Association of hypoxia-inducible factor-1α (HIF1α) 1772C/T gene polymorphism with susceptibility to renal cell carcinoma/prostate cancer

HONGYAN LI¹,²; CHUNLING LIAO²; WENJUAN WENG²; HONGZHEN ZHONG²; TIANBIAO ZHOU³;*¹

¹ Department of Nephrology, Huadu District People’s Hospital of Guangzhou, Southern Medical University, Guangzhou, China
² Department of Nephrology, The Second Affiliated Hospital of Shantou University Medical College, Shantou, 515041, China

Key words: Renal cell carcinoma (RCC), Prostate cancer, Hypoxia-inducible factor-1α (HIF1α), 1772C/T gene polymorphism, Meta-analysis

Abstract: In this study, we used a meta-analysis method to evaluate the relationship between hypoxia-inducible factor-1α (HIF1α) 1772C/T gene polymorphism (rs 11549465) and renal cell carcinoma (RCC)/prostate cancer risk. We searched for relevant studies (before March 1, 2019) on Cochrane Library, Embase, and PubMed. Studies meeting the inclusion criteria were recruited into this meta-analysis. The outcome of dichotomous data was showed in the way of odds ratios (OR), and 95% confidence intervals (CI) were also counted. In this investigation, there was no association between HIF1α 1772C/T gene polymorphism and susceptibility to RCC in Caucasians, Asians as well as overall populations. In addition, HIF1α 1772C/T gene polymorphism was not found to be relevant to the survival in RCC. Interestingly, the T allele was relevant to prostate cancer risk in all populations, but not in Caucasians and Asians. However, the TT genotype and the CC genotype were not related to prostate cancer susceptibility in Asian, Caucasian, and all populations. In conclusion, the T allele of the HIF1α 1772C/T gene polymorphism was related to prostate cancer risk in the overall populations.

Introduction

Renal cell carcinoma is one of the most common renal neoplasms, accounting for approximately 3.9% of new cancers, and its morbidity was also on the rise in the past two decades (Pan et al., 2018; Hu et al., 2017). Cancer prognosis is affected by the underlying tumor biology and also by the host inflammatory response to the disease (Chaves et al., 2018). Surgery and other treatments like conventional chemotherapy and radiotherapy are applied to RCC, but it still has the highest mortality and recurrence rate among the genitourinary carcinomas (Pan et al., 2018; Zhang et al., 2018; Zhao et al., 2018). Prostate cancer contributes the most to morbidity and mortality in men all over the world, while its morbidity has had a significant increase in recent years (Ramalho-Carvalho et al., 2018; Bernal-Ramos et al., 2017). In order to overcome the treatment resistance that occurs with recurrence, it is rather critical to developing more effective methods for early diagnosis and treatment for prostate cancer (Wang et al., 2018b). The current evidence suggests that genetic factors contribute to the risk of RCC and prostate cancer.

HIF1α, a member of the HIF transcription factor family, controls various cellular pathways involved in embryonic development and many normal physiological processes such as cell apoptosis, response to hypoxia chemotaxis, and proliferation. HIF1α is also essential for cell survival, energy metabolism, angiogenesis, progression, and metastasis of tumors (Maybin et al., 2018; Qian et al., 2018; Wang et al., 2018a; Wilkes et al., 2018). HIF1α 1772C/T (rs11549465) gene polymorphism increases the risk of certain cancers (Wang et al., 2018a; Kang et al., 2011; Anam et al., 2015; Li et al., 2015). However, some investigations revealed that the HIF1α 1772C/T (rs 11549465) gene polymorphism was not related to the risk of other cancers like hepatocellular carcinoma and colorectal cancer (Liu et al., 2014; Xu et al., 2014). The available evidence is insufficient to justify the divergence and sparse data in the reported studies. This meta-analysis was performed to assess whether the gene polymorphism of HIF1α 1772C/T (rs 11549465) is related to the susceptibility to RCC and prostate cancer.

Methods

Search strategy

We searched Cochrane Library, Embase, and PubMed (from inception to March 1, 2019) to identify eligible studies using the search terms “hypoxia-inducible factor-1α” or “HIF1α”.  

