

## Original Article

# Prognostic significance of circulating insulin growth-like factor 1 and insulin growth-like factor binding protein 3 in renal cell carcinoma patients

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**Abstract:** Insulin growth-like factor-1 (IGF-1) and its main binding protein insulin growth-like factor binding protein 3 (IGFBP-3) play important roles in cancer development and progression. We hypothesize that circulating IGF-1 and IGFBP-3 may have significant prognostic values in renal cell carcinoma (RCC) patients. We used 1,010 histologically confirmed RCC patients in this case series study to test this hypothesis. We constructed a weighted genetic risk score (GRS) using a large panel of genome-wide association study (GWAS)-identified single nucleotide polymorphisms (SNPs) to predict circulating IGF-1 and IGFBP-3 level, respectively. We analyzed the associations of the GRS with the prognosis of RCC patients using multivariate Cox proportional hazards model. We found significant associations between genetically predicted circulating IGF-1 level, but not IGFBP-3, and RCC prognosis. RCC patients with better prognosis had significantly higher baseline circulating IGF-1 level than those with worse prognosis. Dichotomized at the median value of GRS, patients with high IGF-1 exhibited significantly lower risks of recurrence (HR=0.81, 95% CI, 0.65-0.99, P=0.045) and death (HR=0.74, 95% CI, 0.60-0.91, P=0.004). If patients were dichotomized at the 75% value of GRS, those with the highest quarter of GRS had 27% lower risk of recurrence (OR=0.73, 95% CI, 0.55-0.96, P=0.025) and 34% lower risk of death (OR=0.66, 95% CI, 0.50-0.87, P=0.003) than the other three quarters of patients. High IGF-1/IGFBP-3 ratio was also associated with reduced risks of recurrence and survival. In conclusion, high circulating IGF-1 level and IGF-1/IGFBP-3 ratio at diagnosis is associated with better prognosis in RCC patients.

**Keywords:** Renal cell carcinoma, IGF-1, IGFBP-3, recurrence, survival, genetic risk score

## Introduction

Cancers of kidney and renal pelvis are the sixth most common cancer in men and ninth in women, with an estimated incidence of 76,080 in 2021 in the United States [1]. The incidences of kidney cancer continue to increase in both men and women in the U.S. [1, 2]. Renal cell carcinoma (RCC) accounts for approximately 90% of adult kidney cancers and is the most lethal genitourinary cancer. About two thirds of RCC patients present with localized diseases at diagnosis and one third are diagnosed with regional and distant metastatic diseases [2].

Patients with localized diseases can be cured by nephrectomy, however, up to 40% of patients will develop local and distant recurrence and eventually succumb to this disease [3]. To improve prognosis of locoregional RCC, effective adjuvant therapy is clearly needed. Targeted and immune checkpoint therapies have been and are being actively tested as adjuvant therapies for RCC in clinical trials [4, 5]. Sunitinib was approved by FDA as an adjuvant therapy for RCC and improved disease-free survival time by 1.2 years, but significant adverse events occurred that caused dose reductions in over one third and discontinua-

tions in 28.1% of the patients [6]. If clinicians can pre-select patient for adjuvant therapy based on accurate risk stratification algorithm, then only those patients with better prognosis would be good candidates for adjuvant therapy, maximizing clinical benefit whereas avoiding unnecessary adverse effects. The current clinically used nomograms for predicting recurrence risk in surgically resected RCC rely solely on clinicopathologic variables, such as histology, TNM stage, Fuhrman grade, tumor size, and performance status [4]. Identifying independent prognostic biomarkers has the potential to supplement clinical variables and improve the prediction efficiency of recurrence and survival in locoregional RCC patients [7, 8].

Insulin and insulin-like growth factor-1 (IGF-1) is a key molecule in energy metabolism and plays numerous cellular functions including proliferation, differentiation, migration, and apoptosis [9, 10]. Most IGF-1 proteins are bound by IGF-binding proteins (IGFBP), among which IGFBP-3 is the most abundant and binds to approximately 80% of IGF-1 [11, 12]. Binding of IGFBP-3 to IGF-1 blocks the binding of IGF-1 to its receptor and inhibits downstream signaling events, therefore, IGFBP-3 is a negative regulator of IGF-1. Dysregulation of IGF-1 signaling pathways has been implicated in a variety of cancer development and progression, including RCC [9, 10, 13-15]. IGF-1 is highly expressed in over 80% of RCC tumors, whereas IGF-2 is not detectable in RCC tumors [16]. Higher circulating level of IGF-1 has been associated with increased risks of prostate, breast, and colorectal cancers in large prospective UK Biobank study [17, 18]. The association of circulating IGF-1 and RCC risk remains controversial, with inverse, null, and positive associations all being reported [17-20]. In contrast to the numerous studies evaluating the associations between circulating IGF-1/IGFBP-3 levels and cancer risks [17, 18, 21-27], very few studies have assessed the associations of circulating IGF-1/IGFBP-3 with clinical outcomes. To date, only one early study evaluated the prognostic values of serum IGF-1 and IGFBP-3 in RCC, which reported high serum IGF-1 level at diagnosis was associated with better survival than those with low serum IGF-1 [28].

Serologic measurements of IGF-1/IGFBP-3 are influenced by numerous preanalytical variables

including blood collection, handling, processing and storage procedures, environmental exposures and lifestyle factors, and physiological and medical conditions, as well as analytical variables including assay platforms and quality control procedures. Recently, there have been an increasing number of studies using genetic variants as instruments to predict a risk factor/biomarker and analyzing its association with disease risks and outcomes, an approach called Mendelian randomization (MR) [29]. Several recent MR studies have analyzed the associations of genetically predicted circulating IGF-1 and IGFBP-3 level with cancer risks [30-34]. No study has applied an MR approach to study IGF-1 and IGFBP-3 in RCC prognosis. In this study, for the first time, we analyzed the prognostic values of genetically predicted circulating IGF-1 and IGFBP-3 in RCC patients using an MR approach.

### Materials and methods

#### *Study population and data collection*

This study included 1,010 histologically confirmed RCC patients recruited from the University of Texas MD Anderson Cancer Center. All patients were of European descent. Epidemiological data including demographics, tobacco exposure, occupational history, family history of cancer, medical history, and medication were collected via personal interview by trained MD Anderson study interviewers. Clinical and follow-up data, including histology, tumor size, clinical and pathological stage, tumor grade, treatment type (surgery, cytokine therapy, targeted therapy, chemotherapy, radiotherapy, and other therapy), local recurrence and distant metastasis (date of first recurrence/metastasis), current vital status (date of death and cause of death), co-morbid conditions, pre-treatment performance status, pre-treatment weight loss, were abstracted from medical records. Time to recurrence/death was computed from date of surgery to date of last follow-up or recurrence/death.

#### *Genotyping and imputation*

Whole genome SNP array was performed using the Illumina HumanHap660W chips and the bioinformatics and quality control for genotyping have been described previously [35]. We

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**Table 1.** Selected characteristics of the study patients

| Characteristics                     | N (%)       |
|-------------------------------------|-------------|
| Age, Mean (SD)                      | 59.3 (10.6) |
| Sex                                 |             |
| Men                                 | 674 (66.7)  |
| Women                               | 336 (33.3)  |
| Smoking status at diagnosis         |             |
| Never-smoker                        | 455 (45.9)  |
| Former smoker                       | 397 (40.1)  |
| Current smoker                      | 139 (14.0)  |
| BMI at diagnosis, kg/m <sup>2</sup> |             |
| <25                                 | 154 (20.5)  |
| 25-29.99 (overweight)               | 277 (36.8)  |
| ≥30 (obese)                         | 321 (42.7)  |
| Histology                           |             |
| Clear Cell                          | 781 (77.3)  |
| Other                               | 229 (22.7)  |
| Clinical Stage                      |             |
| I                                   | 381 (38.4)  |
| II                                  | 71 (7.2)    |
| III                                 | 271 (27.4)  |
| IV                                  | 267 (27.0)  |
| Fuhrman Grade                       |             |
| 2                                   | 332 (35.9)  |
| 3                                   | 393 (42.5)  |
| 4                                   | 199 (21.5)  |
| Surgery                             |             |
| Yes                                 | 920 (93.6)  |
| No                                  | 63 (6.4)    |
| Recurrence                          |             |
| Yes                                 | 389 (38.5)  |
| No                                  | 621 (61.5)  |
| Survival status                     |             |
| Dead                                | 415 (41.1)  |
| Alive                               | 595 (58.9)  |

randomly selected 2% of the samples as duplicates for genotyping and the genotype concordance rate for duplicated samples was 99.2%. We excluded samples with overall SNP call rates lower than 95%. We used the Michigan Imputation Server (<https://imputationserver.sph.umich.edu/>) for imputation [36]. The mean imputation accuracy ( $R^2$ ) was 0.96. Previous GWAS identified 413 SNPs associated with circulating IGF-1 and 4 SNPs with IGFBP-3 [31, 32, 37, 38], and we used these SNPs to construct genetic risk scores.

### Genetic Risk Score (GRS)

We constructed weighted GRS using 413 IGF-1 and four IGFBP-3 associated SNPs, respectively, according to the following formula,

$$GRS_i = \sum_{j=1}^N w_j x_{ij}$$

In which  $GRS_i$  is the risk score for individual  $i$ ,  $x_{ij}$  ( $x_{ij}=0, 1$  or  $2$ ) is the number of IGF-1 or IGFBP-3 risk alleles for the  $j$ -th SNP, and  $w_j$  is the effect coefficient ( $\beta$  estimate) for each SNP. The  $\beta$  estimates for SNP-IGF-1 and SNP-IGFBP-3 association were obtained from published GWAS [31, 32, 37, 38]. “N” is the number of SNPs. A higher GRS value represents higher genetically predicted circulating IGF-1 or IGFBP-3 level.

### Statistical analysis

For each individual SNP, we evaluated its association with the risk of recurrence or death by calculating the hazard ratio (HR) and corresponding 95% confidence interval (95% CI) using multivariate Cox proportional hazards model, adjusting for age, gender, smoking status, BMI, stage, grade, and treatment. To analyze the association between GRS and the risk of recurrence or death, we dichotomized GRS at the median value or 75% value and used multivariate Cox proportional hazards model to calculate HR and corresponding 95% CI adjusting for age, gender, smoking status, BMI, stage, grade, and treatment.

## Results

### Patient characteristics

**Table 1** shows the selected characteristics of the 1,010 RCC patients. The mean age (standard deviation) at diagnosis was 59.3 (10.6) years. About two thirds (674, 66.7%) of the patients were men and one third were women (336, 33.3%). The prevalence of never, former, and current smokers was 45.9%, 40.1%, and 14.0%, respectively. Most patients were either overweight (36.8%) or obese (42.7%). Clear cell RCC is the predominant histology (77.3%). The distribution of clinical stages was: stage I, 381 (38.4%); stage II, 71 (7.2%); stage III, 271 (27.4%), and stage IV, 267 (27.0%). The vast majority (93.6%) of patients received nephrectomy. Recurrence occurred in 389 (38.5%)

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**Table 2.** GRS predictive of IGF-1 is associated with recurrence in RCC patients

| GRS                      | No Recurrence<br>N (%) | Recurrence<br>N (%) | Adjusted HR<br>(95% CI)* | P<br>value |
|--------------------------|------------------------|---------------------|--------------------------|------------|
| Continuous               |                        |                     |                          |            |
| Mean (SD)                | 0.59 (0.27)            | 0.48 (0.25)         | 0.63 (0.42-0.93)         | 0.021      |
| Dichotomize at median    |                        |                     |                          |            |
| Low                      | 273 (54.06)            | 232 (45.94)         | Reference                |            |
| High                     | 348 (68.91)            | 157 (31.09)         | 0.81 (0.65-0.99)         | 0.045      |
| Dichotomize at 75% value |                        |                     |                          |            |
| Low                      | 434 (57.26)            | 324 (42.74)         | Reference                |            |
| High                     | 187 (74.21)            | 65 (25.79)          | 0.73 (0.55-0.96)         | 0.025      |

\*Adjusted by age, gender, smoking status, BMI, histology, stage, grade, and treatment.

**Table 3.** GRS predictive of IGF-1 is associated with survival in RCC patients

| GRS                      | Alive<br>N (%) | Dead<br>N (%) | Adjusted HR<br>(95% CI)* | P<br>value |
|--------------------------|----------------|---------------|--------------------------|------------|
| Continuous               |                |               |                          |            |
| Mean (SD)                | 0.59 (0.27)    | 0.49 (0.25)   | 0.65 (0.44-0.95)         | 0.027      |
| Dichotomize at median    |                |               |                          |            |
| Low                      | 261 (51.68)    | 244 (48.32)   | Reference                |            |
| High                     | 334 (66.14)    | 171 (33.86)   | 0.74 (0.60-0.91)         | 0.004      |
| Dichotomize at 75% value |                |               |                          |            |
| Low                      | 410 (54.09)    | 348 (45.91)   | Reference                |            |
| High                     | 185 (73.41)    | 67 (26.59)    | 0.66 (0.50-0.87)         | 0.003      |

\*Adjusted by age, gender, smoking status, BMI, histology, stage, grade, and treatment.

patients and 415 (41.1%) patients died from the disease.

### Associations of SNPs and GRS with prognosis of RCC

The individual associations of the 413 IGF-1-associated and 4 IGFBP-3-associated SNPs with recurrence and death were shown in [Supplementary Table 1](#). There were 40 SNPs reaching nominal significance ( $P < 0.05$ ) and 12 SNPs reaching  $P < 0.01$  in recurrence analysis, and 39 SNPs with  $P < 0.05$  and 10 SNPs with  $P < 0.01$  in survival analysis. Ten SNPs showed consistent association ( $P < 0.05$ ) with both recurrence survival in the same direction. The host genes of these 10 SNPs included *AC07-3901.1*, *RAI1*, *TNXB*, *TIGD2*, *ZNRF3*, *RBFOX1*, *WLS*, *ATP6V1G2*, *ASTN2*, and *PAPPA2*. One of the four IGFBP-3 SNPs reached  $P < 0.05$  in either the recurrence or survival analysis ([Supplementary Table 1](#)). None of these individual associations reached significance after Bonferroni correction or false discovery rate calculation (data not shown).

We then constructed a weighted GRS to predict IGF-1 and IGFBP-3, respectively, and analyzed the associations of the GRS with RCC prognosis. As a continuous variable, GRS for IGF-1 exhibited a significant inverse association with recurrence (HR=0.63 per SD increase, 95% CI, 0.42-0.93,  $P = 0.021$ ). We also analyzed GRS as a categorical variable. We dichotomized patients into two groups based on the median value of GRS, patients with high GRS (high circulating IGF-1) had 19% reduced risk of recurrence (HR=0.81, 95% CI, 0.65-0.99,  $P = 0.045$ ) compared to those with low GRS (low circulating IGF-1). When we dichotomized patients into two groups based on the 75% value of GRS, those with the highest

quarter of GRS had 27% lower risk of recurrence (OR=0.73, 95% CI, 0.55-0.96,  $P = 0.025$ ) than the other three quarters of patients ([Table 2](#)).

We observed similar associations between genetically predicted circulating IGF-1 level and risk of death. Patients with higher GRS had a significantly reduced risk of death (HR=0.65 per SD increase, 95% CI, 0.44-0.95,  $P = 0.027$ ). When GRS was analyzed as a categorical variable, the HR for patients with the high GRS was 0.74 (95% CI, 0.60-0.91,  $P = 0.004$ ) and 0.66 (95% CI, 0.50-0.87,  $P = 0.003$ ), respectively, compared to patient with low GRS when patients were dichotomized into two groups based on the median and 75% GRS values, respectively ([Table 3](#)).

