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Using Mendelian randomization to investigate etiologic heterogeneity across renal cell carcinoma subtypes

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Abstract

Background: Renal cell carcinoma (RCC) histological subtypes clear cell RCC (ccRCC; >75% of cases) and papillary RCC (papRCC; ~15%) exhibit distinct molecular and genetic profiles, patient demographics, and prognoses. Previous epidemiologic studies have identified several risk factors for overall RCC, although few have explored differences in etiology across subtypes.

Methods: For this, we applied two-sample Mendelian randomization (MR) to findings from a genome-wide association study of RCC (27,213 cases, 488,019 controls) to investigate effects of RCC risk factors with ccRCC (15,507 cases) and papRCC (2,103 cases). We also conducted case-only MR analyses contrasting ccRCC and papRCC cases to test for heterogeneity in risk factor effects across subtypes.

Results: MR for overall RCC confirmed associations with obesity, blood pressure, smoking and several other suspected risk factors. In subtype-specific analyses, we observed stronger associations with ccRCC than for papRCC for anthropometric measures such as body mass index (ccRCC odds ratio [OR_{ccRCC}]=1.58 per standard deviation increase, 95% CI=1.50–1.68; papRCC

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Author contributions

Study concept and design: D.D., M.J.M., M.P.P., S.J.C., P.B., M.J., Acquisition of data: S.J.C., M.P.P., P.B., M.J., The Renal Cancer Genetics Consortium. Analysis and interpretation of data: O.J., T.W., D.D., Drafting of the original manuscript: D.D., O.J., T.D.W., M.J.M., M.P.P., S.J.C. Critical revision of the manuscript for important intellectual content: All authors.

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Use of AI tools. No Artificial intelligence tool was used.

odds ratio [OR_{papRCC}]=1.24, 95% CI=1.07–1.42; $P_{heterogeneity}= 2.7\times10^{-4}$), while stronger associations with papRCC were observed for chronic kidney disease (OR_{ccRCC}=1.07, CI=0.99–1.15; OR_{papRCC}=1.39, CI =1.16–1.66; $P_{heterogeneity}= 5.42\times10^{-5}$), creatinine-based estimated glomerular filtration rate (OR_{ccRCC}=0.96, CI=0.92–1.01; OR_{papRCC}=0.71, CI=0.64–0.79; $P_{heterogeneity}=7.76\times10^{-5}$) and telomere length ($OR_{ccRCC}$=1.98, CI=1.93–2.06; OR_{papRCC}=2.50, CI=2.28–2.72; $P_{heterogeneity}=6.2\times10^{-3}$). Further analysis identified colocalization of significant RCC risk loci and 20 risk factors along with potential target genes through transcriptomic analysis.

Conclusions: These results highlight the heterogeneous nature of RCC etiology and the importance of considering histologic subtype in etiologic and genetic studies.

Keywords

Renal cell carcinoma; histologic subtypes; mendelian randomization; risk factors; case-only analysis; etiologic heterogeneity; colocalization

Introduction

Kidney cancer represents a significant global health challenge with incidence rates increasing in most countries(1,2). Over 85% of kidney cancers are renal cell carcinoma (RCC), which includes several distinct histologic subtypes, most commonly clear cell (ccRCC; >75% of RCC cases) and papillary (papRCC; ~15%) carcinomas. These subtypes have distinct molecular and genetic profiles(3,4), as well as differences in patient characteristics (such as age, sex, and race/ethnicity)(5) and prognosis(6). The markedly elevated risks associated with hereditary RCC syndromes are also often subtype-specific(7).

Epidemiologic studies of RCC have identified several risk factors(8); in particular, obesity, blood pressure and smoking have been estimated to account for half of all diagnosed cases(9–12). However, the majority of epidemiologic studies of this malignancy have not examined differences in effects of risk factors by histologic subtypes. The limited number of studies which have explored this question have found promising evidence of etiologic heterogeneity, such as a stronger association with obesity for ccRCC compared to papRCC(13). However, such studies are often limited by issues of small sample sizes for individual subtypes, incomplete data on tumor histology, or – for clinical studies of cases with known histology – inadequate risk factor data(5,14,15). Furthermore, due to the observational nature of traditional epidemiological studies, it is difficult to pinpoint which modifiable factors directly influence risk of RCC and its subtypes and which are merely correlated with the underlying causal factor.