Doi: 10.32604/biocell.2020.08826 www.techscience.com/journal/biocell
### TABLE 1

Characteristics of studies evaluating the effects of hypoxia-inducible factor-1α (HIF1α) 1772C/T gene polymorphism on renal cell carcinoma and prostate cancer risk

| Cancer Types               | Author, Year | Country   | Ethnicity | Case     | Control | Case     | Control | Odds Ratio M-H, Fixed, 95% CI | Year |
|----------------------------|--------------|-----------|-----------|----------|---------|----------|---------|-------------------------------|------|
| Renal cell carcinoma       | Clifford 2001 | UK        | Caucasian | 0 6 42   | 6 27 110 |          |         |                                |      |
|                            | Ollerenshaw 2004 | UK         | Caucasian | 90 54 16 | 71 90 1   |          |         |                                |      |
|                            | Morris 2009    | Poland    | Caucasian | 3 39 290 | 5 46 262  |          |         |                                |      |
|                            | Qin 2012       | China     | Asian     | 2 46 572 | 3 43 578  |          |         |                                |      |
| Prostate cancer            | Chau 2005      | USA       | Mix       | 6 29 161 | 3 14 179  |          |         |                                |      |
|                            | Li 2007        | USA       | Mix       | 14 209 818 | 18 221 995 |          |         |                                |      |
|                            | Orr-Urtreger 2007 | Israel   | Caucasian | 16 99 287 | 3 80 217  |          |         |                                |      |
|                            | Foley 2009     | Ireland   | Caucasian | 0 30 65  | 0 13 175  |          |         |                                |      |
|                            | Li 2012        | China     | Asian     | 2 48 612 | 0 57 659  |          |         |                                |      |
|                            | Fraga 2014     | Portugal  | Caucasian | 11 164 579| 14 156 566|          |         |                                |      |

**FIGURE 1.** Association between hypoxia-inducible factor-1α (HIF1α) 1772C/T gene polymorphism and renal cell carcinoma susceptibility in overall populations.
and “renal cell carcinoma” or “renal cancer” or “RCC” or “prostate cancer”.

Inclusion and exclusion criteria
Inclusion criteria: (1) the disease had to be renal cancer, prostate cancer; (2) two comparison groups (case group vs. control group) had to be included; (3) the detailed genotype distribution data should be provided.

Exclusion criteria: (1) editorials, case reports, and review articles; (2) when the main results did not include HIF1α 1772C/T and outcome; (3) the effect of HIF1α gene levels on disease was investigated and (4) when detailed genotype distribution of HIF1α 1772C/T was not provided.

Data extraction and synthesis
From every eligible investigation, we extracted the important information, which was the first author’s surname, publication year, and number of patients with RCC, prostate cancer and control patients for HIF1α 1772C/T genotypes. The frequency of HIF1α 1772C/T in each control and case group was counted in accordance with the corresponding genotype distribution. Survival data of renal cell or prostate cancer was also extracted.

Statistical analysis
Each statistical analysis was conducted by means of the Cochrane Review Manager Version 5 (Cochrane Library, UK). The calculated statistics were summarized with the help of a fixed-effects model, but once the p-value of the heterogeneity test was under 0.1, a random-effects model (Der Simonian-Laird method) had to be used. The outcomes were expressed as the odds ratio (OR) of the binary data with 95% confidence intervals (CI). Statistical significance was found when the pooled OR had a P < 0.05. The heterogeneity test was tested by I²-value among included studies.