Similar analyses were performed for IGFBP-3 and no significant association between genetically predicted IGFBP-3 and RCC prognosis was observed (HR=0.97 per SD increase, 95% CI, 0.63-1.52,  $P = 0.910$  for recurrence, and

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**Table 4.** Associations of GRS predictive of IGFBP-3 with recurrence and survival in RCC patients

| GRS                      | No Recurrence<br>N (%) | Recurrence<br>N (%) | Adjusted HR<br>(95% CI)* | P<br>value | Alive<br>N (%) | Dead<br>N (%) | Adjusted HR<br>(95% CI)* | P<br>value |
|--------------------------|------------------------|---------------------|--------------------------|------------|----------------|---------------|--------------------------|------------|
| Continuous               |                        |                     |                          |            |                |               |                          |            |
| Mean (SD)                | 0.59 (0.24)            | 0.59 (0.23)         | 0.97 (0.63-1.52)         | 0.910      | 0.59 (0.24)    | 0.59 (0.23)   | 0.91 (0.59-1.40)         | 0.659      |
| Dichotomize at median    |                        |                     |                          |            |                |               |                          |            |
| Low                      | 309 (60.71)            | 200 (39.29)         | Reference                |            | 297 (58.35)    | 212 (41.65)   | Reference                |            |
| High                     | 312 (62.28)            | 189 (37.72)         | 0.98 (0.80-1.21)         | 0.874      | 298 (59.48)    | 203 (40.52)   | 1.00 (0.82-1.23)         | 0.958      |
| Dichotomize at 75% value |                        |                     |                          |            |                |               |                          |            |
| Low                      | 466 (61.48)            | 292 (38.52)         | Reference                |            | 466 (61.48)    | 292 (38.52)   |                          |            |
| High                     | 155 (61.51)            | 97 (38.49)          | 0.94 (0.74-1.19)         | 0.610      | 155 (61.51)    | 97 (38.49)    | 0.82 (0.64-1.04)         | 0.096      |

\*Adjusted by age, gender, smoking status, BMI, histology, stage, grade, and treatment.

**Table 5.** Associations of IGF-1/IGFBP-3 ratio with recurrence and survival in RCC patients

| GRS                      | No Recurrence<br>N (%) | Recurrence<br>N (%) | Adjusted HR<br>(95% CI)* | P<br>value | Alive<br>N (%) | Dead<br>N (%) | Adjusted HR<br>(95% CI)* | P<br>value |
|--------------------------|------------------------|---------------------|--------------------------|------------|----------------|---------------|--------------------------|------------|
| Continuous               |                        |                     |                          |            |                |               |                          |            |
| Mean (SD)                | 1.31 (1.28)            | 1.11 (1.28)         | 0.94 (0.86-1.03)         | 0.227      | 1.34 (1.42)    | 1.07 (1.04)   | 0.89 (0.81-0.99)         | 0.028      |
| Dichotomize at median    |                        |                     |                          |            |                |               |                          |            |
| Low                      | 278 (55.49)            | 223 (44.51)         | Reference                |            | 267 (53.29)    | 234 (46.71)   | Reference                |            |
| High                     | 337 (67.27)            | 164 (32.73)         | 0.80 (0.65-0.99)         | 0.037      | 323 (64.47)    | 178 (35.53)   | 0.79 (0.65-0.97)         | 0.023      |
| Dichotomize at 75% value |                        |                     |                          |            |                |               |                          |            |
| Low                      | 438 (58.24)            | 314 (41.76)         | Reference                |            | 423 (56.25)    | 329 (43.75)   | Reference                |            |
| High                     | 177 (70.80)            | 73 (29.20)          | 0.71 (0.55-0.93)         | 0.011      | 167 (66.80)    | 83 (33.20)    | 0.65 (0.50-0.84)         | 0.001      |

\*Adjusted by age, gender, smoking status, BMI, histology, stage, grade, and treatment.

HR=0.91 per SD increase, 95% CI, 0.59-1.40, P=0.659 for survival) (**Table 4**).

We then calculated the IGF-1/IGFBP-3 ratio and analyzed the associations of IGF-1/IGFBP-3 ratio with RCC prognosis (**Table 5**). As a continuous variable, IGF-1/IGFBP-3 ratio was associated with modestly reduced risks of recurrence (HR=0.94 per SD increase, 95% CI, 0.86-1.03, P=0.227) and survival (HR=0.89 per SD increase, 95% CI, 0.81-0.99, P=0.028). Dichotomized at the median value of IGF-1/IGFBP-3 ratio, patients with high IGF-1/IGFBP-3 ratio had 20% reduced risk of recurrence (HR=0.80, 95% CI, 0.65-0.99, P=0.037) and 21% reduced risk of death (HR=0.79, 95% CI, 0.65-0.97, P=0.023) compared to those with low IGF-1/IGFBP-3 ratio. Dichotomized at the 75% value of IGF-1/IGFBP-3 ratio, patients with the highest quarter of IGF-1/IGFBP-3 ratio had 29% lower risk of recurrence (OR=0.71, 95% CI, 0.55-0.93, P=0.011) and 35% lower risk of recurrence (OR=0.65, 95% CI, 0.50-0.84, P=0.001) than the other three quarters of patients (**Table 5**).

### Discussion

In this study, we showed that genetically predicted circulating IGF-1 is an independent pre-

dictor of prognosis in RCC patients. To our knowledge, this is the first study to use an MR approach to investigate the prognostic roles of circulating IGF-1 and IGFBP-3 in RCC.

The involvement of insulin and insulin-like growth factors in cancer development and progression has been known for many years [9, 10, 15]. IGF-1 can stimulate cancer cell growth and its receptor, IGF-1R, is overexpressed in multiple human cancers [9, 10]. IGF-1R is a tyrosine kinase and targeting IGF-1R by specific antibody has shown anti-tumor efficacy in preclinical models and clinical trials [9, 10]. IGF-1 binds to IGF-1R and activates downstream cascades of kinases such as PI3K-Akt and Ras-MAPK signaling pathways [9]. Given the growth-stimulating effects of IGF-1, it follows that high circulating IGF-1 level should favor cancer development. Several recent analyses of the prospective UK Biobank cohort with baseline serum IGF-1 measurements and follow-up data have shown that high baseline serum IGF-1 level is associated with significantly increased risks of multiple cancers, including breast, prostate, colorectal, thyroid, and malignant skin cancer [17, 18, 30-32].

In contrast to the multiple reports of positive associations between high serum IGF-1 and



increased cancer risks from large prospective studies, the associations between serum IGF-1 and cancer prognosis were quite heterogeneous. Many studies demonstrated an inverse correlation, i.e., high circulating IGF-1 level at diagnosis is associated with reduced risk of death and longer survival [28, 39-43]. For example, an early lung study reported high pre-treatment plasma IGF-1 level was predictive of longer progression-free ( $P=0.001$ ) and overall survival ( $P=0.025$ ) [39]. Two studies have shown that high baseline plasma IGF-1 level correlated with significantly reduced risk of death and longer overall survival in hepatocellular carcinoma patients [40, 41]. A study of 527 metastatic colorectal cancer patients enrolled in a randomized trial of first-line chemotherapy showed higher baseline plasma IGF-1 level was associated with improved overall survival ( $P=0.0001$ ) [42]. Another recent large study consisting of 2,682 surgically resected invasive breast cancer patients found patients with high preoperative serum IGF-1 concentration had lower risks of all-cause mortality (HR, 0.53; 95% CI, 0.29-0.96) and breast cancer-specific mortality (HR, 0.53; 95% CI, 0.27-1.02) [43]. The only previous study in RCC showed that when patients were dichotomized at the median baseline serum IGF-1 level, those with high serum IGF-1 had a 38% reduced risk of death (HR=0.62, 95% CI, 0.41-0.95,  $P=0.028$ ) compared to those with low serum IGF-1 [28]. Our results of significant associations between high genetically predicted circulating IGF-1 and reduced risks of recurrence and death are consistent with that RCC study using serologically measured IGF-1. Our study is the first to use an MR approach, which is not affected by preanalytical and analytical factors related to serological measurements of IGF-1. Our results provide strong evidence for a causal relationship between high circulating IGF-1 and better prognosis in RCC patients.

The inverse associations between circulating IGF-1 and prognosis appear counterintuitive because the growth-stimulating effect of IGF-1 would presumably promote cancer progression. However, there was no correlation between circulating IGF-1 and RCC tumor stage and grade [28]. "Obesity paradox" is a well-known phenomenon in RCC that describes the opposing roles of obesity in cancer initiation and prognosis, i.e., obesity is a major risk factor for RCC [44-48], but obese and overweight RCC patients have better prognosis [49-51]. The IGF-1 axis contributes to obesity-induced

biological changes and the association of high circulating IGF-1 with better prognosis of RCC patients may be related to obesity-related biology. In addition, IGF-1 is a marker of nutritional state [52] and low circulating IGF-1 may reflect poor nutritional status and impaired performance status, thus resulting in worse prognosis. The exact mechanisms underlying the inverse association between circulating IGF-1 and prognosis in RCC patients warrant further investigation.

This is the first MR study of circulating IGF-1 and IGFBP-3 in RCC prognosis. We found that genetically predicted higher circulating IGF-1, but not IGFBP-3, is associated with lower risks of recurrence and death in RCC patients. Our results are consistent with the only published report of serologically measured IGF-1 and IGFBP-3 in RCC prognosis [28]. There are a few limitations in this study. First, the genetic instruments only explain 9.4% and 6.1% of variability in circulating IGF-1 and IGFBP-3 levels, respectively [31]. Additional SNPs are needed to increase the instrument strength. Second, this is a single center study. Validations in additional RCC patient cohorts would further strengthen the notion that IGF-1 is a favorable prognostic factor in RCC patients. Third, we only included European ancestry patients in this study. Future studies are warranted to assess the prognostic roles of IGF-1 and IGFBP-3 in other races/ethnicities.

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### Disclosure of conflict of interest

None.

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**Supplementary Table 1.** Association parameters of instrumental SNPs with risk factors (IGF-1 or IGFBP-3) and RCC recurrence and death

| SNP ID      | Chr. | Position  | Gene                   | Allele* | EAF   | $\beta_1$ | SNP-Recurrence |                  |                             | SNP-Death |                  |                             |
|-------------|------|-----------|------------------------|---------|-------|-----------|----------------|------------------|-----------------------------|-----------|------------------|-----------------------------|
|             |      |           |                        |         |       |           | $\beta_2$      | HR (95% CI)      | P value                     | $\beta_3$ | HR (95% CI)      | P value                     |
| IGF-1 SNPs  |      |           |                        |         |       |           |                |                  |                             |           |                  |                             |
| rs10860237  | 12   | 98157010  | AC007424.1             | G/A     | 0.338 | -0.030    | -0.318         | 0.73 (0.61-0.86) | <b>2.18×10<sup>-4</sup></b> | -0.086    | 0.92 (0.79-1.07) | 0.2647                      |
| rs7323205   | 13   | 110365525 | LINC00676              | C/T     | 0.381 | 0.015     | -0.271         | 0.76 (0.65-0.89) | <b>6.60×10<sup>-4</sup></b> | -0.135    | 0.87 (0.75-1.01) | 0.0712                      |
| rs702878    | 2    | 65702609  | AC007389.1             | A/G     | 0.439 | 0.014     | -0.197         | 0.82 (0.71-0.95) | <b>0.0070</b>               | -0.100    | 0.9 (0.79-1.04)  | 0.1591                      |
| rs12666306  | 7    | 115082406 | <b>AC073901.1</b>      | G/A     | 0.493 | 0.017     | -0.246         | 0.78 (0.67-0.91) | <b>0.0011</b>               | -0.175    | 0.84 (0.73-0.97) | <b>0.0190</b>               |
| rs4394044   | 4    | 186607420 | SORBS2                 | T/C     | 0.416 | 0.014     | -0.244         | 0.78 (0.67-0.91) | <b>0.0019</b>               | -0.083    | 0.92 (0.79-1.07) | 0.2697                      |
| rs112436634 | 1    | 10637709  | PEX14                  | C/T     | 0.320 | -0.016    | -0.258         | 0.77 (0.65-0.91) | <b>0.0022</b>               | -0.135    | 0.87 (0.75-1.02) | 0.0776                      |
| rs8075153   | 17   | 17622666  | <b>RAI1</b>            | C/T     | 0.412 | 0.021     | -0.225         | 0.8 (0.69-0.93)  | <b>0.0030</b>               | -0.203    | 0.82 (0.71-0.94) | <b>0.0063</b>               |
| rs17265513  | 20   | 39832628  | ZHX3                   | C/T     | 0.820 | -0.022    | 0.315          | 1.37 (1.11-1.69) | <b>0.0032</b>               | -0.015    | 0.99 (0.81-1.2)  | 0.8835                      |
| rs1150752   | 6    | 32064726  | <b>TNXB</b>            | C/T     | 0.893 | -0.031    | 0.362          | 1.44 (1.12-1.85) | <b>0.0049</b>               | 0.301     | 1.35 (1.05-1.73) | <b>0.0181</b>               |
| rs12710648  | 2    | 17989500  | SMC6                   | A/G     | 0.478 | 0.017     | -0.197         | 0.82 (0.71-0.95) | <b>0.0071</b>               | -0.023    | 0.98 (0.85-1.12) | 0.7428                      |
| rs2280099   | 4    | 90035549  | <b>TIGD2</b>           | G/A     | 0.816 | 0.025     | 0.256          | 1.29 (1.07-1.56) | <b>0.0081</b>               | 0.200     | 1.22 (1.02-1.47) | <b>0.0332</b>               |
| rs1532824   | 16   | 10532211  | ATF7IP2                | C/A     | 0.276 | -0.017    | 0.219          | 1.24 (1.06-1.47) | <b>0.0083</b>               | 0.093     | 1.1 (0.93-1.29)  | 0.2566                      |
| rs12520263  | 5    | 44122508  | RNU6-381P              | G/T     | 0.269 | -0.017    | 0.039          | 1.04 (0.89-1.22) | 0.6361                      | 0.257     | 1.29 (1.12-1.5)  | <b>6.42×10<sup>-4</sup></b> |
| rs73954943  | 2    | 111890432 | BCL2L11                | G/A     | 0.059 | -0.031    | 0.103          | 1.11 (0.81-1.52) | 0.5220                      | 0.473     | 1.6 (1.21-2.13)  | <b>0.0010</b>               |
| rs8138950   | 22   | 29448643  | <b>ZNRF3</b>           | C/T     | 0.519 | 0.015     | -0.187         | 0.83 (0.71-0.96) | <b>0.0144</b>               | -0.237    | 0.79 (0.68-0.91) | <b>0.0014</b>               |
| rs74774288  | 16   | 5922263   | <b>RBFOX1</b>          | G/T     | 0.179 | 0.027     | -0.240         | 0.79 (0.64-0.96) | <b>0.0184</b>               | -0.312    | 0.73 (0.6-0.89)  | <b>0.0018</b>               |
| rs72858776  | 11   | 15772953  | AC087379.1             | G/T     | 0.061 | 0.030     | 0.261          | 1.3 (0.94-1.8)   | 0.1187                      | 0.432     | 1.54 (1.16-2.05) | <b>0.0030</b>               |
| rs2227819   | 5    | 76012745  | F2R                    | C/T     | 0.094 | -0.022    | -0.116         | 0.89 (0.68-1.16) | 0.3904                      | -0.388    | 0.68 (0.52-0.89) | <b>0.0048</b>               |
| rs3791679   | 2    | 56096892  | EFEMP1                 | A/G     | 0.234 | -0.018    | 0.093          | 1.1 (0.93-1.3)   | 0.2816                      | 0.235     | 1.26 (1.07-1.49) | <b>0.0052</b>               |
| rs143885630 | 1    | 183482785 | SMG7                   | G/A     | 0.116 | 0.030     | -0.057         | 0.94 (0.74-1.2)  | 0.6457                      | 0.303     | 1.35 (1.09-1.69) | <b>0.0067</b>               |
| rs1170158   | 13   | 42701941  | DGKH                   | T/G     | 0.190 | 0.021     | -0.072         | 0.93 (0.77-1.12) | 0.4440                      | -0.250    | 0.78 (0.65-0.94) | <b>0.0080</b>               |
| rs218291    | 6    | 108467024 | OSTM1/OSTM1-AS1        | G/A     | 0.373 | 0.016     | -0.069         | 0.93 (0.8-1.09)  | 0.3913                      | -0.205    | 0.81 (0.7-0.95)  | <b>0.0082</b>               |
| rs1430753   | 1    | 68692642  | <b>WLS</b>             | G/A     | 0.175 | -0.021    | 0.248          | 1.28 (1.06-1.55) | <b>0.0111</b>               | 0.237     | 1.27 (1.05-1.52) | <b>0.0119</b>               |
| rs9267488   | 6    | 31514247  | <b>ATP6V1G2-DDX39B</b> | G/A     | 0.887 | -0.031    | 0.264          | 1.3 (1.03-1.65)  | <b>0.0278</b>               | 0.316     | 1.37 (1.08-1.75) | <b>0.0107</b>               |
| rs7872812   | 9    | 119341544 | <b>ASTN2</b>           | C/T     | 0.143 | -0.026    | -0.227         | 0.8 (0.64-0.99)  | <b>0.0386</b>               | -0.234    | 0.79 (0.63-0.99) | <b>0.0394</b>               |
| rs12749024  | 1    | 176522365 | <b>PAPPA2</b>          | C/T     | 0.127 | -0.075    | -0.246         | 0.78 (0.62-0.99) | <b>0.0438</b>               | -0.271    | 0.76 (0.6-0.97)  | <b>0.0283</b>               |
| rs12593755  | 15   | 89111712  | AC013489.2             | G/T     | 0.403 | -0.016    | -0.132         | 0.88 (0.75-1.02) | 0.0831                      | -0.064    | 0.94 (0.81-1.09) | 0.3889                      |
| rs7719168   | 5    | 53292390  | ARL15                  | A/C     | 0.118 | -0.030    | 0.010          | 1.01 (0.81-1.26) | 0.9277                      | 0.013     | 1.01 (0.82-1.26) | 0.9095                      |
| rs6827641   | 4    | 145653694 | GYPA/HHIP              | C/T     | 0.454 | -0.014    | -0.090         | 0.91 (0.79-1.06) | 0.2385                      | -0.021    | 0.98 (0.85-1.13) | 0.7778                      |
| rs8017377   | 14   | 24883887  | NYNRIN                 | A/G     | 0.517 | -0.017    | 0.033          | 1.03 (0.9-1.19)  | 0.6470                      | 0.035     | 1.04 (0.9-1.19)  | 0.6240                      |
| rs17145738  | 7    | 72982874  | TBL2                   | C/T     | 0.103 | -0.034    | -0.169         | 0.84 (0.66-1.08) | 0.1807                      | -0.022    | 0.98 (0.77-1.25) | 0.8569                      |
| rs117564283 | 12   | 52300110  | ACVRL1                 | C/T     | 0.061 | -0.029    | 0.323          | 1.38 (1.06-1.8)  | <b>0.0174</b>               | 0.148     | 1.16 (0.87-1.54) | 0.3128                      |
| rs116971887 | 16   | 51170026  | SALL1                  | G/T     | 0.041 | 0.036     | -0.313         | 0.73 (0.5-1.08)  | 0.1128                      | -0.167    | 0.85 (0.58-1.23) | 0.3773                      |
| rs45505697  | 1    | 153651058 | NPR1                   | C/A     | 0.015 | 0.030     | 0.264          | 1.3 (0.68-2.47)  | 0.4214                      | -0.027    | 0.97 (0.52-1.81) | 0.9308                      |