Mendelian randomization (MR), a method to investigate causal relationships between potential risk factors and disease, offers promise as a tool to investigate etiologic heterogeneity across cancer subtypes(16). It utilizes germline genetic variants as instrumental variables (or proxies) for risk factors (or exposures) and subsequently tests their association with a disease (or outcome). Compared with traditional observational epidemiological studies, MR has the conceptual advantage of being less susceptible to both confounding and reverse causation and can thus provide etiologic insights into new and established risk factors and outcomes(17).

Recently, we reported the largest genome-wide association study (GWAS) of RCC to date, consisting of 29,020 cases and 835,670 controls across four major ancestries. Notably, this included 16,231 and 2,193 cases of ccRCC and papRCC respectively(18) and identified shared as well as distinct susceptibility loci associated to each of these histologic subtypes. Integrating results from this GWAS with other publicly available GWAS for modifiable risk factors, we investigated the role of these factors in genetic etiology of RCC, and especially its histologic subtypes, using a two-sample MR framework(16,19–21) In particular, we explored the heterogeneity in effects of such risk factors across ccRCC and papRCC to highlight the similarities and differences between the genetic etiology of the histologic subtypes, through a case-only analysis. To provide additional context for the MR findings, we interrogated individual RCC loci using colocalization analysis to illuminate the functional mechanisms by which RCC risk loci may influence risk via the risk factors.

Methods

Identification of risk factors.

We assembled a list of 25 risk factors that have been reported or suspected to have a causal link to RCC and has publicly available GWAS data with at least 50,000 individuals (Supplementary Table S1). GWAS data sources for these risk factors included UK Biobank(22), Genetic Investigation of ANthropometric Traits (GIANT)(23), Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC)(24), GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN)(25), Diabetes Genetics Replication And Meta-analysis (DIAGRAM)(26), and Chronic Kidney Disease Genetics consortium (CKDGen)(27).

GWAS results for RCC and subtypes (outcomes).

For MR, we used summary statistics from our recent multi-ancestry RCC GWAS meta-analysis(18) that combined summary statistics from published studies (n=7; six involving subjects of European ancestry, the seventh involving African Americans), large biobanks (n=2; FinnGen, Biobank Japan) and newly genotyped studies (n=6). Although UK Biobank had been included in our published GWAS meta-analysis, we excluded it from MR analysis because it was the GWAS data source for many of the selected risk factors. The resulting GWAS meta-analysis included 27,213 cases and 488,019 controls for overall RCC, 15,507 cases and 394,655 controls for ccRCC, and 2103 cases and 391,992 controls for papRCC.

Testing for etiologic heterogeneity

To test for differences in the magnitudes of risk factor effects between ccRCC and papRCC, we re-analyzed available individual-level data from the RCC GWAS using a case-only design. The case-only approach enables the computation of the ratio of the genetic effects of risk factors (odds ratio [OR]) on ccRCC to that on papRCC; the corresponding test of this parameter represents a statistical test of the null hypothesis that there is not significant difference between the effects of the risk factors on ccRCC and papRCC(28). We performed the case-only GWAS analyses following the same analysis pipeline as described in Purdue et al(18) using SAIGE(29) within 7 studies with available individual-level data (10,680 ccRCC and 1,546 papRCC; Supplementary Table S2); the majority of included subjects

were of European ancestry (9,199 ccRCC and 1,194 papRCC). Briefly, for each study with available subtype information, we performed a GWAS using a generalized linear mixed model adjusting for sex and genetic principal components (20 for NCI-3 and 10 for the rest; Supplementary Table S2), accounting for sample relatedness implemented using SAIGE. We restricted these analyses to bi-allelic genetic variants with imputation score > 0.3 and minor allele frequency > 0.1%. We then meta-analyzed study-specific case-only findings through using METAL software(30) under default settings.