Results

| Cancer Type          | Group and subgroups | Studies Number | Q test p-value | Model selected | OR (95%CI)          | P     |
|----------------------|---------------------|----------------|----------------|----------------|---------------------|-------|
| Renal cell carcinoma | T vs. C             | 4              | 0.15           | Fixed          | 0.91 (0.73, 1.12)  | 0.37  |
|                      | Caucasian           | 3              | 0.10           | Fixed          | 0.85 (0.66, 1.10)  | 0.21  |
|                      | Asian               | 1              | –              | Fixed          | 1.07 (0.71, 1.61)  | 0.74  |
|                      | TT vs. TC+CC        | 4              | 0.28           | Fixed          | 1.37 (0.92, 2.04)  | 0.12  |
|                      | Caucasian           | 3              | 0.16           | Fixed          | 1.39 (0.92, 2.08)  | 0.11  |
|                      | Asian               | 1              | –              | Fixed          | 1.00 (0.14, 7.16)  | 1.00  |
|                      | CC vs. TC+TT        | 4              | 0.02           | Random         | 1.60 (0.84, 3.04)  | 0.15  |
|                      | Caucasian           | 3              | 0.03           | Random         | 2.47 (0.87, 6.97)  | 0.09  |
|                      | Asian               | 1              | –              | Fixed          | 0.93 (0.61, 1.42)  | 0.73  |
| Prostate cancer      | T vs. C             | 6              | <0.0001        | Random         | 1.38 (1.02, 1.87)  | 0.04  |
|                      | Caucasian           | 3              | <0.0001        | Random         | 1.64 (0.86, 3.13)  | 0.13  |
|                      | Asian               | 1              | –              | Fixed          | 0.99 (0.67, 1.45)  | 0.94  |
|                      | TT vs. TC+CC        | 6              | 0.13           | Fixed          | 1.29 (0.84, 1.98)  | 0.24  |
|                      | Caucasian           | 3              | 0.02           | Random         | 1.65 (0.31, 8.71)  | 0.55  |
|                      | Asian               | 1              | –              | Fixed          | 5.42 (0.26, 113.18)| 0.28  |
|                      | CC vs. TC+TT        | 6              | <0.00001       | Random         | 0.71 (0.51, 1.00)  | 0.05  |
|                      | Caucasian           | 3              | <0.00001       | Random         | 0.59 (0.28, 1.23)  | 0.16  |
|                      | Asian               | 1              | –              | Fixed          | 1.06 (0.71, 1.57)  | 0.78  |
| Survival of renal cell carcinoma | T vs. C | 2 | 0.08 | Random | 0.88 (0.07, 10.66) | 0.92 |
|                      | TT vs. TC+CC        | 2              | –              | Fixed          | 2.80 (0.30, 25.92) | 0.36  |
|                      | CC vs. TC+TT        | 2              | 0.07           | Random         | 1.14 (0.08, 16.32) | 0.92  |

Statistical analysis
Each statistical analysis was conducted by means of the Cochrane Review Manager Version 5 (Cochrane Library, UK). The calculated statistics were summarized with the help of a fixed-effects model, but once the p-value of the heterogeneity test was under 0.1, a random-effects model (Der Simonian-Laird method) had to be used. The outcomes were expressed as the odds ratio (OR) of the binary data with 95% confidence intervals (CI). Statistical significance was found when the pooled OR had a P < 0.05. The heterogeneity test was tested by I²-value among included studies.

Results

Study characteristics for relationship between the HIF1α 1772C/T gene polymorphism and susceptibility to RCC
In order to study the relationship between HIF1α 1772C/T gene polymorphism and RCC risk (Tab. 1), our meta-analysis recruited four studies (Clifford et al., 2001; Ollerenshaw et al., 2004; Morris et al., 2009; Qin et al., 2012), which contained 1160 case series and 1241 controls. And the relevant data was extracted by the first author's
surname, publication year, and the number of patients with RCC and controls for the HIF1α 1772C/T genotype (Tab. 1).

**Study characteristics for relationship between HIF1α 1772C/T gene polymorphism and susceptibility to prostate cancer**

Six studies (Orr-Urtreger et al., 2007; Li et al., 2007, 2012; Foley et al., 2009; Fraga et al., 2014; Chau et al., 2005) including 3150 case series and 3370 controls were included in our research to find the relationship between HIF1α 1772C/T gene polymorphism and the prostate cancer risk (Tab. 1).

**Study characteristics for the relationship between the HIF1α 1772C/T gene polymorphism and the RCC survival**

Two studies (Qin et al., 2012; Ferreira et al., 2017) were recruited into our research to find the association of the HIF1α 1772C/T gene polymorphism with the RCC survival.

**Association of the HIF1α 1772C/T gene polymorphism with prostate cancer susceptibility**

T allele was relevant to the susceptibility to prostate cancer in the whole populations, but not in Asians or Caucasians (the whole populations: T: OR = 1.38, 95% CI: 1.02–1.87, P = 0.04; Fig. 2 and Tab. 2). TT genotype and CC genotype were not relevant to prostate cancer susceptibility in the overall population, Asians, and Caucasians (Overall: TT: OR = 1.29, 95% CI: 0.84–1.98, P = 0.24; CC: OR = 0.71, 95% CI: 0.51–1.00, P = 0.05; Fig. 2 and Tab. 2).

**Association of the HIF1α 1772C/T gene polymorphism with the survival of RCC**

HIF1α 1772C/T gene polymorphism is not related to RCC survival in the overall population (T: OR = 0.88, 95% CI: 0.73–1.12, P = 0.37; TT: OR = 1.37, 95% CI: 0.92–2.04, P = 0.12; CC: OR = 1.60, 95% CI: 0.84–3.04, P = 0.15; Fig. 1 and Tab. 2), Caucasians and Asians.