## IGF-1, IGFBP-3 and prognosis of renal cancer

|             |    |           |             |     |       |        |        |                  |               |        |                  |               |
|-------------|----|-----------|-------------|-----|-------|--------|--------|------------------|---------------|--------|------------------|---------------|
| rs72758321  | 5  | 41464841  | PLCXD3      | A/G | 0.023 | -0.047 | -0.093 | 0.91 (0.55-1.52) | 0.7231        | 0.111  | 1.12 (0.69-1.81) | 0.6536        |
| rs118081390 | 13 | 49671053  | FNDC3A      | G/A | 0.048 | 0.028  | -0.077 | 0.93 (0.65-1.32) | 0.6670        | -0.108 | 0.9 (0.63-1.27)  | 0.5399        |
| rs17393144  | 1  | 9210262   | MIR34A      | G/A | 0.294 | -0.016 | -0.049 | 0.95 (0.81-1.12) | 0.5470        | -0.044 | 0.96 (0.82-1.12) | 0.5941        |
| rs4988483   | 16 | 1129010   | SSTR5       | A/C | 0.992 | -0.172 | 0.300  | 1.35 (0.53-3.41) | 0.5254        | 0.403  | 1.5 (0.55-4.1)   | 0.4339        |
| rs10851736  | 15 | 64940718  | ZNF609      | C/T | 0.092 | -0.027 | -0.157 | 0.85 (0.66-1.1)  | 0.2282        | -0.321 | 0.73 (0.56-0.94) | <b>0.0169</b> |
| rs11012712  | 10 | 21760015  | -           | C/T | 0.203 | 0.022  | -0.058 | 0.94 (0.79-1.13) | 0.5313        | -0.074 | 0.93 (0.78-1.1)  | 0.3997        |
| rs1986692   | 7  | 133743393 | EXOC4       | A/G | 0.373 | -0.015 | 0.145  | 1.16 (0.97-1.38) | 0.1062        | 0.014  | 1.01 (0.86-1.2)  | 0.8678        |
| rs10892564  | 11 | 120224650 | ARHGEF12    | A/G | 0.392 | -0.017 | -0.012 | 0.99 (0.85-1.15) | 0.8773        | 0.021  | 1.02 (0.88-1.19) | 0.7826        |
| rs2819336   | 1  | 44015809  | PTPRF       | C/T | 0.360 | -0.027 | -0.012 | 0.99 (0.85-1.15) | 0.8704        | -0.085 | 0.92 (0.8-1.06)  | 0.2498        |
| rs2786185   | 6  | 147595554 | STXBP5      | G/A | 0.453 | 0.019  | 0.088  | 1.09 (0.94-1.27) | 0.2463        | -0.093 | 0.91 (0.79-1.05) | 0.2003        |
| rs10246481  | 7  | 156184748 | lincRNA     | A/G | 0.395 | -0.015 | 0.075  | 1.08 (0.93-1.25) | 0.3268        | 0.034  | 1.03 (0.89-1.2)  | 0.6456        |
| rs11678946  | 2  | 222302730 | EPHA4       | C/A | 0.487 | -0.014 | 0.103  | 1.11 (0.95-1.3)  | 0.2010        | 0.093  | 1.1 (0.93-1.29)  | 0.2581        |
| rs11230983  | 11 | 55541284  | OR5D13      | A/G | 0.882 | 0.035  | 0.150  | 1.16 (0.92-1.46) | 0.1990        | 0.005  | 1.01 (0.81-1.25) | 0.9641        |
| rs329122    | 5  | 133864599 | JADE2       | G/A | 0.431 | -0.018 | 0.035  | 1.04 (0.89-1.2)  | 0.6447        | 0.050  | 1.05 (0.91-1.22) | 0.5016        |
| rs10136874  | 14 | 101202022 | DLK1        | G/T | 0.487 | 0.023  | -0.041 | 0.96 (0.83-1.11) | 0.5760        | -0.019 | 0.98 (0.85-1.13) | 0.7959        |
| rs12442867  | 15 | 62489128  | AC126323.2  | C/A | 0.396 | -0.017 | 0.114  | 1.12 (0.95-1.32) | 0.1651        | 0.068  | 1.07 (0.92-1.24) | 0.3792        |
| rs2424396   | 20 | 21630280  | LINC01726   | A/G | 0.072 | -0.033 | 0.110  | 1.12 (0.85-1.47) | 0.4332        | -0.142 | 0.87 (0.66-1.15) | 0.3161        |
| rs6895953   | 5  | 39084471  | RICTOR      | G/A | 0.431 | 0.024  | -0.023 | 0.98 (0.84-1.14) | 0.7639        | -0.121 | 0.89 (0.76-1.03) | 0.1107        |
| rs1046011   | 1  | 65898996  | LEPR/LEPROT | C/T | 0.302 | -0.021 | 0.034  | 1.03 (0.88-1.22) | 0.6807        | -0.077 | 0.93 (0.79-1.08) | 0.3269        |
| rs4980661   | 11 | 69306579  | CCND1       | A/G | 0.477 | 0.014  | -0.161 | 0.85 (0.73-0.99) | <b>0.0348</b> | 0.132  | 1.14 (0.99-1.32) | 0.0744        |
| rs7625680   | 3  | 11378069  | ATG7        | A/G | 0.364 | 0.015  | -0.053 | 0.95 (0.81-1.1)  | 0.4970        | -0.061 | 0.94 (0.81-1.09) | 0.4177        |
| rs7545345   | 1  | 205690941 | NUCKS1      | T/C | 0.123 | -0.026 | -0.008 | 0.99 (0.8-1.24)  | 0.9436        | -0.177 | 0.84 (0.67-1.04) | 0.1154        |
| rs1050327   | 7  | 44808017  | ZMIZ2       | G/A | 0.482 | -0.017 | -0.077 | 0.93 (0.8-1.08)  | 0.3183        | 0.122  | 1.13 (0.98-1.31) | 0.1036        |
| rs73382439  | 6  | 20404420  | E2F3        | C/T | 0.166 | 0.019  | -0.095 | 0.91 (0.74-1.11) | 0.3534        | -0.182 | 0.83 (0.68-1.03) | 0.0869        |
| rs12471768  | 2  | 64928603  | SERTAD2     | C/T | 0.288 | 0.022  | -0.072 | 0.93 (0.79-1.1)  | 0.3974        | 0.122  | 1.13 (0.96-1.33) | 0.1352        |
| rs6180      | 5  | 42719239  | GHR         | C/A | 0.538 | -0.035 | 0.010  | 1.01 (0.87-1.17) | 0.8993        | 0.067  | 1.07 (0.92-1.24) | 0.3757        |
| rs62302688  | 4  | 46448465  | GABRA2      | G/A | 0.057 | 0.039  | -0.088 | 0.92 (0.66-1.26) | 0.5913        | -0.083 | 0.92 (0.68-1.24) | 0.5896        |
| rs2075995   | 1  | 23847464  | E2F2        | A/C | 0.505 | -0.014 | -0.100 | 0.91 (0.78-1.05) | 0.1939        | -0.018 | 0.98 (0.85-1.13) | 0.8074        |
| rs9819762   | 3  | 178914879 | PIK3CA      | T/C | 0.192 | 0.019  | -0.045 | 0.96 (0.8-1.15)  | 0.6274        | 0.013  | 1.01 (0.85-1.21) | 0.8832        |
| rs34312198  | 7  | 99674870  | ZNF3        | C/A | 0.109 | -0.024 | 0.042  | 1.04 (0.84-1.3)  | 0.7026        | -0.204 | 0.82 (0.65-1.03) | 0.0876        |
| rs7740433   | 6  | 42908013  | CNPY3       | A/G | 0.238 | 0.017  | -0.151 | 0.86 (0.72-1.03) | 0.1033        | -0.203 | 0.82 (0.68-0.98) | <b>0.0256</b> |
| rs9611565   | 22 | 41767486  | TEF         | T/C | 0.236 | 0.029  | 0.118  | 1.13 (0.94-1.35) | 0.2014        | 0.075  | 1.08 (0.9-1.29)  | 0.4077        |
| rs6853741   | 4  | 148982559 | ARHGAP10    | A/G | 0.256 | 0.024  | -0.074 | 0.93 (0.78-1.11) | 0.4110        | -0.062 | 0.94 (0.79-1.11) | 0.4730        |
| rs7758644   | 6  | 156583467 | snoRNA      | C/A | 0.164 | -0.019 | -0.018 | 0.98 (0.8-1.21)  | 0.8703        | 0.026  | 1.03 (0.84-1.26) | 0.8034        |
| rs11024614  | 11 | 18326758  | HPS5        | T/C | 0.403 | -0.023 | -0.010 | 0.99 (0.85-1.16) | 0.9029        | -0.013 | 0.99 (0.85-1.14) | 0.8627        |
| rs4402747   | 2  | 225457173 | CUL3        | G/A | 0.460 | -0.016 | -0.021 | 0.98 (0.84-1.14) | 0.7789        | -0.026 | 0.97 (0.84-1.13) | 0.7269        |
| rs2896395   | 7  | 127511705 | SND1        | C/T | 0.297 | 0.015  | -0.024 | 0.98 (0.83-1.15) | 0.7688        | 0.023  | 1.02 (0.88-1.19) | 0.7659        |
| rs13195402  | 6  | 26463575  | BTN2A1      | T/G | 0.928 | -0.038 | -0.011 | 0.99 (0.74-1.32) | 0.9430        | 0.139  | 1.15 (0.86-1.54) | 0.3541        |
| rs13069961  | 3  | 124358715 | KALRN       | A/G | 0.203 | -0.018 | 0.027  | 1.03 (0.85-1.24) | 0.7799        | -0.195 | 0.82 (0.69-0.98) | <b>0.0311</b> |