Statistical Analysis

Mendelian Randomization. We performed MR using GSMR(19) (Link: https://yanglab.westlake.edu.cn/software/gcta/) which can efficiently handle summary-level data from GWAS and uses the inverse variance weighted (IVW) method to estimate the effect of a risk factor on the outcome. Using GWAS summary statistics from both the risk factor and outcome, GSMR identifies genetic instruments via clumping, removes potentially pleiotropic SNPs via HEIDI (See Supplementary Methods) and uses the final list of genetic instruments to perform MR. GSMR further accounts for mild LD ($r^2 < 0.1$) between the variants beyond LD clumping, estimated from an appropriate ancestry-matched reference panel. We estimated the association odds ratio (OR) for each pair of risk factor and outcome. For the risk factors for which GWAS was conducted using the raw phenotype values, we converted the estimated OR to OR per standard deviation (OR_{SD}) scale. An association $P<2\times10^{-3}$, reflecting the Bonferroni threshold for 25 risk factors, was declared statistically significant. Any association with p-value < 0.05 but > 2×10^{-3} was considered to be nominally significant. We repeated GSMR analysis using the summary data from the meta-analysis of case-only GWAS (see above) to test for heterogeneity in risk factor effects between ccRCC and papRCC.

Colocalization Analyses. To complement and provide context to the MR findings, we performed colocalization analysis using R package coloc 5.2.3(31) for the GWAS significant RCC loci to identify potential loci-specific associations with risk factors. For each sentinel SNP mentioned in Purdue et al(18), we set a window size of ± 500 kb around the SNP and used the default priors, with approximate bayes factor computation to estimate posterior probabilities of different causal scenarios. Evidence for colocalization was assessed using the posterior probability (PP.H4) for hypothesis 4 (indicating there is an association for both risk factor and RCC and they are driven by the same causal variant(s)). We used PP.H4 > 0.8 as a threshold to suggest that associations were highly colocalized.

Results

Association with overall RCC.

Our MR findings for overall RCC are summarized in Figure 1 and Supplementary Table S3. We observed positive associations at p-values below the Bonferroni-corrected significance threshold for leukocyte telomere length (LTL; OR=1.99 per SD increase; $P=5.6\times10^{-92}$), body fat percentage (OR=1.51; $P=2.0\times10^{-44}$), whole body fat mass (OR=1.48, $P=2.2\times10^{-47}$), BMI (OR=1.45, $P=1.3\times10^{-48}$), waist to hip ratio (OR=1.28, $P=3.5\times10^{-17}$), smoking initiation (OR=1.28, $P=1.0\times10^{-4}$), diastolic blood pressure (DBP;

OR=1.12, P=5.1×10^{-5}), white blood cell count (OR=1.11, P=2.0×10^{-8}), systolic blood pressure (SBP; OR=1.10, P=8.0×10^{-4}), and red blood cell count (OR=1.05, P=1.3x10^{-3}), as well as inverse associations with eGFR-creatinine (OR=0.91, P=1.3×10^{-6}) and random glucose (OR=0.34; P=2.8×10^{-5}). Nominally significant findings were observed for several other factors, including positive associations with fasting insulin (OR=1.27, P=0.043), chronic kidney disease (CKD; OR=1.09, P=4.9×10^{-3}), hematocrit (OR=1.06, P=5.0×10^{-3}) and hemoglobin (OR=1.05, P=7.2×10^{-3}), as well as inverse associations with pulse pressure (OR=0.93, P=4.9×10^{-3}), two-hour glucose test (2HrGlu; OR=0.87, P=3.6×10^{-3}), alcohol consumption measured in drinks per week (OR=0.83, P=9.7×10^{-3}) and HbA1c (OR=0.80, P=2.8×10^{-3}). No association with RCC was observed for type 2 diabetes, urate, blood urea nitrogen (BUN) or eGFR-cystatin. We further identified a significant effect of LTL (OR=1.96, P=4.9×10^{-72}) even after removing a 5Mb region around the *TERT* gene (chromosome 5p15.33) from the analysis. Analyses with normalized BMI in a larger dataset from a meta-analysis GIANT and UK Biobank produced similar results (OR = 1.43; P=1.8×10^{-54}; Supplementary Table S4). Results from analyses of RCC restricted to European-ancestry individuals produced similar findings (Supplementary Table S5) and no significant deviation due to pleiotropy or choice of method was detected (Supplementary Figures S1–S4 and Supplementary Table S6–S7). Additional analyses with smoking endpoints identified significant association with cigarettes per day and nominal association with smoking cessation (Supplementary Table S4) but needs further investigation for sensitivity and presence of pleiotropy.

