outcome of renal cell carcinoma patients (CI: confidence interval)

earlier tumor stage. And current evidence might not be in favor of the target therapy of AR inhibitors for advanced or metastatic RCC patients. In future, high-quality prospective studies are required for evaluating the association of AR with RCC risk.

Authors' Contributions study concepts and design: P Yuan, ZQ Ye, H Xu, ZQ Chen; literature research: P Yuan, Y Ge, S Wang; study selection, data extraction and quality assessment: P Yuan, Y Ge, X Liu, ZQ Chen; statistical analysis: P Yuan, Y Ge, X Liu; manuscript preparation: P Yuan, Y Ge, ZQ Chen; manuscript editing: P Yuan, S Wang, ZQ Chen; manuscript review: ZQ Ye, H Xu, ZQ Chen; All authors approved the final version to be published.

Data Availability All data were extracted from the articles cited in this manuscript.

Compliance with Ethical Standards

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Competing Interests The authors declare that they have no competing interests.

Abbreviations *AR,* Androgen receptor; *ccRCC,* Clear cell RCC; *CI,* Confidential interval; *CSS,* cancer-specific survival; *DCC,* Dextran-coated charcoal; *HIF,* Hypoxia-induced factor; *IHC,* Immunohistochemistry; *mTOR,* Mammalian target of rapamycin; *NA,* Not available; *OR,* Odds ratio; *PCR,* Polymerase chain reaction; *PDGF,* Platelet-derived growth factor; *PRISMA,* Preferred Reporting Items for Systematic Reviews and Meta-analyses; *pT,* pathological T; *RCC,* Renal cell carcinoma; *VEGF,* Vascular endothelial growth factor; *WB,* Western blot

References

1. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA Cancer J Clin 68:7–30
2. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, Clark PE, Davis BJ, Derweesh IH, Giambarresi L, Gervais DA, Hu SL, Lane BR, Leibovich BC, Pierorazio PM (2017) Renal mass and localized renal Cancer: AUA guideline. J Urol 198:520–529
3. Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, Egevad L, Algaba F, Moch H, Grignon DJ, Montironi R, Srigley JR, Members of the ISUP Renal Tumor Panel (2013) The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol 37:1490–1504
4. Kuthi L, Jenei A, Hajdu A, Németh I, Varga Z, Bajory Z, Pajor L, Iványi B (2017) Prognostic factors for renal cell carcinoma subtypes diagnosed according to the 2016 WHO renal tumor classification: a study involving 928 patients. Pathol Oncol Res 23:689–698
5. He D, Li L, Zhu G, Liang L, Guan Z, Chang L, Chen Y, Yeh S, Chang C (2014) ASC-J9 suppresses renal cell carcinoma progression by targeting an androgen receptor-dependent HIF2α/VEGF signaling pathway. Cancer Res 74:4420–4430
6. Zhang HL, Sheng XN, Li XS, Wang HK, Chi ZH, He ZS, Ye DW, Guo J (2017) Sorafenib versus sunitinib as first-line treatment agents in Chinese patients with metastatic renal cell carcinoma: the largest multicenter retrospective analysis of survival and prognostic factors. BMC Cancer 17:16
7. Chiarini F, Evangelisti C, McCubrey JA, Martelli AM (2015) Current treatment strategies for inhibiting mTOR in cancer. Trends Pharmacol Sci 36:124–135