### IGF-1, IGFBP-3 and prognosis of renal cancer

|             |    |           |                   |     |       |        |        |                  |               |        |                  |        |
|-------------|----|-----------|-------------------|-----|-------|--------|--------|------------------|---------------|--------|------------------|--------|
| rs10769621  | 11 | 49860463  | TRIM51FP          | T/C | 0.671 | 0.020  | 0.020  | 1.02 (0.87-1.2)  | 0.8053        | -0.053 | 0.95 (0.81-1.1)  | 0.4949 |
| rs13178887  | 5  | 88355993  | MEF2C-AS1         | T/C | 0.391 | 0.023  | 0.117  | 1.12 (0.97-1.3)  | 0.1091        | 0.104  | 1.11 (0.96-1.28) | 0.1449 |
| rs41285260  | 6  | 126661502 | CENPW             | T/G | 0.967 | 0.039  | 0.041  | 1.04 (0.65-1.67) | 0.8643        | -0.047 | 0.95 (0.6-1.52)  | 0.8442 |
| rs4719393   | 7  | 14219213  | DGKB              | T/G | 0.289 | 0.027  | -0.097 | 0.91 (0.77-1.07) | 0.2485        | -0.103 | 0.9 (0.77-1.06)  | 0.2124 |
| rs9398891   | 6  | 129314749 | LAMA2             | C/T | 0.317 | -0.017 | 0.006  | 1.01 (0.86-1.17) | 0.9351        | 0.087  | 1.09 (0.94-1.27) | 0.2524 |
| rs13379043  | 14 | 74250126  | ELMSAN1           | T/C | 0.288 | 0.025  | -0.047 | 0.95 (0.8-1.13)  | 0.5957        | -0.047 | 0.95 (0.81-1.13) | 0.5809 |
| rs12927172  | 16 | 27325021  | IL4R              | G/A | 0.390 | -0.015 | 0.079  | 1.08 (0.93-1.26) | 0.3024        | 0.003  | 1 (0.87-1.16)    | 0.9681 |
| rs77542162  | 17 | 67081278  | ABCA6             | G/A | 0.989 | 0.054  | 0.127  | 1.14 (0.53-2.43) | 0.7430        | -0.144 | 0.87 (0.43-1.76) | 0.6914 |
| rs9321106   | 6  | 128355316 | PTPRK             | A/G | 0.165 | 0.018  | -0.074 | 0.93 (0.76-1.14) | 0.4803        | -0.154 | 0.86 (0.7-1.05)  | 0.1428 |
| rs1498603   | 5  | 58333125  | PDE4D             | T/G | 0.065 | 0.031  | 0.178  | 1.19 (0.89-1.61) | 0.2441        | -0.058 | 0.94 (0.7-1.27)  | 0.6986 |
| rs11057265  | 12 | 123805950 | SBN01             | G/A | 0.024 | 0.044  | 0.048  | 1.05 (0.69-1.61) | 0.8246        | 0.007  | 1.01 (0.65-1.55) | 0.9758 |
| rs33969824  | 3  | 42679777  | NKTR              | G/T | 0.874 | 0.020  | 0.195  | 1.22 (0.97-1.52) | 0.0892        | -0.193 | 0.82 (0.67-1.01) | 0.0599 |
| rs1800574   | 12 | 121416864 | HNF1A             | T/C | 0.983 | 0.145  | 0.037  | 1.04 (0.52-2.05) | 0.9142        | -0.535 | 0.59 (0.33-1.04) | 0.0668 |
| rs8112883   | 19 | 7179320   | INSR              | G/T | 0.275 | 0.017  | -0.019 | 0.98 (0.83-1.16) | 0.8188        | 0.115  | 1.12 (0.95-1.32) | 0.1630 |
| rs35036084  | 4  | 97552791  | LINC02267         | T/C | 0.389 | 0.017  | 0.024  | 1.02 (0.88-1.19) | 0.7534        | -0.028 | 0.97 (0.84-1.13) | 0.7140 |
| rs116454156 | 10 | 95347041  | FFAR4             | A/G | 0.992 | 0.078  | -0.241 | 0.79 (0.25-2.48) | 0.6814        | -0.858 | 0.42 (0.16-1.16) | 0.0934 |
| rs7910087   | 10 | 77209145  | LRMDA             | C/T | 0.439 | -0.017 | -0.050 | 0.95 (0.82-1.11) | 0.5145        | -0.051 | 0.95 (0.82-1.1)  | 0.5001 |
| rs2250243   | 7  | 6690240   | ZNF316            | T/C | 0.238 | -0.024 | -0.008 | 0.99 (0.84-1.17) | 0.9260        | -0.077 | 0.93 (0.78-1.1)  | 0.3731 |
| rs2362755   | 3  | 24716668  | THRB-AS1          | G/T | 0.439 | -0.016 | -0.122 | 0.89 (0.75-1.05) | 0.1518        | -0.157 | 0.85 (0.73-1.01) | 0.0596 |
| rs10252510  | 7  | 31023108  | GHRHR             | G/A | 0.265 | 0.020  | -0.064 | 0.94 (0.78-1.13) | 0.4968        | 0.112  | 1.12 (0.94-1.34) | 0.2195 |
| rs9292578   | 5  | 35230075  | PRLR              | C/A | 0.034 | 0.040  | -0.504 | 0.6 (0.37-0.98)  | <b>0.0402</b> | -0.093 | 0.91 (0.6-1.39)  | 0.6657 |
| rs67257872  | 11 | 8530218   | STK33             | A/G | 0.431 | 0.014  | 0.120  | 1.13 (0.97-1.32) | 0.1243        | 0.043  | 1.04 (0.9-1.21)  | 0.5704 |
| rs78598185  | 14 | 92791479  | SLC24A4           | A/G | 0.091 | -0.029 | 0.083  | 1.09 (0.85-1.39) | 0.5108        | -0.014 | 0.99 (0.78-1.25) | 0.9069 |
| rs2378662   | 9  | 86707289  | AL390838.1        | A/G | 0.448 | -0.017 | -0.016 | 0.98 (0.85-1.14) | 0.8341        | -0.036 | 0.96 (0.84-1.11) | 0.6239 |
| rs668799    | 17 | 40716235  | COASY             | C/T | 0.260 | 0.018  | -0.053 | 0.95 (0.8-1.12)  | 0.5453        | -0.078 | 0.93 (0.79-1.08) | 0.3344 |
| rs4273010   | 15 | 44947434  | SPG11             | T/C | 0.012 | 0.128  | 0.385  | 1.47 (0.59-3.63) | 0.4045        | 0.203  | 1.23 (0.45-3.35) | 0.6921 |
| rs7254601   | 19 | 36147315  | COX6B1            | A/G | 0.251 | -0.016 | -0.069 | 0.93 (0.79-1.11) | 0.4352        | -0.095 | 0.91 (0.77-1.07) | 0.2595 |
| rs6749680   | 2  | 73685852  | ALMS1             | A/G | 0.393 | 0.015  | -0.115 | 0.89 (0.77-1.04) | 0.1344        | 0.050  | 1.05 (0.91-1.22) | 0.5080 |
| rs10841649  | 12 | 20954879  | SLC01B3           | C/T | 0.105 | 0.021  | -0.136 | 0.87 (0.66-1.15) | 0.3321        | 0.140  | 1.15 (0.9-1.47)  | 0.2606 |
| rs28929474  | 14 | 94844947  | SERPINA1          | T/C | 0.982 | -0.063 | 0.110  | 1.12 (0.62-2.02) | 0.7140        | -0.393 | 0.68 (0.41-1.11) | 0.1224 |
| rs6924225   | 6  | 45584732  | RUNX2             | G/A | 0.156 | 0.019  | -0.115 | 0.89 (0.73-1.09) | 0.2675        | -0.024 | 0.98 (0.8-1.19)  | 0.8088 |
| rs6701954   | 1  | 22022176  | USP48             | T/G | 0.464 | 0.014  | -0.130 | 0.88 (0.76-1.02) | 0.0935        | -0.069 | 0.93 (0.8-1.08)  | 0.3671 |
| rs4823324   | 22 | 46238123  | ATXN10            | T/C | 0.394 | 0.016  | 0.056  | 1.06 (0.91-1.22) | 0.4552        | -0.001 | 1 (0.87-1.15)    | 0.9877 |
| rs10908903  | 9  | 92228559  | GADD45G           | T/G | 0.472 | 0.015  | 0.075  | 1.08 (0.94-1.24) | 0.2974        | -0.002 | 1 (0.87-1.15)    | 0.9734 |
| rs1535793   | 13 | 47154966  | LRCH1             | A/G | 0.266 | 0.024  | 0.035  | 1.04 (0.88-1.23) | 0.6784        | -0.011 | 0.99 (0.85-1.16) | 0.8929 |
| rs6602909   | 13 | 114551993 | GAS6              | T/C | 0.320 | -0.020 | -0.105 | 0.9 (0.76-1.06)  | 0.2154        | 0.051  | 1.05 (0.89-1.24) | 0.5421 |
| rs13418037  | 2  | 218314141 | DIRC3             | C/T | 0.181 | -0.020 | 0.055  | 1.06 (0.87-1.28) | 0.5716        | 0.137  | 1.15 (0.96-1.38) | 0.1396 |
| rs114949263 | 7  | 150498245 | TMEM176B/TMEM176A | T/C | 0.088 | 0.027  | 0.113  | 1.12 (0.86-1.46) | 0.4031        | 0.084  | 1.09 (0.85-1.4)  | 0.5112 |



## IGF-1, IGFBP-3 and prognosis of renal cancer

|             |    |           |                   |     |       |        |        |                  |               |        |                  |               |
|-------------|----|-----------|-------------------|-----|-------|--------|--------|------------------|---------------|--------|------------------|---------------|
| rs7921105   | 10 | 13535398  | BEND7             | T/C | 0.429 | -0.016 | -0.034 | 0.97 (0.84-1.12) | 0.6512        | 0.170  | 1.19 (1.03-1.37) | <b>0.0176</b> |
| rs9657541   | 8  | 10643164  | SOX7/PINX1/PINX1  | C/T | 0.224 | 0.020  | 0.002  | 1 (0.84-1.2)     | 0.9790        | -0.054 | 0.95 (0.79-1.13) | 0.5515        |
| rs6544549   | 2  | 42693056  | KCNG3             | T/C | 0.128 | 0.024  | 0.049  | 1.05 (0.84-1.32) | 0.6712        | -0.043 | 0.96 (0.77-1.19) | 0.6957        |
| rs1495741   | 8  | 18272881  | NAT2              | A/G | 0.219 | -0.026 | 0.059  | 1.06 (0.89-1.27) | 0.5209        | 0.038  | 1.04 (0.87-1.24) | 0.6757        |
| rs28650790  | 5  | 55861464  | C5orf67           | C/T | 0.191 | -0.018 | 0.075  | 1.08 (0.89-1.3)  | 0.4425        | 0.102  | 1.11 (0.92-1.33) | 0.2719        |
| rs2250014   | 17 | 57836134  | VMP1              | T/C | 0.164 | -0.021 | 0.061  | 1.06 (0.88-1.29) | 0.5326        | 0.163  | 1.18 (0.98-1.41) | 0.0781        |
| rs7783012   | 7  | 114116881 | FOXP2             | A/G | 0.408 | -0.016 | -0.046 | 0.96 (0.83-1.1)  | 0.5334        | -0.074 | 0.93 (0.81-1.07) | 0.3093        |
| rs79076440  | 15 | 63803863  | USP3              | A/G | 0.163 | 0.019  | 0.083  | 1.09 (0.89-1.32) | 0.4024        | -0.007 | 0.99 (0.82-1.21) | 0.9414        |
| rs6532798   | 4  | 100054827 | ADH4              | T/C | 0.312 | 0.037  | 0.001  | 1 (0.85-1.17)    | 0.9936        | 0.032  | 1.03 (0.88-1.21) | 0.6915        |
| rs10777540  | 12 | 94150321  | CRADD             | T/G | 0.482 | -0.018 | -0.163 | 0.85 (0.73-0.99) | <b>0.0344</b> | 0.077  | 1.08 (0.93-1.25) | 0.3071        |
| rs1786342   | 8  | 101676363 | SNX31             | T/C | 0.395 | 0.017  | -0.114 | 0.89 (0.77-1.03) | 0.1313        | -0.028 | 0.97 (0.84-1.13) | 0.7076        |
| rs2978062   | 8  | 134571618 | ST3GAL1           | T/G | 0.163 | -0.019 | 0.064  | 1.07 (0.87-1.3)  | 0.5263        | -0.024 | 0.98 (0.8-1.19)  | 0.8115        |
| rs10821713  | 10 | 62055781  | ANK3              | C/T | 0.414 | -0.017 | -0.129 | 0.88 (0.75-1.03) | 0.1043        | -0.080 | 0.92 (0.79-1.07) | 0.2927        |
| rs1832007   | 10 | 5254847   | AKR1C4            | A/G | 0.164 | -0.057 | -0.018 | 0.98 (0.81-1.19) | 0.8536        | -0.038 | 0.96 (0.8-1.16)  | 0.6896        |
| rs6440008   | 3  | 141154542 | ZBTB38            | T/C | 0.377 | 0.035  | -0.029 | 0.97 (0.83-1.14) | 0.7215        | 0.049  | 1.05 (0.9-1.23)  | 0.5307        |
| rs1165196   | 6  | 25813150  | SLC17A1           | A/G | 0.464 | -0.029 | 0.157  | 1.17 (1-1.36)    | <b>0.0430</b> | -0.029 | 0.97 (0.83-1.13) | 0.7079        |
| rs9892862   | 17 | 7439014   | POLR2A            | G/A | 0.206 | 0.022  | 0.042  | 1.04 (0.87-1.25) | 0.6558        | -0.059 | 0.94 (0.78-1.13) | 0.5260        |
| rs6760135   | 2  | 26088769  | ASXL2             | C/T | 0.204 | -0.050 | 0.041  | 1.04 (0.87-1.25) | 0.6636        | 0.192  | 1.21 (1.02-1.44) | <b>0.0327</b> |
| rs7574340   | 2  | 40621239  | SLC8A1            | C/T | 0.285 | -0.017 | 0.185  | 1.2 (1.01-1.43)  | <b>0.0355</b> | 0.082  | 1.09 (0.92-1.29) | 0.3406        |
| rs117529631 | 11 | 46159633  | AC024475.4        | C/T | 0.034 | -0.041 | -0.099 | 0.91 (0.61-1.35) | 0.6249        | -0.034 | 0.97 (0.67-1.39) | 0.8564        |
| rs1061657   | 12 | 115108136 | TBX3              | T/C | 0.260 | -0.022 | 0.074  | 1.08 (0.88-1.31) | 0.4654        | -0.157 | 0.85 (0.7-1.04)  | 0.1136        |
| rs585187    | 18 | 58177124  | MRPS5P4           | T/G | 0.539 | 0.015  | 0.128  | 1.14 (0.98-1.31) | 0.0858        | 0.036  | 1.04 (0.9-1.2)   | 0.6225        |
| rs202676    | 11 | 49227620  | FOLH1             | G/A | 0.767 | 0.021  | -0.014 | 0.99 (0.82-1.18) | 0.8809        | 0.016  | 1.02 (0.85-1.21) | 0.8626        |
| rs340837    | 1  | 214162734 | PROX1             | T/G | 0.485 | -0.021 | -0.127 | 0.88 (0.76-1.02) | 0.0900        | -0.100 | 0.9 (0.78-1.04)  | 0.1700        |
| rs11782452  | 8  | 26361601  | BNIP3L            | G/A | 0.400 | 0.015  | -0.194 | 0.82 (0.7-0.96)  | <b>0.0163</b> | -0.133 | 0.88 (0.75-1.02) | 0.0879        |
| rs10509746  | 10 | 102656897 | PAX2              | C/T | 0.431 | 0.027  | 0.081  | 1.08 (0.93-1.26) | 0.3032        | 0.084  | 1.09 (0.93-1.26) | 0.2778        |
| rs8097893   | 18 | 74983055  | GALR1             | A/G | 0.041 | 0.058  | 0.185  | 1.2 (0.81-1.79)  | 0.3591        | 0.163  | 1.18 (0.8-1.73)  | 0.4085        |
| rs1825813   | 1  | 92708973  | C1orf146          | G/A | 0.190 | -0.023 | -0.059 | 0.94 (0.78-1.14) | 0.5485        | -0.068 | 0.93 (0.77-1.13) | 0.4855        |
| rs4545755   | 15 | 51549044  | MIR4713HG/CYP19A1 | G/A | 0.435 | 0.016  | 0.019  | 1.02 (0.88-1.19) | 0.8029        | -0.067 | 0.94 (0.8-1.09)  | 0.3872        |
| rs78357146  | 17 | 64305051  | PRKCA             | A/G | 0.010 | -0.090 | -0.007 | 0.99 (0.48-2.04) | 0.9839        | -0.075 | 0.93 (0.43-2)    | 0.8474        |
| rs870796    | 7  | 45426435  | ELK1P1            | G/A | 0.454 | 0.017  | -0.056 | 0.95 (0.8-1.12)  | 0.5216        | -0.061 | 0.94 (0.79-1.12) | 0.4889        |
| rs11031058  | 11 | 30375889  | ARL14EP           | C/T | 0.146 | -0.022 | -0.129 | 0.88 (0.71-1.09) | 0.2358        | -0.077 | 0.93 (0.76-1.13) | 0.4598        |
| rs296361    | 19 | 48389363  | SULT2A1           | G/A | 0.158 | -0.025 | 0.056  | 1.06 (0.88-1.27) | 0.5564        | -0.156 | 0.86 (0.71-1.03) | 0.1041        |
| rs11111274  | 12 | 102838128 | IGF1              | A/G | 0.270 | -0.080 | 0.175  | 1.19 (1.02-1.4)  | <b>0.0303</b> | 0.086  | 1.09 (0.94-1.27) | 0.2662        |
| rs1039481   | 11 | 48182237  | PTPRJ             | A/G | 0.262 | -0.042 | -0.069 | 0.93 (0.79-1.11) | 0.4223        | -0.008 | 0.99 (0.84-1.17) | 0.9221        |
| rs7314285   | 12 | 111522026 | CUX2              | T/G | 0.074 | -0.052 | 0.242  | 1.27 (0.99-1.65) | 0.0640        | 0.093  | 1.1 (0.84-1.43)  | 0.4903        |
| rs61904289  | 11 | 85994731  | AP003084.1        | C/T | 0.311 | -0.016 | -0.012 | 0.99 (0.84-1.16) | 0.8831        | -0.160 | 0.85 (0.73-0.99) | <b>0.0423</b> |
| rs1351394   | 12 | 66351826  | HMGA2             | C/T | 0.458 | 0.024  | -0.056 | 0.95 (0.81-1.1)  | 0.4619        | -0.021 | 0.98 (0.84-1.14) | 0.7843        |
| rs76708468  | 17 | 62206299  | ERN1              | T/C | 0.008 | -0.087 | 0.385  | 1.47 (0.68-3.17) | 0.3267        | 0.000  | 1 (0.45-2.23)    | 0.9997        |