---

**FIGURE 2.** Association between hypoxia-inducible factor-1α (HIF1α) 1772C/T gene polymorphism and prostate cancer susceptibility in overall populations.
In this study, we investigated the relationship between the HIF1α 1772C/T gene polymorphism (rs11549465) and susceptibility to RCC/prostate cancer. We did not find a relationship between HIF1α 1772C/T gene polymorphism and RCC susceptibility or survival for the overall population, neither for Caucasians nor Asian populations individually. It was interesting to find that the T allele was related to prostate cancer risk in overall populations, but not in Caucasians and Asian populations. However, the TT and CC genotypes had no relationship with prostate cancer susceptibility in the whole populations, Asians, and Caucasians.

There were some other meta-analyses in previous papers from this group. Li et al. (2015) completed a meta-analysis on the association of HIF1α 1772C/T gene polymorphism with cancer risk, reporting that HIF1α 1772C/T gene polymorphism is not associated with susceptibility to renal cell carcinoma/prostate cancer. Li et al. (2013) made a meta-analysis reporting that HIF1α 1772C/T gene polymorphism was not either associated with susceptibility to renal cell carcinoma/prostate cancer. Anam et al. (2015) reported that the HIF1α 1772C/T gene polymorphism was not related to susceptibility to RCC/prostate cancer by means of a meta-analysis containing genome-wide association studies of HIF1α 1772C/T polymorphism with cancer risk. These meta-analyses mentioned above were not performed by ethnicity. Our results revealed that the HIF1α 1772C/T gene polymorphism was not related to the RCC risk among Caucasians, Asians, and overall populations. Additionally, there was no association between the HIF1α 1772C/T gene polymorphism and survival in RCC. Interestingly, the T allele was related to the risk of prostate cancer among all populations, but not among Caucasians and Asian populations. However, the TT genotype and the CC genotype were not related to prostate cancer susceptibility among Asians, Caucasians, and overall populations. These results add new information inferred by our further analysis considering the different ethnic groups.

**Conclusion**

This meta-analysis suggests that the T allele was related to the risk of prostate cancer in the overall populations, but not in Caucasians and Asians. However, additional correlation research is needed to further confirm their association.

**Abbreviations:** HIF1α: hypoxia-inducible factor-1α; OR: Odds ratios; CI: confidence intervals.

**Funding Statement:** This study was supported by the Guangzhou Medical Key Discipline Construction Project (2017-2019) and the Science and Technology Project of Shantou (Shanfuke (2019) 106-4: 190606165268433).

**Conflicts of Interest:** The authors declare that they have no conflicts of interest to report regarding the present study.

**Availability of Data and Materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors’ Contributions:** TBZ was in charge of conceiving and designing the study. TBZ, CLL and HYL were responsible for the collection of data and performing the statistical analysis and manuscript preparation. CLL and WJJ were responsible for checking the data. All authors were responsible for drafting the manuscript, reading it, and approving the final version.

**References**

Anam MT, Ishika A, Hassain MB, Jesmin (2015). A meta-analysis of hypoxia inducible factor 1-alpha (HIF1A) gene polymorphisms: association with cancers. *Biomarker Research* **3**: 29. DOI 10.1186/s40364-015-0054-z.

Bernal-Ramos G, Hernández-Gallegos E, Vera E, Chávez-López MG, Zúñiga-García V, Sánchez-Pérez Y, Garrido E, Camacho J (2017). Astemizole inhibits cell proliferation in human prostate tumorigenic cells expressing ether α-go-go-1 potassium channels. *Cellular and Molecular Biology* **63**: 11–13. DOI 10.14715/cmb/2017.63.12.4.

Chaves KC, Costa EM, Teixeira LF, Bellini MH (2018). Impact of endostatin gene therapy on myeloid-derived suppressor cells from a metastatic renal cell carcinoma. *Experimental Oncology* **40**: 24–32. DOI 10.31768/2312-8852.2018.40 (1):24-32.

Chau CH, Pemterm MG, Steinberg SM, Retter AS, Dahut WL, Price DK, Figg WD (2005). Polymorphism in the hypoxia-inducible factor 1α gene may confer susceptibility to androgen-independent prostate cancer. *Cancer Biology & Therapy* **4**: 1222–1225. DOI 10.4161/cbt.4.11.2091.