Heterogeneity in effects on subtypes.

Table 1 and Figure 2 summarize the MR findings for the two major histologic subtypes, ccRCC and papRCC. BMI had a stronger effect on ccRCC, with each SD increase resulting in a 58% higher risk of ccRCC, compared to a 24% increase for papRCC (Figure 2; $P_{heterogeneity}$=2.7×10^{-4}). Additional related anthropometric measures demonstrated similarly stronger effects for ccRCC, such as body fat percentage ($P_{heterogeneity}$=6.3×10^{-4}) and whole-body fat mass ($P_{heterogeneity}$=1.5×10^{-4}). Blood-related traits also demonstrated significantly stronger associations with ccRCC, particularly red blood cell (RBC) characteristics related to oxygen carrying capacity such as hematocrit ($P_{heterogeneity}$=5.3×10^{-5}) and hemoglobin ($P_{heterogeneity}$=7.3×10^{-4}). In contrast, several other risk factors were found to have stronger associations with papRCC compared to ccRCC, including CKD (Figure 2; $P_{heterogeneity}$ = 5.4×10^{-5}), eGFR creatinine levels ($P_{heterogeneity}$=7.8×10^{-5}), and LTL ($P_{heterogeneity}$=6.2×10^{-3}). Weaker suggestive evidence of heterogeneity across subtypes was observed for fasting insulin ($P_{heterogeneity}$ =0.03), with a stronger effect for ccRCC.

Colocalization Analysis.

We pursued colocalization analysis to provide support for the MR results. Across autosomal regions with GWAS-identified susceptibility loci for RCC, we observed strong colocalization (*PP.H4*>0.8) with at least 20 risk factors, highlighting genetic regions influencing RCC risk via effects on proximal molecular targets (Figure 3; Supplementary Table S8). Five regions strongly colocalized with BMI and other anthropometric traits (1p36.21, 10p12.31, 12p21.1, 12p11.23, 15q22.31) and RCC-related variants in these regions serve as expression quantitative trait loci (eQTLs) for genes like *CASP9*

and multiple additional genes in relevant tissues including adipose, blood and brain (Supplementary Table S9). For the blood cell traits, we identified three RCC associated regions (2q22.3, 8p12, and 19p13.3) that nominally colocalize (*PP.H4*>0.4) with all blood cell traits (WBC, RBC, hematocrit, hemoglobin). Three additional regions (2p21, 2q31.1, and 20q13.33) colocalize with only the RBC traits but not WBC; notably, the 2p21 harbors *EPAS1*, which encodes the important ccRCC oncogene HIF2α. Eight RCC-associated regions colocalized with LTL, harboring eQTLs for known telomere maintenance genes (Supplementary Table S8–S9). Kidney function traits, particularly chronic kidney disease (CKD), also showed significant colocalization at 3q23 and 12q24.31 while eGFR creatinine colocalized with 9 loci.