## IGF-1, IGFBP-3 and prognosis of renal cancer

|             |    |           |                   |     |       |        |        |                  |               |        |                  |               |
|-------------|----|-----------|-------------------|-----|-------|--------|--------|------------------|---------------|--------|------------------|---------------|
| rs147491123 | 16 | 72567795  | LINC01572         | C/T | 0.020 | 0.036  | -0.022 | 0.98 (0.56-1.72) | 0.9391        | 0.474  | 1.61 (1.04-2.47) | <b>0.0312</b> |
| rs8024330   | 15 | 67443926  | SMAD3             | C/T | 0.305 | 0.018  | -0.087 | 0.92 (0.78-1.08) | 0.2976        | 0.029  | 1.03 (0.88-1.2)  | 0.7107        |
| rs12141189  | 1  | 221053545 | HLX               | C/T | 0.774 | -0.045 | -0.164 | 0.85 (0.72-1)    | 0.0535        | 0.020  | 1.02 (0.86-1.2)  | 0.8158        |
| rs12108803  | 5  | 77158507  | TBCA              | T/G | 0.042 | -0.033 | -0.007 | 0.99 (0.69-1.42) | 0.9677        | 0.259  | 1.3 (0.92-1.82)  | 0.1365        |
| rs708108    | 1  | 228189855 | WNT3A             | C/T | 0.369 | -0.015 | -0.121 | 0.89 (0.75-1.05) | 0.1632        | 0.035  | 1.04 (0.88-1.22) | 0.6727        |
| rs2207132   | 20 | 39142516  | MAFB              | G/A | 0.006 | 0.048  | -0.014 | 0.99 (0.45-2.18) | 0.9717        | 0.211  | 1.24 (0.57-2.67) | 0.5904        |
| rs9532512   | 13 | 40769897  | LINC00598         | G/A | 0.185 | -0.043 | -0.187 | 0.83 (0.68-1.01) | 0.0637        | -0.002 | 1 (0.83-1.2)     | 0.9848        |
| rs11954036  | 5  | 59028853  | PDE4D             | T/C | 0.347 | 0.037  | -0.004 | 1 (0.85-1.17)    | 0.9643        | -0.038 | 0.96 (0.83-1.12) | 0.6291        |
| rs2724373   | 1  | 207999200 | C1orf132          | C/T | 0.330 | 0.019  | -0.077 | 0.93 (0.79-1.08) | 0.3320        | -0.053 | 0.95 (0.81-1.11) | 0.5068        |
| rs569356    | 1  | 29136686  | OPRD1             | A/G | 0.122 | -0.027 | -0.059 | 0.94 (0.76-1.18) | 0.6049        | -0.041 | 0.96 (0.78-1.19) | 0.7034        |
| rs11677980  | 2  | 30522137  | LBH               | A/G | 0.318 | -0.015 | -0.158 | 0.85 (0.72-1.02) | 0.0755        | -0.082 | 0.92 (0.78-1.09) | 0.3337        |
| rs6501601   | 17 | 71124903  | SLC39A11          | G/A | 0.354 | 0.015  | 0.014  | 1.01 (0.86-1.19) | 0.8654        | 0.040  | 1.04 (0.89-1.22) | 0.6109        |
| rs16897515  | 6  | 27278020  | POM121L2          | A/C | 0.845 | -0.023 | 0.226  | 1.25 (1.01-1.56) | <b>0.0402</b> | 0.076  | 1.08 (0.88-1.33) | 0.4738        |
| rs62136965  | 2  | 44347953  | snRNA             | T/C | 0.037 | -0.037 | 0.157  | 1.17 (0.83-1.65) | 0.3754        | -0.003 | 1 (0.71-1.41)    | 0.9869        |
| rs11149612  | 16 | 83980965  | AC009119.2        | C/T | 0.402 | 0.027  | 0.097  | 1.1 (0.92-1.32)  | 0.2882        | 0.062  | 1.06 (0.9-1.26)  | 0.4657        |
| rs17714046  | 5  | 180661980 | TRIM41            | C/T | 0.999 | 0.042  | N/A    | N/A              | N/A           | N/A    | N/A              | N/A           |
| rs13301073  | 9  | 128284378 | MAPKAP1           | G/A | 0.353 | 0.022  | -0.029 | 0.97 (0.84-1.13) | 0.7026        | 0.150  | 1.16 (1-1.34)    | <b>0.0450</b> |
| rs17050272  | 2  | 121306440 | AC073257.2        | G/A | 0.413 | 0.024  | -0.100 | 0.9 (0.77-1.06)  | 0.2057        | -0.042 | 0.96 (0.82-1.12) | 0.5936        |
| rs10913351  | 1  | 177447742 | AL122019.1        | G/A | 0.056 | -0.032 | -0.109 | 0.9 (0.64-1.25)  | 0.5164        | 0.046  | 1.05 (0.77-1.42) | 0.7672        |
| rs76393968  | 8  | 16282937  | MSR1              | G/A | 0.003 | 0.060  | -0.064 | 0.94 (0.23-3.89) | 0.9294        | -0.363 | 0.7 (0.09-5.1)   | 0.7213        |
| rs7267595   | 20 | 10643850  | JAG1              | A/C | 0.481 | 0.015  | -0.032 | 0.97 (0.84-1.12) | 0.6715        | 0.024  | 1.02 (0.89-1.18) | 0.7350        |
| rs35641591  | 2  | 70323994  | PCBP1-AS1         | C/T | 0.016 | 0.050  | -0.295 | 0.74 (0.37-1.51) | 0.4153        | 0.582  | 1.79 (1.04-3.09) | <b>0.0363</b> |
| rs58387407  | 2  | 152924773 | CACNB4            | A/G | 0.202 | -0.018 | -0.065 | 0.94 (0.79-1.12) | 0.4646        | -0.109 | 0.9 (0.76-1.06)  | 0.2054        |
| rs6916994   | 6  | 87991236  | GJB7              | C/T | 0.505 | 0.029  | -0.016 | 0.98 (0.85-1.14) | 0.8303        | -0.037 | 0.96 (0.84-1.11) | 0.6134        |
| rs10869022  | 9  | 74057313  | TRPM3             | C/T | 0.203 | 0.021  | 0.068  | 1.07 (0.88-1.3)  | 0.4892        | 0.153  | 1.16 (0.97-1.4)  | 0.0998        |
| rs142377191 | 17 | 61649170  | DCAF7             | G/A | 0.002 | -0.125 | N/A    | N/A              | N/A           | N/A    | N/A              | N/A           |
| rs17258904  | 6  | 21928131  | CASC15            | A/G | 0.264 | -0.017 | -0.153 | 0.86 (0.74-1)    | 0.0524        | -0.038 | 0.96 (0.83-1.12) | 0.6140        |
| rs62182127  | 2  | 219279588 | VIL1              | A/G | 0.455 | 0.019  | -0.062 | 0.94 (0.81-1.09) | 0.4118        | 0.008  | 1.01 (0.87-1.16) | 0.9104        |
| rs411717    | 7  | 94033031  | COL1A2            | C/T | 0.448 | -0.015 | -0.045 | 0.96 (0.82-1.11) | 0.5488        | -0.025 | 0.98 (0.85-1.12) | 0.7249        |
| rs1061638   | 14 | 77928525  | AHSA1             | G/A | 0.302 | 0.018  | -0.083 | 0.92 (0.79-1.08) | 0.3035        | -0.042 | 0.96 (0.82-1.12) | 0.6045        |
| rs1465529   | 2  | 231039037 | SP110             | T/C | 0.294 | 0.019  | -0.100 | 0.91 (0.77-1.07) | 0.2350        | -0.134 | 0.87 (0.75-1.02) | 0.0944        |
| rs75088740  | 14 | 69819101  | GALNT16           | G/A | 0.151 | -0.019 | 0.113  | 1.12 (0.91-1.38) | 0.2922        | -0.063 | 0.94 (0.76-1.16) | 0.5566        |
| rs7539178   | 1  | 65383002  | JAK1              | A/C | 0.112 | -0.026 | 0.151  | 1.16 (0.94-1.43) | 0.1578        | -0.041 | 0.96 (0.77-1.2)  | 0.7182        |
| rs78607331  | 12 | 57648644  | R3HDM2            | T/C | 0.987 | -0.037 | -0.391 | 0.68 (0.36-1.28) | 0.2320        | -0.044 | 0.96 (0.5-1.84)  | 0.8948        |
| rs2607748   | 3  | 14158725  | CHCHD4            | T/C | 0.438 | -0.017 | 0.012  | 1.01 (0.88-1.17) | 0.8737        | 0.077  | 1.08 (0.94-1.24) | 0.2815        |
| rs10145154  | 14 | 79939525  | NRXN3             | C/T | 0.202 | -0.018 | -0.054 | 0.95 (0.79-1.14) | 0.5659        | 0.193  | 1.21 (1.02-1.45) | <b>0.0312</b> |
| rs11077337  | 16 | 3492048   | AC025283.2/ZNF597 | T/G | 0.455 | 0.015  | 0.099  | 1.1 (0.95-1.28)  | 0.1916        | -0.133 | 0.88 (0.76-1.01) | 0.0709        |
| rs11928797  | 3  | 33457493  | UBP1              | A/C | 0.902 | 0.030  | 0.115  | 1.12 (0.87-1.45) | 0.3827        | -0.040 | 0.96 (0.77-1.2)  | 0.7239        |

## IGF-1, IGFBP-3 and prognosis of renal cancer

|             |    |           |                     |     |       |        |        |                  |               |        |                  |               |
|-------------|----|-----------|---------------------|-----|-------|--------|--------|------------------|---------------|--------|------------------|---------------|
| rs4946810   | 6  | 107420270 | BEND3               | A/C | 0.381 | -0.016 | 0.014  | 1.01 (0.87-1.19) | 0.8643        | -0.083 | 0.92 (0.79-1.07) | 0.2833        |
| rs6437249   | 2  | 242175331 | HDLBP               | C/T | 0.277 | 0.019  | 0.045  | 1.05 (0.88-1.25) | 0.6169        | 0.137  | 1.15 (0.97-1.36) | 0.1088        |
| rs207212    | 7  | 130547217 | LINC00513           | C/T | 0.033 | 0.028  | -0.128 | 0.88 (0.5-1.56)  | 0.6616        | 0.161  | 1.17 (0.7-1.97)  | 0.5409        |
| rs62280667  | 3  | 101084604 | SENP7               | T/C | 0.315 | -0.028 | -0.110 | 0.9 (0.75-1.07)  | 0.2256        | -0.039 | 0.96 (0.81-1.14) | 0.6457        |
| rs2366398   | 5  | 89437963  | LINC01339           | G/T | 0.216 | -0.018 | -0.026 | 0.97 (0.81-1.17) | 0.7849        | 0.025  | 1.03 (0.86-1.22) | 0.7833        |
| rs112893170 | 3  | 57211863  | IL17RD              | T/C | 0.185 | 0.020  | -0.035 | 0.97 (0.8-1.17)  | 0.7185        | 0.077  | 1.08 (0.89-1.31) | 0.4283        |
| rs3772102   | 3  | 98502628  | ST3GAL6             | T/G | 0.453 | -0.020 | -0.036 | 0.96 (0.84-1.11) | 0.6149        | -0.040 | 0.96 (0.84-1.1)  | 0.5682        |
| rs62263345  | 3  | 107252190 | BBX                 | A/G | 0.118 | 0.028  | -0.069 | 0.93 (0.74-1.18) | 0.5665        | 0.052  | 1.05 (0.84-1.32) | 0.6494        |
| rs11187838  | 10 | 96038686  | PLCE1               | G/A | 0.426 | 0.024  | 0.023  | 1.02 (0.88-1.18) | 0.7604        | 0.095  | 1.1 (0.96-1.26)  | 0.1772        |
| rs11029620  | 11 | 3771924   | NUP98               | C/T | 0.227 | 0.022  | 0.126  | 1.13 (0.95-1.35) | 0.1605        | -0.061 | 0.94 (0.79-1.12) | 0.4968        |
| rs35862187  | 7  | 69625029  | AUTS2               | A/G | 0.035 | 0.031  | -0.413 | 0.66 (0.43-1.03) | 0.0647        | -0.275 | 0.76 (0.5-1.15)  | 0.1933        |
| rs7790246   | 7  | 32976416  | AVL9/RP9P           | C/T | 0.287 | -0.017 | 0.122  | 1.13 (0.96-1.32) | 0.1295        | -0.042 | 0.96 (0.82-1.12) | 0.5929        |
| rs504371    | 6  | 165724052 | C6orf118            | C/A | 0.350 | -0.015 | -0.076 | 0.93 (0.78-1.1)  | 0.3766        | 0.058  | 1.06 (0.9-1.25)  | 0.4877        |
| rs840809    | 5  | 87173927  | TMEM161B            | A/C | 0.257 | 0.016  | -0.100 | 0.9 (0.77-1.06)  | 0.2239        | -0.153 | 0.86 (0.73-1)    | 0.0565        |
| rs6435156   | 2  | 203425475 | BMPR2               | C/T | 0.248 | 0.024  | 0.124  | 1.13 (0.96-1.34) | 0.1407        | 0.040  | 1.04 (0.88-1.23) | 0.6267        |
| rs2674492   | 2  | 172422338 | CYBRD1              | G/A | 0.379 | -0.014 | 0.043  | 1.04 (0.89-1.22) | 0.5863        | 0.043  | 1.04 (0.89-1.22) | 0.5890        |
| rs750952    | 16 | 31093954  | ZNF646              | C/T | 0.396 | 0.032  | 0.026  | 1.03 (0.88-1.2)  | 0.7371        | 0.081  | 1.08 (0.94-1.26) | 0.2840        |
| rs165316    | 1  | 91533297  | RPL5P6              | A/G | 0.203 | -0.073 | 0.019  | 1.02 (0.86-1.21) | 0.8280        | -0.011 | 0.99 (0.84-1.16) | 0.8953        |
| rs13108218  | 4  | 3443931   | HGFAC               | G/A | 0.401 | 0.017  | 0.175  | 1.19 (1.01-1.4)  | <b>0.0383</b> | 0.000  | 1 (0.86-1.17)    | 0.9965        |
| rs2512525   | 11 | 77923019  | USP35               | T/C | 0.165 | 0.024  | 0.003  | 1 (0.82-1.22)    | 0.9763        | -0.146 | 0.86 (0.71-1.05) | 0.1428        |
| rs584955    | 6  | 7097141   | RREB1               | A/G | 0.038 | 0.036  | 0.099  | 1.1 (0.77-1.59)  | 0.5939        | 0.133  | 1.14 (0.8-1.63)  | 0.4625        |
| rs115805235 | 4  | 69764890  | AC021146.3          | C/T | 0.040 | 0.039  | 0.165  | 1.18 (0.81-1.71) | 0.3809        | -0.091 | 0.91 (0.63-1.33) | 0.6364        |
| rs3734166   | 5  | 137665323 | CDC25C              | A/G | 0.723 | 0.028  | -0.152 | 0.86 (0.73-1.01) | 0.0725        | -0.151 | 0.86 (0.74-1.01) | 0.0588        |
| rs1051006   | 11 | 47306585  | MADD                | A/G | 0.839 | 0.040  | -0.071 | 0.93 (0.76-1.13) | 0.4767        | -0.042 | 0.96 (0.79-1.16) | 0.6675        |
| rs625245    | 11 | 94192103  | MRE11               | T/G | 0.327 | -0.016 | 0.030  | 1.03 (0.89-1.2)  | 0.7009        | -0.041 | 0.96 (0.83-1.11) | 0.5885        |
| rs11175935  | 12 | 40693806  | LRRK2               | G/T | 0.183 | 0.020  | -0.004 | 1 (0.82-1.21)    | 0.9687        | -0.102 | 0.9 (0.76-1.08)  | 0.2646        |
| rs3858325   | 10 | 117988795 | GFRA1               | C/T | 0.472 | -0.019 | 0.043  | 1.04 (0.9-1.21)  | 0.5649        | -0.004 | 1 (0.86-1.15)    | 0.9529        |
| rs903908    | 1  | 2202967   | SKI                 | T/C | 0.502 | -0.016 | 0.085  | 1.09 (0.93-1.27) | 0.2805        | 0.036  | 1.04 (0.89-1.21) | 0.6446        |
| rs9361489   | 6  | 79816785  | PHIP                | T/C | 0.459 | 0.022  | 0.116  | 1.12 (0.96-1.31) | 0.1456        | 0.067  | 1.07 (0.92-1.24) | 0.3688        |
| rs2397112   | 6  | 52684333  | GSTA6P              | A/G | 0.430 | 0.019  | -0.084 | 0.92 (0.79-1.07) | 0.2653        | -0.050 | 0.95 (0.82-1.1)  | 0.4987        |
| rs5755948   | 22 | 36179095  | RBFOX2              | G/A | 0.130 | -0.028 | 0.087  | 1.09 (0.88-1.35) | 0.4231        | 0.042  | 1.04 (0.84-1.3)  | 0.7050        |
| rs12106594  | 22 | 31885316  | DRG1/EIF4ENIF1/SFI1 | C/T | 0.051 | -0.036 | 0.132  | 1.14 (0.83-1.57) | 0.4163        | 0.064  | 1.07 (0.77-1.48) | 0.7033        |
| rs7498665   | 16 | 28883241  | SH2B1               | G/A | 0.583 | 0.019  | -0.036 | 0.96 (0.83-1.12) | 0.6397        | -0.069 | 0.93 (0.8-1.08)  | 0.3705        |
| rs17747633  | 15 | 40916237  | KNL1                | G/A | 0.579 | 0.015  | -0.095 | 0.91 (0.78-1.05) | 0.2054        | -0.157 | 0.85 (0.74-0.99) | <b>0.0357</b> |
| rs62334147  | 4  | 169345005 | DDX60L              | T/C | 0.160 | -0.019 | 0.243  | 1.27 (1.04-1.56) | <b>0.0179</b> | 0.050  | 1.05 (0.86-1.29) | 0.6325        |
| rs2738787   | 20 | 62328375  | TNFRSF6B/RTKL1      | G/A | 0.080 | -0.037 | 0.012  | 1.01 (0.78-1.32) | 0.9289        | 0.120  | 1.13 (0.87-1.47) | 0.3717        |
| rs9322822   | 6  | 105369598 | LIN28B-AS1          | C/T | 0.326 | 0.015  | -0.005 | 1 (0.85-1.16)    | 0.9537        | -0.119 | 0.89 (0.77-1.03) | 0.1112        |
| rs9583151   | 13 | 107666257 | -                   | C/T | 0.502 | 0.014  | 0.001  | 1 (0.86-1.16)    | 0.9844        | -0.005 | 1 (0.86-1.15)    | 0.9491        |
| rs7517340   | 1  | 243710190 | AKT3                | C/T | 0.198 | 0.035  | -0.045 | 0.96 (0.79-1.15) | 0.6402        | -0.070 | 0.93 (0.78-1.12) | 0.4532        |