Clifford SC, Astuti D, Hooper L, Maxwell PH, Ratcliffe PJ, Maher ER (2001). The pVHL-associated SCF ubiquitin ligase complex: molecular genetic analysis of elongin B and C, Rbx1 and HIF-1α in renal cell carcinoma. *Oncogene* **20**: 5067–5074. DOI 10.1038/sj.onc.1204602.

Ferreira M, Teixeira A, Maurice J, Lobo F, Morais A, Medeiros R (2017). Hypoxia and renal cell carcinoma: the influence of HIF1A+1772C/T functional genetic polymorphism on prognosis. *Urologic Oncology: Seminars and Original Investigations* **35**: 532.e25–532.e30. DOI 10.1016/j.urologic.2017.04.002.

Foley R, Marignol L, Thomas AZ, Cullen IM, Perry AS, Tewari P, O’Grady A, Kay E, Dunne B, Loftus B, Watson WR, Fitzpatrick JM, Woodson K, Lehman T, Hollywood D, Lynch TH, Lawler M (2009). The HIF-1α C1772T polymorphism may be associated with susceptibility to clinically localised prostate cancer but not with elevated expression of hypoxic biomarkers. *Cancer Biology & Therapy* **8**: 118–124. DOI 10.4161/cbt.8.2.7086.

Fraga A, Ribeiro R, Principe P, Lobato C, Pina F, Mauricio J, Monteiro C, Sousa H, Calais da Silva F, Lopes C, Medeiros R (2014). The HIF1A functional genetic polymorphism at locus +1772 associates with progression to metastatic prostate cancer and refractoriness to hormonal castration. *European Journal of Cancer* **50**: 359–365. DOI 10.1016/j.ejca.2013.09.001.

Hu SH, Zhao MJ, Wang WX, Xu CW, Wang GD (2017). TRIM59 is a key regulator of growth and migration in renal cell carcinoma. *Cellular and Molecular Biology* **63**: 68–74. DOI 10.14715/cmb/2017.63.5.13.
Kang MJ, Jung SA, Jung JM, Kim SE, Jung HK, Kim TH, Shin KN, Yi SY, Yoo K, Moon IH (2011). Associations between single nucleotide polymorphisms of MPP2, VEGF, and HIF1A genes and the risk of developing colorectal cancer. *Anticancer Research* **31**: 575–584.

Li P, Cao Q, Shao PF, Cai HZ, Zhou H, Chen JW, Qin C, Zhang ZD, Ju XB, Yin CJ (2012). Genetic polymorphisms in HIF1A are associated with prostate cancer risk in a Chinese population. *Asian Journal of Andrology* **14**: 864–869. DOI 10.1038/aja.2012.101.

Li D, Liu J, Zhang W, Ren J, Yan L, Liu H, Xu Z (2013). Association between HIF1A P582S and A588T polymorphisms and the risk of urinary cancers: a meta-analysis. *PloS One* **8**: e63445. DOI 10.1371/journal.pone.0063445.

Li H, Bubley GJ, Balk SP, Gaziano JM, Pollak M, Stampfer MJ, Ma J (2007). Hypoxia-inducible factor-1α (HIF-1α) gene polymorphisms, circulating insulin-like growth factor binding protein (IGFBP)-3 levels and prostate cancer. *Prostate* **67**: 1354–1361. DOI 10.1002/pros.20589.

Li Y, Li C, Shi H, Lou L, Liu P (2015). The association between the rs11549465 polymorphism in the hif-1α gene and cancer risk: a meta-analysis. *International Journal of Clinical and Experimental Medicine* **8**: 1561–1574.

Liu Y, Sui J, Zhai L, Yang S, Huang L, Huang L, Mo C, Wu J, Li S, Qin X (2014). Genetic polymorphisms in hypoxia-inducible factor-1α gene and its association with HBV-related hepatocellular carcinoma in a Chinese population. *Medical Oncology* **31**: 200. DOI 10.1007/s12032-014-0200-8.

Maybin JA, Murray AA, Saunders PTK, Hirani N, Carmeliet P, Critchley HOD (2018). Hypoxia and hypoxia inducible factor-1α are required for normal endometrial repair during menstruation. *Nature Communications* **9**: 295. DOI 10.1038/s41467-017-02357-6.