Discussions

In this two-sample MR analysis of known and suspected kidney cancer risk factors, our results for overall RCC are, unsurprisingly, consistent with the published epidemiologic literature for the major modifiable kidney cancer risk factors, with increased cancer risks associated with genetically predicted measures of obesity, diastolic blood pressure and smoking initiation. Importantly, we also observed findings that provide additional support for suspected risk factors where the epidemiologic evidence is less well established; these include positive associations with chronic kidney disease and eGFR-creatinine and an inverse association with consumption of alcoholic beverages. The etiologic relevance of some other findings are less clear. Our MR association for WBC is supported by a recent UK Biobank analysis(32) of measured WBC blood count indices and kidney cancer, possibly reflecting proinflammatory conditions contributing to tumor development, whereas a U-shaped relationship between measured RBC and kidney cancer in UK Biobank analysis conflicts with our findings for RBC traits. Our results for diabetes-related traits are complex, with no association for type II diabetes, a positive association with insulin sensitivity, in line with previous reports, and inverse associations with HbA1C, fasting glucose and random glucose. These findings may suggest a role in RCC pathogenesis for pathways directly stimulated by insulin, and not hyperglycemia-related effects, although more research is needed before causal inferences can be drawn.

Our two-sample MR analysis investigating known and suspected kidney cancer risk factor associations with ccRCC and papRCC represents, to our knowledge, the largest and most comprehensive investigation of etiologic heterogeneity across RCC subtypes conducted to date, and the first MR investigation of its kind. We identified several instances of RCC risk factors more strongly associated with, or specific to, a given subtype; some of these results support previously reported epidemiologic evidence, while other findings are novel.

Our MR findings provide clear evidence that measures of excess weight such as BMI, body fat percentage, and whole-body fat mass have stronger associations with ccRCC compared to papRCC, in alignment with the epidemiologic evidence(13,33,34). Excess weight may be a particularly strong risk factor for ccRCC given its capacity to induce hypoxia through obesity-related effects such as adipocyte hypertrophy, obesity-induced kidney injury, obesity hypoventilation syndrome and obstructive sleep apnea. Hypoxic conditions in the kidney induce upregulated expression of oncogenic hypoxia-inducible factors (HIFs) such as

HIF2α, which play a central role in the pathogenesis of ccRCC. We also observed ccRCC-specific effects for hemoglobin and hematocrit, key measures of red blood cell volume and oxygen transport. While these factors are also relevant to renal hypoxia, the direction of the MR associations are unexpected; we would have expected measures indicative of low oxygen transport to be associated with an increased risk of ccRCC. As a consequence, we advise caution in interpreting these red blood cell trait findings as evidence of causation.

Using colocalization, which was intended to provide additional support for MR results, we observed several GWAS-identified RCC risk loci colocalizing with BMI and related traits, suggesting that variants at these loci may influence RCC risk by impacting such risk factors. At these colocalized regions, we observed significant eQTLs in relevant tissues like adipose, blood and brain which might be potential candidate genes via which the effect of BMI and related factors are cascaded (Supplementary Table S9). For example, this includes genes such as *SH3PXD2A*, associated with obesity, subcutaneous adipose, and leptin levels(35), in brain frontal cortex tissue or *CASP9,* implicated in adipocyte turnover(36), in both subcutaneous and visceral adipose tissue. In fact, *CASP9* has also been identified to be associated with kidney function and RCC through TWAS analysis(37) as well as previously published studies(38). Additional studies regarding the biological mechanisms underlying the effects of these loci are warranted.

We also observed stronger MR associations with papRCC than with ccRCC for selected risk factors, including CKD, eGFR-creatinine and telomere length. Our CKD finding is consistent with the observation that papRCC is reported to occur more frequently in patients with end-stage kidney disease(39–41) and kidney transplantation recipients[41]. Acute kidney injury has also been found to be associated preferentially with papillary tumors, both in an epidemiologic study and experimentally using mouse models(42). These findings suggest that pro-neoplastic effects related to cellular damage and repair may be potent in papRCC development. In contrast, there is little epidemiologic evidence evaluating eGFR values in relation to RCC subtype; the only identified study of this kind reported a stronger association for ccRCC vs. non-clear cell RCC (papRCC was not evaluated specifically)(43). Some of the loci identified by colocalization analysis have been previously linked to biomarkers of kidney function. Notably, rs6488945 (12q24.31) has a significant whole blood eQTL with *SCARB1* (Supplementary Table S9), implicated in lipid handling, oxidative stress, and inflammation in kidney cells(44); a previous TWAS in kidney cancer transcriptome identified a significant association with RCC(37). In addition, rs11709427 (3p21.1) which colocalizes with the related traits, creatinine and urate, has a significant eQTL with *ITIH4*, a proposed biomarker for CKD(45), in kidney cortex (Supplementary Table S9) and was further implicated in RCC through TWAS analysis in normal kidney cortex.