8. Ciccarese C, Brunelli M, Montironi R, Fiorentino M, Iacovelli R, Heng D, Tortora G, Massari F (2016) The prospect of precision therapy for renal cell carcinoma. Cancer Treat Rev 49:37–44
9. Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, Chang YH, Escudier B, Donskov F, Magheli A, Carteni G, Laguerre B, Tomczak P, Breza J, Gerletti P, Lechuga M, Lin X, Martini JF, Ramaswamy K, Casey M, Staehler M, Patard JJ, S-TRAC Investigators (2016) Adjuvant Sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med 375:2246–2254
10. Matsumoto T, Sakari M, Okada M, Yokoyama A, Takahashi S, Kouzmenko A, Kato S (2013) The androgen receptor in health and disease. Annu Rev Physiol 75:201–224
11. Pihlajamaa P, Sahu B, Janne OA (2015) Determinants of receptor- and tissue-specific actions in androgen signaling. Endocr Rev 36:357–384
12. Bennett NC, Gardiner RA, Hooper JD, Johnson DW, Gobe GC (2010) Molecular cell biology of androgen receptor signalling. Int J Biochem Cell Biol 42:813–827
13. Yonekura S, Terauchi F, Hoshi K, Yamaguchi T, Kawai S (2018) Androgen receptor predicts first and multiple recurrences in non-muscle invasive urothelial carcinoma of the bladder. Pathol Oncol Res. https://doi.org/10.1007/s12253-018-0431-7
14. Olsen JR, Azeem W, Hellem MR, Marvyin K, Hua Y, Qu Y, Li L, Lin B, Ke XIS, Øyan AM, Kalland KH (2016) Context dependent regulatory patterns of the androgen receptor and androgen receptor target genes. BMC Cancer 16:377
15. Liang L, Li L, Tian J, Lee SO, Dang Q, Huang CK, Yeh S, Erturk E, Bushinsky D, Chang LS, He D, Chang C (2014) Androgen receptor enhances kidney stone-CaOx crystal formation via modulation of oxalate biosynthesis & oxidative stress. Mol Endocrinol 28:1291–1303
16. Li JY, Zhou T, Gao X, Xu C, Sun Y, Peng Y, Chang Z, Zhang Y, Jiang J, Wang L, Hou J (2010) Testosterone and androgen receptor in human nephrolithiasis. J Urol 184:2360–2363
17. Chow WH, Dong LM, Devesa SS (2010) Epidemiology and risk factors for kidney cancer. Nat Rev Urol 7:245–257
18. Bennett NC, Rajandram R, Ng KL, Gobe GC (2014) Evaluation of steroid hormones and their receptors in development and progression of renal cell carcinoma. J Kidney Cancer VHL 1:17–25
19. Langner C, Ratschek M, Rehak P, Schips L, Zigeuner R (2004) Steroid hormone receptor expression in renal cell carcinoma: an immunohistochemical analysis of 182 tumors. J Urol 171:611–614
20. Noh SJ, Kang MJ, Kim KM et al (2013) Acetylation status of P53 and the expression of DBC1, SIRT1, and androgen receptor are associated with survival in clear cell renal cell carcinoma patients. Pathology 45:574–580
21. Huang Q, Sun Y, Ma X, Gao Y, Li X, Niu Y, Zhang X, Chang C (2017) Androgen receptor increases hematogenous metastasis yet decreases lymphatic metastasis of renal cell carcinoma. Nat Commun 8:918
22. Foersch S, Schindeldecker M, Keith M, Tagscherer KE, Fernandez A, Stenzel PJ, Pahernik S, Hohenfellner M, Schirmacher P, Roth W,