IGF-1, IGFBP-3 and prognosis of renal cancer

|             |    |           |                |     |       |        |        |                  |               |        |                  |               |
|-------------|----|-----------|----------------|-----|-------|--------|--------|------------------|---------------|--------|------------------|---------------|
| rs3127579   | 6  | 160674632 | SLC22A2        | G/A | 0.131 | -0.033 | 0.131  | 1.14 (0.93-1.39) | 0.2010        | 0.125  | 1.13 (0.93-1.38) | 0.2203        |
| rs12912439  | 15 | 95828705  | LINC01197      | C/T | 0.318 | -0.022 | -0.152 | 0.86 (0.74-1)    | 0.0549        | -0.028 | 0.97 (0.84-1.12) | 0.7039        |
| rs2104476   | 20 | 54852856  | -              | A/G | 0.261 | -0.020 | -0.042 | 0.96 (0.81-1.14) | 0.6270        | -0.118 | 0.89 (0.76-1.04) | 0.1482        |
| rs1431015   | 8  | 77131580  | HNFB4G         | C/T | 0.401 | 0.020  | 0.043  | 1.04 (0.9-1.22)  | 0.5818        | -0.025 | 0.98 (0.84-1.13) | 0.7422        |
| rs273956    | 7  | 137603188 | CREB3L2        | G/A | 0.410 | -0.021 | -0.151 | 0.86 (0.74-1.01) | 0.0583        | -0.105 | 0.9 (0.78-1.04)  | 0.1616        |
| rs2042253   | 5  | 143059433 | MIR5197        | T/C | 0.212 | 0.023  | -0.013 | 0.99 (0.82-1.19) | 0.8906        | 0.005  | 1.01 (0.84-1.21) | 0.9568        |
| rs56352849  | 8  | 73769173  | KCNB2          | G/A | 0.279 | -0.016 | -0.017 | 0.98 (0.83-1.17) | 0.8452        | 0.029  | 1.03 (0.87-1.21) | 0.7282        |
| rs6106324   | 20 | 20964988  | AL133465.1     | T/C | 0.392 | 0.019  | -0.113 | 0.89 (0.76-1.05) | 0.1582        | 0.120  | 1.13 (0.97-1.32) | 0.1300        |
| rs12194618  | 6  | 38091030  | ZFAND3         | G/A | 0.369 | -0.017 | -0.030 | 0.97 (0.83-1.14) | 0.7131        | 0.069  | 1.07 (0.92-1.25) | 0.3918        |
| rs12790261  | 11 | 66988048  | KDM2A          | C/A | 0.026 | -0.031 | -0.020 | 0.98 (0.62-1.54) | 0.9310        | -0.206 | 0.81 (0.48-1.38) | 0.4429        |
| rs76914895  | 1  | 23292603  | LACTBL1        | T/C | 0.043 | -0.027 | 0.065  | 1.07 (0.72-1.57) | 0.7438        | -0.296 | 0.74 (0.49-1.13) | 0.1627        |
| rs4418728   | 10 | 94839724  | CYP26A1        | G/T | 0.441 | 0.024  | -0.139 | 0.87 (0.76-1)    | <b>0.0493</b> | -0.041 | 0.96 (0.84-1.1)  | 0.5568        |
| rs12975366  | 19 | 54759361  | LILRB5         | C/T | 0.655 | -0.020 | -0.096 | 0.91 (0.73-1.12) | 0.3766        | -0.074 | 0.93 (0.74-1.16) | 0.5204        |
| rs60862542  | 8  | 109275071 | EIF3E          | G/A | 0.221 | 0.017  | 0.022  | 1.02 (0.86-1.21) | 0.8010        | -0.115 | 0.89 (0.75-1.06) | 0.1883        |
| rs62102136  | 19 | 34700561  | LSM14A         | C/T | 0.228 | 0.016  | -0.119 | 0.89 (0.72-1.09) | 0.2621        | -0.122 | 0.88 (0.72-1.08) | 0.2387        |
| rs2230281   | 12 | 89917518  | POC1B-GALNT4   | G/A | 0.276 | -0.016 | 0.110  | 1.12 (0.95-1.31) | 0.1835        | 0.106  | 1.11 (0.95-1.3)  | 0.1810        |
| rs15052     | 19 | 41813375  | HNRNPUL1/TGFB1 | T/C | 0.099 | -0.018 | 0.104  | 1.11 (0.86-1.43) | 0.4242        | 0.247  | 1.28 (1-1.64)    | 0.0523        |
| rs168961    | 14 | 69282930  | ZFP36L1        | A/G | 0.495 | -0.018 | 0.089  | 1.09 (0.94-1.27) | 0.2591        | 0.021  | 1.02 (0.88-1.19) | 0.7912        |
| rs75681856  | 1  | 174916323 | RABGAP1L       | C/T | 0.115 | -0.023 | 0.135  | 1.14 (0.9-1.45)  | 0.2639        | -0.146 | 0.86 (0.67-1.11) | 0.2462        |
| rs2273058   | 20 | 20033319  | CRNKL1         | G/A | 0.529 | -0.022 | 0.011  | 1.01 (0.88-1.16) | 0.8761        | 0.025  | 1.03 (0.9-1.18)  | 0.7133        |
| rs67868323  | 19 | 4048561   | ZBTB7A         | T/G | 0.216 | 0.016  | -0.034 | 0.97 (0.8-1.17)  | 0.7305        | -0.107 | 0.9 (0.74-1.09)  | 0.2840        |
| rs17400325  | 2  | 178565913 | PDE11A         | C/T | 0.973 | 0.054  | 0.100  | 1.1 (0.71-1.72)  | 0.6592        | 0.093  | 1.1 (0.7-1.73)   | 0.6883        |
| rs12454712  | 18 | 60845884  | BCL2           | T/C | 0.372 | 0.018  | 0.044  | 1.04 (0.9-1.21)  | 0.5598        | 0.019  | 1.02 (0.88-1.18) | 0.8018        |
| rs199525    | 17 | 44847834  | WNT3           | T/G | 0.209 | -0.020 | 0.116  | 1.12 (0.94-1.34) | 0.2014        | -0.188 | 0.83 (0.69-1)    | <b>0.0483</b> |
| rs190102446 | 18 | 57048571  | -              | C/T | 0.027 | 0.041  | 0.419  | 1.52 (1-2.3)     | <b>0.0474</b> | 0.019  | 1.02 (0.66-1.58) | 0.9338        |
| rs11152071  | 18 | 56087417  | AC105105.3     | C/T | 0.238 | 0.020  | -0.102 | 0.9 (0.76-1.07)  | 0.2355        | 0.016  | 1.02 (0.86-1.2)  | 0.8441        |
| rs35668185  | 5  | 168256455 | SLIT3          | T/C | 0.187 | 0.056  | -0.029 | 0.97 (0.8-1.18)  | 0.7669        | 0.186  | 1.2 (1-1.45)     | <b>0.0480</b> |
| rs8095538   | 18 | 1616505   | -              | T/G | 0.304 | -0.020 | -0.053 | 0.95 (0.81-1.11) | 0.5150        | -0.070 | 0.93 (0.8-1.09)  | 0.3801        |
| rs11079157  | 17 | 53360799  | HLF            | G/T | 0.220 | -0.020 | 0.043  | 1.04 (0.87-1.25) | 0.6411        | -0.112 | 0.89 (0.74-1.07) | 0.2339        |
| rs4789227   | 17 | 73794354  | UNK            | T/C | 0.366 | 0.015  | 0.055  | 1.06 (0.9-1.24)  | 0.5044        | -0.018 | 0.98 (0.84-1.15) | 0.8261        |
| rs1548917   | 16 | 56109333  | CES5A          | C/T | 0.464 | -0.015 | -0.020 | 0.98 (0.84-1.15) | 0.8038        | 0.059  | 1.06 (0.91-1.23) | 0.4489        |
| rs6510033   | 19 | 30710785  | AC005597.1     | A/G | 0.265 | 0.020  | -0.029 | 0.97 (0.81-1.17) | 0.7551        | 0.008  | 1.01 (0.85-1.2)  | 0.9271        |
| rs7578633   | 2  | 113978650 | PAX8           | C/T | 0.358 | -0.018 | -0.039 | 0.96 (0.82-1.13) | 0.6301        | 0.065  | 1.07 (0.92-1.24) | 0.3847        |
| rs445036    | 8  | 81408409  | ZBTB10         | T/C | 0.292 | 0.019  | -0.048 | 0.95 (0.81-1.12) | 0.5574        | -0.040 | 0.96 (0.82-1.13) | 0.6235        |
| rs12549853  | 8  | 145020636 | PLEC           | G/A | 0.399 | -0.016 | -0.023 | 0.98 (0.83-1.15) | 0.7865        | -0.047 | 0.95 (0.81-1.12) | 0.5633        |
| rs111443396 | 4  | 124773202 | LINC01091      | T/C | 0.125 | -0.026 | 0.093  | 1.1 (0.89-1.35)  | 0.3877        | -0.204 | 0.82 (0.65-1.02) | 0.0690        |
| rs4936759   | 11 | 122763516 | C11orf63       | C/T | 0.449 | 0.016  | 0.189  | 1.21 (1.03-1.41) | <b>0.0177</b> | 0.114  | 1.12 (0.97-1.3)  | 0.1337        |
| rs17429745  | 4  | 106038169 | AC096577.1     | G/T | 0.329 | 0.026  | 0.059  | 1.06 (0.91-1.24) | 0.4650        | -0.009 | 0.99 (0.85-1.16) | 0.9125        |
| rs2287922   | 19 | 49232226  | RASIP1         | A/G | 0.512 | -0.030 | -0.030 | 0.97 (0.83-1.14) | 0.7115        | 0.035  | 1.04 (0.89-1.21) | 0.6527        |



## IGF-1, IGFBP-3 and prognosis of renal cancer

|             |    |           |              |     |       |        |        |                  |               |        |                  |               |
|-------------|----|-----------|--------------|-----|-------|--------|--------|------------------|---------------|--------|------------------|---------------|
| rs28396553  | 14 | 36673392  | lincRNA      | T/C | 0.443 | 0.015  | -0.148 | 0.86 (0.72-1.04) | 0.1128        | 0.152  | 1.16 (0.96-1.41) | 0.1175        |
| rs6037508   | 20 | 3217989   | SLC4A11      | T/G | 0.287 | -0.017 | 0.100  | 1.1 (0.93-1.31)  | 0.2423        | -0.020 | 0.98 (0.83-1.16) | 0.8166        |
| rs17360994  | 1  | 27278573  | KDF1         | C/T | 0.926 | -0.042 | 0.024  | 1.02 (0.78-1.35) | 0.8655        | -0.055 | 0.95 (0.72-1.25) | 0.6982        |
| rs7628689   | 3  | 88216647  | C3orf38      | G/A | 0.135 | 0.029  | -0.066 | 0.94 (0.75-1.17) | 0.5609        | -0.057 | 0.94 (0.76-1.17) | 0.6078        |
| rs5896      | 11 | 46745003  | F2           | T/C | 0.885 | 0.036  | 0.058  | 1.06 (0.84-1.34) | 0.6246        | -0.096 | 0.91 (0.73-1.13) | 0.3982        |
| rs2296198   | 6  | 18399750  | RNF144B      | C/T | 0.248 | 0.016  | 0.062  | 1.06 (0.89-1.28) | 0.5075        | 0.082  | 1.09 (0.91-1.3)  | 0.3680        |
| rs66707192  | 3  | 186382065 | HRG          | G/A | 0.256 | 0.018  | -0.079 | 0.92 (0.78-1.1)  | 0.3640        | -0.040 | 0.96 (0.82-1.13) | 0.6244        |
| rs62020698  | 15 | 43237414  | UBR1         | C/T | 0.039 | 0.047  | 0.179  | 1.2 (0.75-1.91)  | 0.4554        | 0.080  | 1.08 (0.66-1.78) | 0.7537        |
| rs8059803   | 16 | 81603001  | CMIP         | A/G | 0.285 | 0.031  | 0.042  | 1.04 (0.88-1.24) | 0.6285        | -0.024 | 0.98 (0.83-1.15) | 0.7722        |
| rs26822     | 5  | 102518795 | PPIP5K2      | A/G | 0.289 | -0.017 | -0.174 | 0.84 (0.72-0.99) | <b>0.0319</b> | 0.052  | 1.05 (0.91-1.22) | 0.4931        |
| rs9738365   | 12 | 31997635  | -            | C/A | 0.261 | -0.058 | 0.032  | 1.03 (0.88-1.21) | 0.6953        | -0.020 | 0.98 (0.84-1.15) | 0.8034        |
| rs17299478  | 16 | 69775500  | -            | C/T | 0.143 | 0.032  | -0.177 | 0.84 (0.67-1.05) | 0.1237        | -0.106 | 0.9 (0.73-1.11)  | 0.3323        |
| rs247917    | 12 | 46265916  | ARID2        | C/T | 0.497 | -0.015 | -0.050 | 0.95 (0.82-1.1)  | 0.5081        | 0.044  | 1.05 (0.9-1.22)  | 0.5671        |
| rs13168379  | 5  | 173382761 | CPEB4        | G/A | 0.070 | -0.031 | -0.145 | 0.86 (0.64-1.17) | 0.3465        | -0.144 | 0.87 (0.65-1.15) | 0.3262        |
| rs6974707   | 7  | 55982894  | ZNF713       | G/A | 0.217 | -0.019 | 0.124  | 1.13 (0.95-1.35) | 0.1689        | -0.032 | 0.97 (0.81-1.15) | 0.7213        |
| rs1427676   | 2  | 204741166 | CTLA4        | T/C | 0.301 | 0.015  | -0.111 | 0.89 (0.77-1.04) | 0.1573        | -0.096 | 0.91 (0.78-1.06) | 0.2133        |
| rs36086195  | 1  | 16510894  | ARHGEF19-AS1 | T/C | 0.428 | -0.019 | 0.048  | 1.05 (0.91-1.21) | 0.5210        | 0.005  | 1.01 (0.87-1.16) | 0.9433        |
| rs8054322   | 16 | 85201405  | GSE1         | G/A | 0.453 | -0.015 | 0.067  | 1.07 (0.91-1.26) | 0.4251        | 0.199  | 1.22 (1.04-1.44) | <b>0.0159</b> |
| rs117104648 | 11 | 65543736  | AP5B1        | T/C | 0.030 | -0.036 | 0.121  | 1.13 (0.73-1.74) | 0.5836        | 0.451  | 1.57 (1.05-2.35) | <b>0.0282</b> |
| rs77369503  | 1  | 163027266 | RGS4         | G/A | 0.008 | 0.045  | -0.386 | 0.68 (0.27-1.7)  | 0.4081        | -0.144 | 0.87 (0.37-2.01) | 0.7378        |
| rs7256521   | 19 | 53837110  | ZNF845       | A/G | 0.484 | -0.015 | -0.006 | 0.99 (0.84-1.17) | 0.9434        | 0.077  | 1.08 (0.92-1.27) | 0.3600        |
| rs998584    | 6  | 43757896  | VEGFA        | A/C | 0.532 | 0.020  | -0.124 | 0.88 (0.73-1.06) | 0.1858        | -0.055 | 0.95 (0.78-1.14) | 0.5674        |
| rs4547160   | 12 | 63503650  | AVPR1A       | G/T | 0.356 | -0.018 | 0.000  | 1 (0.86-1.17)    | 0.9978        | -0.065 | 0.94 (0.8-1.1)   | 0.4216        |
| rs4985062   | 16 | 8996636   | USP7         | T/C | 0.428 | 0.015  | -0.171 | 0.84 (0.72-0.99) | <b>0.0357</b> | -0.136 | 0.87 (0.75-1.02) | 0.0862        |
| rs79936318  | 14 | 64315556  | SYNE2        | G/A | 0.075 | -0.017 | 0.282  | 1.33 (0.9-1.95)  | 0.1530        | 0.301  | 1.35 (0.92-1.97) | 0.1208        |
| rs3804173   | 4  | 121719923 | PRDM5        | A/G | 0.328 | -0.020 | 0.112  | 1.12 (0.96-1.3)  | 0.1513        | 0.033  | 1.03 (0.89-1.19) | 0.6550        |
| rs12244851  | 10 | 114773926 | TCF7L2       | C/T | 0.313 | -0.015 | 0.004  | 1 (0.85-1.19)    | 0.9619        | 0.052  | 1.05 (0.9-1.23)  | 0.5267        |
| rs1260326   | 2  | 27730940  | GCKR         | C/T | 0.399 | 0.063  | 0.083  | 1.09 (0.93-1.27) | 0.2976        | 0.011  | 1.01 (0.87-1.17) | 0.8825        |
| rs716100    | 8  | 135661278 | ZFAT         | G/A | 0.301 | -0.019 | 0.098  | 1.1 (0.94-1.29)  | 0.2317        | 0.108  | 1.11 (0.95-1.3)  | 0.1803        |
| rs16995311  | 20 | 49201102  | PTPN1        | A/C | 0.063 | 0.040  | 0.153  | 1.16 (0.88-1.54) | 0.2857        | 0.128  | 1.14 (0.86-1.5)  | 0.3609        |
| rs34040697  | 15 | 97125666  | -            | A/G | 0.427 | 0.016  | -0.031 | 0.97 (0.82-1.14) | 0.7174        | -0.084 | 0.92 (0.78-1.08) | 0.3127        |
| rs8084351   | 18 | 50726559  | DCC          | G/A | 0.507 | 0.015  | -0.072 | 0.93 (0.8-1.08)  | 0.3437        | -0.088 | 0.92 (0.79-1.06) | 0.2372        |
| rs8033075   | 15 | 68353652  | PIAS1        | A/G | 0.043 | 0.045  | 0.182  | 1.2 (0.83-1.72)  | 0.3261        | 0.423  | 1.53 (1.09-2.14) | <b>0.0137</b> |
| rs11242236  | 5  | 134586980 | C5orf66      | G/A | 0.458 | 0.025  | -0.146 | 0.86 (0.74-1.01) | 0.0672        | 0.011  | 1.01 (0.87-1.18) | 0.8900        |
| rs16845929  | 4  | 72017058  | SLC4A4       | C/T | 0.062 | 0.032  | 0.017  | 1.02 (0.77-1.35) | 0.9057        | -0.178 | 0.84 (0.62-1.13) | 0.2417        |
| rs6473015   | 8  | 78178485  | lincRNA      | A/C | 0.282 | -0.019 | -0.016 | 0.98 (0.83-1.17) | 0.8506        | 0.003  | 1 (0.85-1.18)    | 0.9698        |
| rs33932084  | 6  | 28268824  | PGBD1        | G/A | 0.922 | -0.034 | 0.207  | 1.23 (0.92-1.65) | 0.1653        | 0.197  | 1.22 (0.92-1.62) | 0.1753        |
| rs13073970  | 3  | 170630520 | EIF5A2       | G/T | 0.192 | -0.025 | 0.033  | 1.03 (0.86-1.24) | 0.7212        | -0.110 | 0.9 (0.75-1.08)  | 0.2436        |
| rs2802330   | 1  | 26466831  | PDIK1L       | A/G | 0.176 | -0.031 | -0.130 | 0.88 (0.72-1.07) | 0.1989        | -0.034 | 0.97 (0.8-1.17)  | 0.7235        |