Morris MR, Hughes DJ, Tian YM, Ricketts CJ, Lau KW, Gentle D, Shuib S, Serrano-Fernandez P, Lubinski J, Wiesener MS, Pugh CW, Latif F, Ratcliffe PJ, Maher ER (2009). Mutation analysis of hypoxia-inducible factors HIF1A and HIF2A in renal cell carcinoma. *Anticancer Research* **29**: 4337–4343.

Ollerenshaw M, Page T, Hammonds J, Demaine A (2004). Polymorphisms in the hypoxia inducible factor-1α gene (HIF1A) are associated with the renal cell carcinoma phenotype. *Cancer Genetics and Cytogenetics* **153**: 122–126. DOI 10.1016/j.canregcyto.2004.01.014.

Orr-Urtreger A, Bar-Shira A, Matzkin H, Majbrees N (2007). The homozygous P582S mutation in the oxygen-dependent degradation domain of HIF-1α is associated with increased risk for prostate cancer. *Prostate* **67**: 8–13. DOI 10.1002/pros.20433.

Pan X, Quan J, Li ZW, Zhao LW, Zhou L, Xu JN, Xu WJ, Guan X, Li H, Yang SQ, Gui YT, Lai YQ (2018). miR-566 functions as an oncogene and a potential biomarker for prognosis in renal cell carcinoma. *Biomedicine & Pharmacotherapy* **102**: 718–727. DOI 10.1016/j.biopha.2018.03.072.

Qian J, Shen S, Chen W, Chen N (2018). Propofol reversed hypoxia-induced docetaxel resistance in prostate cancer cells by preventing epithelial-mesenchymal transition by inhibiting hypoxia-inducible factor 1α. *BioMed Research International* **2018**: 4174232.

Qin C, Cao Q, Ju X, Wang M, Meng X, Zhu J, Yan F, Li P, Ding Q, Chen J, Gu M, Zhang W, Yin C, Zhang Z (2012). The polymorphisms in the VHL and HIF1A genes are associated with the prognosis but not the development of renal cell carcinoma. *Annals of Oncology* **23**: 981–989. DOI 10.1093/annonc/mds252.

Ramalho-Carvalho J, Gonçalves CS, Graça I, Bidar D, Pereira-Silva E, Salta S, Godinho MJ, Gomez A, Esteller M, Costa BM, Henrique R, Jerónimo C (2018). A multiplatform approach identifies miR-152-3p as a common epigenetically regulated onco-suppressor in prostate cancer targeting TME9M7. *Clinical Epigenetics* **10**: 40. DOI 10.1186/s13474-018-0475-2.

Wang W, Wu BQ, Chen GB, Zhou Y, Li ZH, Zhang JL, Ding YL, Zhang P, Wang JQ (2018a). Hypoxia-inducible factor-1α rs1154946 C>T and rs11549467 G>A gene polymorphisms are associated with an increased risk of digestive cancers in Asians. *Journal of Cancer Research and Therapeutics* **14**: 46–53.

Wang Q, Yang CS, Ma ZX, Chen JC, Zheng JN, Sun XQ, Wang JQ (2018b). Inhibition of prostate cancer DU145 cell growth with small interfering RNA targeting the SATB1 gene. *Experimental and Therapeutic Medicine* **15**: 3028–3033.

Wilkes JG, O’Leary BR, Du J, Klinger AR, Sibenaller ZA, Doskey CM, Gibson-Corley KN, Alexander MS, Tsai S, Buettner GR, Cullen JJ (2018). Pharmacologic ascorbate (P-AscH2O) suppresses hypoxia-inducible Factor-1α (HIF-1α) in pancreatic adenocarcinoma. *Clinical & Experimental Metastasis* **35**: 37–51. DOI 10.1007/s10585-018-9876-z.

Xu J, Zou LY, Yang L, He XL, Sun M (2014). Common polymorphisms in the HIF-1α gene confer susceptibility to digestive cancer: a meta-analysis. *Genetics and Molecular Research* **13**: 6228–6238. DOI 10.4238/2014.August.15.5.

Zhang S, Ren Y, Qiu J (2018). Dauricine inhibits viability and induces cell cycle arrest and apoptosis via inhibiting the PI3K/Akt signaling pathway in renal cell carcinoma cells. *Molecular Medicine Reports* **17**: 7403–7408.

Zhao Q, Zhu Y, Liu L, Wang H, Jiang S, Hu X, Guo J (2018). STK39 blockage by RNA interference inhibits the proliferation and induces the apoptosis of renal cell carcinoma. *OncoTargets and Therapy* **11**: 1511–1519. DOI 10.2147/OTT.S153806.