Macher-Goeppinger S (2017) Prognostic relevance of androgen receptor expression in renal cell carcinomas. Oncotarget 8:78545–78555
23. Vrabel M (2015) Preferred reporting items for systematic reviews and meta-analyses. Oncol Nurs Forum 42:552–554
24. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25:603–605
25. Ha YS, Lee GT, Modi P, Kwon YS, Ahn H, Kim WJ, Kim IY (2015) Increased expression of androgen receptor mRNA in human renal cell carcinoma cells is associated with poor prognosis in patients with localized renal cell carcinoma. J Urol 194:1441–1448
26. Williams EM, Higgins JP, Sangoi AR, McKenney JK, Troxell ML (2015) Androgen receptor immunohistochemistry in genitourinary neoplasms. Int Urol Nephrol 4:81–85
27. Zhu G, Liang L, Li L, Dang Q, Song W, Yeh S, He D, Chang C (2014) The expression and evaluation of androgen receptor in human renal cell carcinoma. Urology 83:510 e19–5510e24
28. Nakano E, Tada Y, Fujioka H, Matsuda M, Osafune M, Kotake T, Sato B, Takaha M, Sonoda T (1984) Hormone receptor in renal cell carcinoma and correlation with clinical response to endocrine therapy. J Urol 132:240–245
29. Klotzl G, Otto U, Becker H, Klosterhalfen H (1987) Determination of androgen, progestin and estrogen receptors with two different assays in renal cell carcinoma. Urol Int 42:100–104
30. Ronchi E, Pizzocaro G, Miodini P, Piva L, Salvioni R, Di Fronzo G (1984) Steroid hormone receptors in normal and malignant human renal tissue: relationship with progestin therapy. J Steroid Biochem 21:329–335
31. Concolino G, Marocchi A, Toscano V, Di Silverio F (1981) Nuclear androgen receptor as marker of responsiveness to medroxyprogesterone acetate in human renal cell carcinoma. J Steroid Biochem 15:397–402
32. Koryakina Y, Ta HQ, Gioeli D (2014) Androgen receptor phosphorylation: biological context and functional consequences. Endocr Relat Cancer 21:T131–T145
33. Lin WJ, Izumi K (2014) Androgen receptor, ccl2, and epithelial-mesenchymal transition: a dangerous affair in the tumor microenvironment. Oncoimmunology 3:e27871
34. Tonelli F, Alossaimi M, Williamson L, Tate RJ, Watson DG, Chan E, Bittman R, Pyne NJ, Pyne S (2013) The sphingosine kinase inhibitor 2-(p-hyroxyanilino)-4-(p-chlorophenyl) thiazole reduces androgen receptor expression via an oxidative stress- dependent mechanism. Br J Pharmacol 168:1497–1505
35. Carver BS (2014) Strategies for targeting the androgen receptor axis in prostate cancer. Drug Discov Today 19:1493–1497
36. Miyamoto H, Yang Z, Chen YT, Ishiguro H, Uemura H, Kubota Y, Nagashima Y, Chang YJ, Hu YC, Tsai MY, Yeh S, Messing EM, Chang C (2007) Promotion of bladder cancer development and progression by androgen receptor signals. J Natl Cancer Inst 99:558–568
37. Chang C, Lee SO, Yeh S, Chang TM (2014) Androgen receptor (AR) differential roles in hormone-related tumors including prostate, bladder, kidney, lung, breast and liver. Oncogene 33:3225–3234
38. Schweizer MT, Yu EY (2017) AR-signaling in human malignancies: prostate cancer and beyond. Cancers (Basel) 9:7
39. Vera-Badillo FE, Templeton AJ, de Gouveia P, Diaz-Padilla I, Bedard PL, al-Mubarak M, Seruga B, Tannock IF, Ocana A, Amir E (2014) Androgen receptor expression and outcomes in early breast cancer: a systematic review and meta-analysis. J Natl Cancer Inst 106:djt319
40. Grogg A, Trippel M, Pfaltz K, Lädrach C, Droeser RA, Cihoric N, Salhia B, Zweifel M, Tapia C (2015) Androgen receptor status is highly conserved during tumor progression of breast cancer. BMC Cancer 15:872
41. Gucalp A, Tolaney S, Isakoff SJ, Ingle JN, Liu MC, Carey LA, Blackwell K, Rugo H, Nabell L, Forero A, Stearns V, Doane AS, Danso M, Moynahan ME, Momen LF, Gonzalez JM, Akhtar A, Giri DD, Patil S, Feigin KN, Hudis CA, Traina TA, on behalf of the Translational Breast Cancer Research Consortium (TBCRC 011) (2013) Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic breast Cancer. Clin Cancer Res 19:5505–5512
42. Ma WL, Lai HC, Yeh S, Cai X, Chang C (2014) Androgen receptor roles in hepatocellular carcinoma, fatty liver, cirrhosis and hepatitis. Endocr Relat Cancer 21:R165–R182
43. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, Kuczyk MA, Lam T, Marconi L, Merseburger AS, Mulders P, Powles T, Staehler M, Volpe A, Bex A (2015) EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 67:913–924
44. Tosco L, Van Poppel H, Frea B, Gregoraci G, Joniau S (2013) Survival and impact of clinical prognostic factors in surgically treated metastatic renal cell carcinoma. Eur Urol 63:646–652
45. Kim SH, Kim S, Joo J, Seo HK, Joung JY, Lee KH, Chung J (2016) A retrospective study of predictive factors for unexpectedly prolonged or shortened progression-free survival and overall survival among patients with metastatic renal cell carcinoma who received first-line targeted therapy. BMC Cancer 16:577
46. Wang K, Sun Y, Tao W, Fei X, Chang C (2017) Androgen receptor (AR) promotes clear cell renal cell carcinoma (ccRCC) migration and invasion via altering the circHIAT1/miR-195-5p/29a-3p/29c-3p/CDC42 signals. Cancer Lett 394:1–12
47. Zhai W, Sun Y, Guo C, Hu G, Wang M, Zheng J, Lin WY, Huang Q, Li G, Zheng J, Chang C (2017) LncRNA-SARCC suppresses renal cell carcinoma (RCC) progression via altering the androgen receptor (AR)/miRNA-143-3p signals. Cell Death Differ 24:1502–1517
48. Czarnecka AM, Niedzwiedzka M, Porta C, Szczylik C (2016) Hormone signaling pathways as treatment targets in renal cell cancer (review). Int J Oncol 48:2221–2235