## IGF-1, IGFBP-3 and prognosis of renal cancer

|             |    |           |                |     |       |        |        |                  |               |        |                  |               |
|-------------|----|-----------|----------------|-----|-------|--------|--------|------------------|---------------|--------|------------------|---------------|
| rs73238159  | 3  | 142078759 | XRN1           | T/C | 0.873 | -0.025 | 0.230  | 1.26 (0.99-1.6)  | 0.0633        | 0.001  | 1 (0.79-1.27)    | 0.9911        |
| rs80170948  | 5  | 64020316  | SREK1IP1       | T/G | 0.025 | -0.039 | 0.035  | 1.04 (0.66-1.63) | 0.8812        | -0.275 | 0.76 (0.44-1.3)  | 0.3162        |
| rs293275    | 10 | 53215020  | PRKG1          | T/C | 0.509 | -0.014 | -0.027 | 0.97 (0.84-1.13) | 0.7207        | -0.042 | 0.96 (0.83-1.11) | 0.5663        |
| rs55707100  | 15 | 43820717  | MAP1A          | T/C | 0.974 | -0.151 | 0.173  | 1.19 (0.69-2.06) | 0.5347        | -0.094 | 0.91 (0.56-1.48) | 0.7051        |
| rs5742915   | 15 | 74336633  | PML            | C/T | 0.554 | 0.025  | -0.077 | 0.93 (0.8-1.07)  | 0.3054        | -0.004 | 1 (0.86-1.15)    | 0.9607        |
| rs78460947  | 11 | 56143715  | OR8U1          | G/A | 0.994 | 0.042  | -0.137 | 0.87 (0.27-2.82) | 0.8183        | 31.660 | 0.97 (0.72-1.31) | 1.0000        |
| rs111792934 | 16 | 69131293  | HAS3           | C/T | 0.154 | 0.022  | -0.017 | 0.98 (0.8-1.21)  | 0.8719        | 0.248  | 1.28 (1.06-1.56) | <b>0.0122</b> |
| rs3213223   | 11 | 2156930   | IGF2/INS-IGF-2 | G/A | 0.179 | -0.076 | 0.047  | 1.05 (0.86-1.28) | 0.6363        | -0.114 | 0.89 (0.72-1.1)  | 0.2886        |
| rs12211977  | 6  | 161252770 | lincRNA        | G/A | 0.093 | -0.023 | 0.109  | 1.12 (0.86-1.44) | 0.4029        | 0.232  | 1.26 (0.99-1.61) | 0.0634        |
| rs10779509  | 1  | 209728370 | AL023754.1     | T/C | 0.433 | -0.014 | -0.032 | 0.97 (0.84-1.12) | 0.6744        | -0.115 | 0.89 (0.77-1.03) | 0.1106        |
| rs11717397  | 3  | 23368583  | UBE2E2         | G/A | 0.449 | 0.015  | -0.005 | 1 (0.86-1.16)    | 0.9488        | -0.044 | 0.96 (0.83-1.11) | 0.5551        |
| rs17323117  | 2  | 230162971 | PID1           | A/G | 0.059 | -0.029 | 0.008  | 1.01 (0.74-1.36) | 0.9611        | -0.026 | 0.97 (0.72-1.31) | 0.8639        |
| rs175043    | 14 | 75471803  | EIF2B2         | G/A | 0.444 | 0.018  | -0.144 | 0.87 (0.75-1)    | 0.0515        | -0.156 | 0.86 (0.74-0.99) | <b>0.0308</b> |
| rs12597502  | 16 | 53170069  | CHD9           | A/G | 0.296 | -0.015 | -0.019 | 0.98 (0.82-1.17) | 0.8367        | 0.000  | 1 (0.84-1.19)    | 0.9970        |
| rs12538762  | 7  | 47264328  | TNS3           | C/T | 0.089 | 0.026  | 0.079  | 1.08 (0.82-1.43) | 0.5845        | -0.144 | 0.87 (0.66-1.13) | 0.2940        |
| rs684818    | 1  | 234854779 | AL160408.6     | T/C | 0.470 | 0.024  | -0.067 | 0.93 (0.81-1.08) | 0.3572        | 0.066  | 1.07 (0.93-1.23) | 0.3637        |
| rs2023762   | 16 | 19276597  | SYT17          | T/C | 0.492 | 0.015  | -0.021 | 0.98 (0.84-1.13) | 0.7767        | -0.039 | 0.96 (0.83-1.11) | 0.6049        |
| rs146345029 | 11 | 59596007  | GIF            | G/A | 0.038 | -0.034 | 0.011  | 1.01 (0.68-1.5)  | 0.9547        | -0.290 | 0.75 (0.5-1.12)  | 0.1630        |
| rs1055582   | 4  | 39700173  | UBE2K          | C/T | 0.533 | 0.027  | 0.009  | 1.01 (0.86-1.18) | 0.9148        | 0.034  | 1.03 (0.89-1.2)  | 0.6594        |
| rs11064536  | 12 | 905582    | WNK1           | T/C | 0.095 | 0.020  | -0.070 | 0.93 (0.69-1.25) | 0.6451        | 0.238  | 1.27 (0.98-1.64) | 0.0722        |
| rs4075483   | 17 | 79074817  | BAIAP2         | C/T | 0.365 | 0.017  | -0.025 | 0.98 (0.82-1.16) | 0.7737        | -0.107 | 0.9 (0.76-1.06)  | 0.2029        |
| rs56062334  | 3  | 172299226 | LINC02068      | T/C | 0.457 | 0.017  | 0.136  | 1.15 (0.97-1.36) | 0.1144        | 0.088  | 1.09 (0.93-1.29) | 0.2868        |
| rs8079923   | 17 | 19869544  | AKAP10         | C/T | 0.257 | 0.016  | -0.145 | 0.86 (0.73-1.03) | 0.1050        | -0.150 | 0.86 (0.73-1.02) | 0.0821        |
| rs9573360   | 13 | 74771429  | KLF12          | A/C | 0.445 | 0.014  | 0.067  | 1.07 (0.92-1.24) | 0.3740        | -0.056 | 0.95 (0.82-1.09) | 0.4515        |
| rs35135518  | 2  | 16120506  | RN7SL104P      | T/C | 0.083 | 0.029  | -0.193 | 0.82 (0.63-1.09) | 0.1703        | -0.015 | 0.99 (0.76-1.28) | 0.9121        |
| rs9978775   | 21 | 40694526  | BRWD1-AS1      | G/A | 0.430 | 0.019  | -0.018 | 0.98 (0.85-1.14) | 0.8069        | 0.010  | 1.01 (0.87-1.17) | 0.8971        |
| rs7502910   | 17 | 1638718   | WDR81          | A/G | 0.497 | 0.016  | -0.078 | 0.92 (0.8-1.07)  | 0.2887        | -0.121 | 0.89 (0.77-1.02) | 0.0923        |
| rs4917962   | 10 | 103931931 | NOLC1          | G/T | 0.124 | -0.024 | -0.081 | 0.92 (0.74-1.15) | 0.4796        | 0.048  | 1.05 (0.85-1.3)  | 0.6620        |
| rs9809209   | 3  | 51281664  | DOCK3          | G/A | 0.383 | -0.017 | 0.033  | 1.03 (0.88-1.21) | 0.6789        | 0.060  | 1.06 (0.91-1.24) | 0.4429        |
| rs58560372  | 19 | 38758752  | SPINT2         | C/T | 0.134 | 0.020  | -0.006 | 0.99 (0.79-1.26) | 0.9580        | 0.125  | 1.13 (0.91-1.42) | 0.2717        |
| rs35023999  | 11 | 113266411 | ANKK1          | C/A | 0.514 | 0.015  | -0.037 | 0.96 (0.83-1.12) | 0.6357        | 0.035  | 1.04 (0.89-1.2)  | 0.6446        |
| rs62342064  | 4  | 104665972 | TACR3          | C/T | 0.053 | 0.022  | -0.165 | 0.85 (0.56-1.28) | 0.4291        | 0.341  | 1.41 (0.99-2)    | 0.0564        |
| rs11577063  | 1  | 179341999 | AXDND1         | G/T | 0.220 | -0.020 | -0.024 | 0.98 (0.81-1.17) | 0.8002        | -0.060 | 0.94 (0.79-1.12) | 0.5022        |
| rs10745954  | 12 | 103483094 | AC068643.1     | G/A | 0.501 | 0.015  | 0.092  | 1.1 (0.94-1.27)  | 0.2336        | -0.021 | 0.98 (0.85-1.13) | 0.7727        |
| rs6088579   | 20 | 33284624  | PIGU/NCOA6     | G/A | 0.160 | 0.027  | 0.206  | 1.23 (1-1.5)     | <b>0.0453</b> | 0.109  | 1.11 (0.92-1.36) | 0.2796        |
| rs72761177  | 16 | 1833508   | NUBP2          | A/G | 0.902 | 0.077  | -0.241 | 0.79 (0.62-1)    | 0.0538        | -0.046 | 0.95 (0.75-1.21) | 0.7011        |
| rs61867536  | 11 | 1513700   | MOB2           | C/T | 0.524 | -0.018 | -0.060 | 0.94 (0.8-1.1)   | 0.4566        | 0.008  | 1.01 (0.86-1.18) | 0.9239        |
| rs2228561   | 3  | 48628014  | COL7A1         | A/G | 0.876 | 0.020  | 0.078  | 1.08 (0.86-1.36) | 0.5007        | 0.034  | 1.03 (0.83-1.29) | 0.7624        |
| rs10114121  | 9  | 19440136  | ACER2          | G/A | 0.130 | -0.020 | -0.277 | 0.76 (0.6-0.95)  | <b>0.0171</b> | -0.086 | 0.92 (0.75-1.13) | 0.4168        |

### IGF-1, IGFBP-3 and prognosis of renal cancer

|            |    |           |              |     |       |        |        |                  |               |        |                  |               |
|------------|----|-----------|--------------|-----|-------|--------|--------|------------------|---------------|--------|------------------|---------------|
| rs8182173  | 16 | 4420787   | COR07-PAM16  | C/T | 0.238 | -0.018 | -0.077 | 0.93 (0.77-1.12) | 0.4193        | 0.056  | 1.06 (0.88-1.27) | 0.5404        |
| rs10811787 | 9  | 22871816  | AL391117.1   | T/C | 0.503 | -0.015 | 0.146  | 1.16 (0.99-1.35) | 0.0597        | -0.007 | 0.99 (0.86-1.15) | 0.9222        |
| rs11557154 | 9  | 34107505  | DCAF12       | T/C | 0.884 | 0.024  | 0.048  | 1.05 (0.84-1.31) | 0.6736        | 0.003  | 1 (0.81-1.25)    | 0.9749        |
| rs9398171  | 6  | 108983527 | FOXO3        | T/C | 0.279 | 0.050  | 0.060  | 1.06 (0.9-1.25)  | 0.4821        | -0.072 | 0.93 (0.79-1.1)  | 0.3922        |
| rs2737205  | 8  | 116610180 | TRPS1        | C/T | 0.424 | -0.023 | 0.124  | 1.13 (0.97-1.32) | 0.1163        | 0.042  | 1.04 (0.9-1.21)  | 0.5894        |
| rs72828596 | 6  | 19183591  | AL589647.1   | G/A | 0.088 | -0.019 | 0.090  | 1.09 (0.84-1.42) | 0.4959        | 0.116  | 1.12 (0.87-1.45) | 0.3777        |
| rs12491473 | 3  | 46989904  | CCDC12       | G/A | 0.423 | 0.020  | -0.102 | 0.9 (0.77-1.06)  | 0.2015        | 0.033  | 1.03 (0.89-1.2)  | 0.6637        |
| rs2412973  | 22 | 30529631  | HORMAD2      | C/A | 0.463 | -0.014 | -0.076 | 0.93 (0.79-1.08) | 0.3429        | 0.101  | 1.11 (0.95-1.29) | 0.1919        |
| rs75660441 | 9  | 97662448  | C9orf3       | A/G | 0.053 | 0.039  | -0.006 | 0.99 (0.71-1.4)  | 0.9730        | 0.065  | 1.07 (0.78-1.46) | 0.6841        |
| rs61780439 | 1  | 41490177  | SLFN1-AS1    | G/A | 0.229 | 0.021  | -0.139 | 0.87 (0.73-1.04) | 0.1275        | -0.165 | 0.85 (0.71-1.01) | 0.0620        |
| rs33912345 | 14 | 60976537  | SIX6         | A/C | 0.405 | -0.023 | -0.139 | 0.87 (0.74-1.02) | 0.0808        | -0.133 | 0.88 (0.75-1.02) | 0.0834        |
| rs4306136  | 1  | 221608720 | AL360013.2   | A/G | 0.405 | 0.017  | 0.196  | 1.22 (1.03-1.43) | <b>0.0187</b> | 0.011  | 1.01 (0.86-1.18) | 0.8913        |
| rs3890746  | 6  | 130371055 | L3MBTL3      | T/C | 0.419 | -0.020 | -0.005 | 0.99 (0.86-1.15) | 0.9447        | 0.063  | 1.07 (0.92-1.23) | 0.3812        |
| rs34670419 | 7  | 99130834  | ZKSCAN5      | G/T | 0.033 | -0.036 | 0.472  | 1.6 (1.06-2.42)  | <b>0.0252</b> | 0.070  | 1.07 (0.69-1.66) | 0.7547        |
| rs790513   | 6  | 154420368 | OPRM1        | C/A | 0.241 | 0.025  | -0.078 | 0.93 (0.78-1.1)  | 0.3833        | -0.005 | 0.99 (0.83-1.19) | 0.9541        |
| rs12723255 | 1  | 21233570  | EIF4G3       | T/C | 0.418 | -0.017 | -0.077 | 0.93 (0.8-1.07)  | 0.3002        | -0.075 | 0.93 (0.8-1.07)  | 0.3014        |
| rs2801482  | 10 | 12459773  | CAMK1D       | A/G | 0.021 | -0.050 | 0.329  | 1.39 (0.89-2.16) | 0.1460        | 0.100  | 1.11 (0.69-1.77) | 0.6752        |
| rs12699547 | 7  | 2015970   | MAD1L1       | C/T | 0.376 | 0.021  | 0.188  | 1.21 (1.03-1.41) | <b>0.0185</b> | -0.052 | 0.95 (0.81-1.11) | 0.5039        |
| rs3131646  | 1  | 40383552  | MYCL         | G/T | 0.280 | 0.016  | 0.102  | 1.11 (0.93-1.32) | 0.2503        | -0.033 | 0.97 (0.82-1.15) | 0.7050        |
| rs1127313  | 1  | 154556425 | ADAR         | G/A | 0.493 | 0.024  | -0.026 | 0.97 (0.84-1.13) | 0.7293        | -0.159 | 0.85 (0.74-0.99) | <b>0.0335</b> |
| rs6416868  | 17 | 15924370  | TTC19        | G/A | 0.453 | -0.019 | 0.108  | 1.11 (0.96-1.29) | 0.1520        | 0.012  | 1.01 (0.88-1.17) | 0.8725        |
| rs12935465 | 16 | 17476853  | XYLT1        | T/C | 0.507 | 0.016  | -0.035 | 0.97 (0.83-1.12) | 0.6382        | 0.070  | 1.07 (0.93-1.24) | 0.3418        |
| rs2602717  | 19 | 4902950   | UHRF1/ARRDC5 | C/T | 0.105 | 0.019  | 0.348  | 1.42 (0.98-2.04) | 0.0609        | 0.171  | 1.19 (0.85-1.66) | 0.3198        |
| rs4788220  | 16 | 30063780  | FAM57B       | A/G | 0.487 | -0.017 | -0.097 | 0.91 (0.78-1.05) | 0.2005        | 0.007  | 1.01 (0.87-1.16) | 0.9242        |
| rs811332   | 3  | 138078348 | MRAS         | C/T | 0.183 | 0.019  | 0.005  | 1.01 (0.83-1.22) | 0.9598        | 0.027  | 1.03 (0.85-1.24) | 0.7789        |
| rs940400   | 1  | 200269134 | LINC00862    | C/A | 0.108 | 0.025  | -0.122 | 0.89 (0.68-1.14) | 0.3505        | -0.090 | 0.91 (0.7-1.19)  | 0.4966        |
| rs687339   | 3  | 135932359 | AC092991.1   | T/C | 0.227 | 0.040  | -0.005 | 1 (0.84-1.18)    | 0.9574        | -0.111 | 0.9 (0.76-1.06)  | 0.1908        |
| rs7034716  | 9  | 101858382 | TGFBR1       | C/T | 0.271 | 0.015  | -0.030 | 0.97 (0.82-1.15) | 0.7250        | 0.083  | 1.09 (0.93-1.27) | 0.2866        |
| rs71432868 | 13 | 106559402 | SNORA25      | T/C | 0.016 | -0.028 | 0.212  | 1.24 (0.65-2.37) | 0.5209        | 0.119  | 1.13 (0.58-2.17) | 0.7237        |
| rs17037452 | 1  | 11895675  | CLCN6        | A/G | 0.164 | 0.023  | -0.061 | 0.94 (0.77-1.15) | 0.5566        | 0.030  | 1.03 (0.85-1.25) | 0.7592        |
| rs2348604  | 5  | 136809831 | SPOCK1       | T/C | 0.275 | -0.016 | -0.084 | 0.92 (0.78-1.09) | 0.3307        | 0.030  | 1.03 (0.88-1.21) | 0.7134        |
| rs1055710  | 9  | 96214928  | FAM120AOS    | A/G | 0.664 | -0.018 | -0.143 | 0.87 (0.74-1.01) | 0.0676        | 0.009  | 1.01 (0.86-1.18) | 0.9105        |
| rs670049   | 6  | 100087024 | PRDM13       | A/C | 0.318 | 0.019  | -0.024 | 0.98 (0.83-1.14) | 0.7626        | 0.040  | 1.04 (0.89-1.21) | 0.6083        |
| rs7947951  | 11 | 13356030  | ARNTL        | G/A | 0.311 | 0.020  | 0.119  | 1.13 (0.96-1.32) | 0.1522        | -0.001 | 1 (0.85-1.17)    | 0.9866        |
| rs1115897  | 14 | 93910816  | UNC79        | A/C | 0.308 | 0.021  | -0.114 | 0.89 (0.76-1.05) | 0.1768        | -0.019 | 0.98 (0.84-1.14) | 0.8112        |
| rs1182174  | 7  | 2875420   | GNA12        | G/A | 0.305 | -0.021 | -0.026 | 0.97 (0.83-1.14) | 0.7416        | 0.019  | 1.02 (0.87-1.19) | 0.8087        |
| rs34452566 | 11 | 27793470  | AC103796.1   | G/T | 0.146 | -0.018 | -0.161 | 0.85 (0.67-1.09) | 0.1946        | -0.161 | 0.85 (0.67-1.08) | 0.1862        |
| rs6510177  | 19 | 31211647  | ZNF536       | C/T | 0.108 | -0.023 | -0.039 | 0.96 (0.7-1.32)  | 0.8084        | -0.047 | 0.95 (0.72-1.27) | 0.7453        |
| rs11556924 | 7  | 129663496 | ZC3HC1       | T/C | 0.714 | -0.016 | 0.054  | 1.06 (0.84-1.32) | 0.6411        | -0.102 | 0.9 (0.72-1.13)  | 0.3798        |

## IGF-1, IGFBP-3 and prognosis of renal cancer

|              |    |           |              |     |       |        |        |                  |               |        |                  |               |
|--------------|----|-----------|--------------|-----|-------|--------|--------|------------------|---------------|--------|------------------|---------------|
| rs773116     | 12 | 56486159  | ERBB3        | G/A | 0.458 | 0.016  | 0.098  | 1.1 (0.96-1.27)  | 0.1726        | 0.019  | 1.02 (0.88-1.17) | 0.7965        |
| rs28831479   | 9  | 98254526  | PTCH1        | C/A | 0.245 | 0.022  | 0.115  | 1.12 (0.92-1.37) | 0.2682        | 0.022  | 1.02 (0.84-1.25) | 0.8280        |
| rs599839     | 1  | 109822166 | PSRC1/CELSR2 | A/G | 0.224 | -0.031 | -0.031 | 0.97 (0.81-1.17) | 0.7450        | -0.015 | 0.99 (0.83-1.18) | 0.8727        |
| rs4768       | 3  | 49758764  | RNF123       | A/G | 0.322 | -0.015 | -0.017 | 0.98 (0.85-1.14) | 0.8225        | 0.068  | 1.07 (0.92-1.24) | 0.3693        |
| rs6519133    | 22 | 39096602  | JOSD1        | T/C | 0.458 | 0.029  | -0.115 | 0.89 (0.74-1.08) | 0.2380        | 0.131  | 1.14 (0.95-1.37) | 0.1690        |
| rs11856160   | 15 | 93452846  | CHD2         | A/G | 0.140 | 0.021  | -0.170 | 0.84 (0.68-1.05) | 0.1273        | -0.185 | 0.83 (0.67-1.03) | 0.0913        |
| rs41277821   | 9  | 109689972 | ZNF462       | T/C | 0.984 | 0.062  | 0.090  | 1.09 (0.58-2.08) | 0.7840        | -0.253 | 0.78 (0.44-1.36) | 0.3750        |
| rs56030650   | 17 | 38131187  | GSDMA        | A/C | 0.535 | -0.022 | 0.052  | 1.05 (0.9-1.23)  | 0.5107        | 0.153  | 1.16 (0.99-1.37) | 0.0627        |
| rs2460488    | 12 | 116187660 | -            | G/A | 0.114 | 0.026  | 0.022  | 1.02 (0.75-1.4)  | 0.8873        | -0.262 | 0.77 (0.54-1.1)  | 0.1479        |
| rs4709995    | 6  | 166313447 | PDE10A       | C/T | 0.391 | -0.042 | -0.076 | 0.93 (0.8-1.08)  | 0.3202        | -0.186 | 0.83 (0.72-0.96) | <b>0.0122</b> |
| rs7667562    | 4  | 129133826 | LARP1B       | C/A | 0.253 | 0.016  | -0.074 | 0.93 (0.78-1.11) | 0.4054        | -0.135 | 0.87 (0.74-1.04) | 0.1209        |
| rs73271090   | 5  | 132313550 | AC010240.1   | G/A | 0.118 | 0.044  | 0.016  | 1.02 (0.79-1.31) | 0.9037        | 0.164  | 1.18 (0.92-1.51) | 0.1947        |
| rs7802508    | 7  | 1191689   | ZFAND2A      | G/A | 0.400 | -0.021 | -0.191 | 0.83 (0.71-0.96) | <b>0.0123</b> | -0.027 | 0.97 (0.84-1.13) | 0.7197        |
| rs7774230    | 6  | 152164239 | ESR1         | C/T | 0.437 | -0.026 | -0.103 | 0.9 (0.77-1.05)  | 0.1941        | -0.089 | 0.92 (0.79-1.06) | 0.2512        |
| rs174554     | 11 | 61579463  | FADS1/FADS2  | A/G | 0.335 | 0.022  | 0.014  | 1.01 (0.87-1.18) | 0.8500        | -0.034 | 0.97 (0.84-1.12) | 0.6416        |
| rs11671304   | 19 | 47564643  | ZC3H4        | T/C | 0.320 | -0.018 | -0.022 | 0.98 (0.78-1.23) | 0.8537        | -0.035 | 0.97 (0.75-1.25) | 0.7881        |
| rs6479003    | 9  | 102948685 | INVS         | G/A | 0.056 | 0.024  | -0.303 | 0.74 (0.53-1.03) | 0.0703        | 0.103  | 1.11 (0.84-1.47) | 0.4681        |
| rs2856321    | 12 | 11855773  | ETV6         | A/G | 0.349 | -0.026 | -0.064 | 0.94 (0.81-1.09) | 0.4036        | -0.002 | 1 (0.86-1.15)    | 0.9768        |
| rs10047326   | 10 | 22839463  | PIP4K2A      | A/C | 0.364 | 0.017  | 0.137  | 1.15 (0.98-1.34) | 0.0789        | 0.044  | 1.04 (0.9-1.21)  | 0.5696        |
| rs12935091   | 16 | 71525208  | ZNF19        | A/G | 0.021 | -0.035 | 0.180  | 1.2 (0.72-2)     | 0.4904        | -0.233 | 0.79 (0.46-1.37) | 0.4055        |
| rs12231073   | 12 | 38526901  | -            | G/T | 0.379 | -0.017 | 0.074  | 1.08 (0.89-1.31) | 0.4546        | -0.221 | 0.8 (0.66-0.97)  | <b>0.0246</b> |
| rs74657816   | 7  | 46670682  | HMG11P19     | T/G | 0.039 | 0.047  | 0.278  | 1.32 (0.92-1.9)  | 0.1351        | 0.106  | 1.11 (0.78-1.58) | 0.5546        |
| rs142354201  | 15 | 99524022  | PGPEP1L      | G/A | 0.037 | 0.034  | -0.017 | 0.98 (0.67-1.45) | 0.9328        | 0.012  | 1.01 (0.7-1.47)  | 0.9485        |
| rs10757291   | 9  | 22161884  | CDKN2B-AS1   | A/G | 0.476 | -0.019 | 0.022  | 1.02 (0.88-1.19) | 0.7801        | 0.104  | 1.11 (0.96-1.29) | 0.1673        |
| rs10893499   | 11 | 126241979 | ST3GAL4      | G/A | 0.138 | 0.022  | -0.044 | 0.96 (0.77-1.19) | 0.6869        | -0.111 | 0.9 (0.73-1.1)   | 0.2991        |
| rs1822825    | 3  | 12449963  | PPARG        | A/G | 0.474 | -0.014 | -0.096 | 0.91 (0.78-1.05) | 0.1988        | -0.031 | 0.97 (0.84-1.12) | 0.6627        |
| rs55717031   | 3  | 138848505 | MRPS22       | G/T | 0.285 | 0.032  | 0.060  | 1.06 (0.9-1.26)  | 0.4881        | 0.135  | 1.14 (0.97-1.35) | 0.1144        |
| rs2309401    | 17 | 5471902   | NLRP1        | T/G | 0.392 | 0.015  | 0.068  | 1.07 (0.91-1.26) | 0.4007        | -0.100 | 0.9 (0.77-1.06)  | 0.2139        |
| rs8105174    | 19 | 10347032  | DNMT1        | C/T | 0.178 | 0.050  | -0.056 | 0.95 (0.77-1.16) | 0.5976        | -0.164 | 0.85 (0.69-1.05) | 0.1231        |
| rs2270628    | 7  | 45949570  | IGFBP3       | C/T | 0.204 | -0.033 | -0.030 | 0.97 (0.82-1.15) | 0.7329        | -0.083 | 0.92 (0.77-1.1)  | 0.3498        |
| IGFBP-3 SNPs |    |           |              |     |       |        |        |                  |               |        |                  |               |
| rs11977526   | 7  | 46008110  | IGFBP3       | A/G | 0.593 | 0.287  | 0.028  | 1.03 (0.88-1.2)  | 0.7200        | -0.048 | 0.95 (0.82-1.1)  | 0.5177        |
| rs700753     | 7  | 46753684  | TNS3         | G/C | 0.345 | 0.158  | -0.055 | 0.95 (0.81-1.1)  | 0.4751        | -0.008 | 0.99 (0.86-1.14) | 0.9151        |
| rs4234798    | 4  | 7219933   | SORCS2       | G/T | 0.388 | 0.095  | 0.081  | 1.08 (0.93-1.27) | 0.3079        | 0.048  | 1.05 (0.9-1.22)  | 0.5295        |
| rs1065656    | 16 | 1838836   | NUBP2        | G/C | 0.303 | 0.111  | -0.085 | 0.92 (0.78-1.08) | 0.2932        | 0.002  | 1 (0.86-1.17)    | 0.9831        |

\*Alleles are high allele/low allele. Low allele was used as the reference allele and high allele as effect allele. EAF: effect allele frequency;  $\beta$ 1 estimate of SNP-IGF-1/IGFBP-3 association were from published GWAS;  $\beta$ 2 estimates for SNP-recurrence and  $\beta$ 3 estimates for SNP-death association were from our population. HR was adjusted by age, gender, smoking status, BMI, histology, stage, grade, and treatment. Significant P values (<0.05) were bolded, P<0.01 were shown in red, and SNPs with consistent significant associations with both recurrence and death were highlighted.