We identified a positive association between longer leukocyte telomere length (LTL) and RCC risk, confirming a previous polygenic risk score-based analysis(46), and found this effect to be significantly greater in papRCC. The results remained largely unchanged even after removing the *TERT* gene region from the analysis, indicating that the effect of LTL was not due to this region alone (Supplementary Table S4). Additional colocalization analysis identified eight loci associated with both RCC and LTL, suggesting that variants

at these regions may influence RCC risk via altered telomere maintenance. Notably, variants at 20q13.33 have significant eQTLs with *RTEL1*, a DNA helicase that is involved in the regulation of telomere elongation and stability(47), in whole blood and fibroblasts (Supplementary Table S9). In addition, rs11813268 exhibits a significant eQTL with *STN1*, a part of the Ctc1-Stn1-Ten1 (CST) complex that plays a crucial role in telomere maintenance and protection(48). Both of these genes were previously found to be associated to RCC through a cross-tissue TWAS analysis(37) Additionally, we found moderate colocalization at 5p13.33 region, suggesting involvement of the *TERT* gene.

In conclusion, in this MR of RCC, the largest conducted to date, we found new evidence supporting the etiologic relevance of some suggested risk factors where a causal relationship has been uncertain (CKD, eGFR, alcohol consumption) and provided new evidence supporting the existence of etiologic heterogeneity across ccRCC and papRCC. Our findings of obesity measures as stronger risk factors for ccRCC, and CKD as a stronger risk factor for papRCC, are consistent with the limited epidemiologic evidence. We also found new evidence suggesting etiologic heterogeneity across subtypes that is not found in the epidemiologic literature, such as the stronger observed effects of eGFR and telomere length for papRCC. Our findings advance our understanding of the etiology of RCC and its complexity across different disease subtypes, underscoring the need for more widespread exploration of etiologic heterogeneity in epidemiologic studies, and provide new leads for further research to elucidate the biological mechanisms underpinning the effects of several risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest:

Declaration of interests for the members of Renal Cancer Genetics Consortium listed in Notes which contributed towards acquisition of the individual level data can be referred to previously(18). Members of the Renal Cancer Genetics Consortium have the following declarations: D.S. has received funds from Janssen for consulting outside of the submitted work. N.S.V. has received grants, personal fees and non-financial support from Bristol Myers Squibb; personal fees and non-financial support from Ipsen and EUSA Pharma; and personal fees from Merck Serono, Pfizer, Eisai Ltd and 4D Pharma, all outside the submitted work. G.D.S. has received educational grants from Pfizer and AstraZeneca; consultancy fees from Pfizer, Merck, EUSA Pharma and MSD; travel expenses from Pfizer and speaker fees from Pfizer, all outside the submitted work. M.S. has received honoraria from Covidien/Medtronic for teaching on courses and speaker fees from Pfizer, all outside the submitted work. L.M.C.

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Appendix

Appendix

Notes:

Full List of **The Renal Cancer Genetics Consortium** Members (including authors named in the article). For details, affiliations and contact see Supplementary Table S10:

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Data availability:

This analysis used publicly available GWAS summary statistics. GWAS summary statistics for RCC, ccRCC and papRCC are publicly available as outlined in Purdue et al. on dbGaP (phs003505.v1.p1) and also in GWAS Catalog (GCST90320043 – GCST90320065). UK Biobank summary statistics were available from Neale lab: https://www.nealelab.is/uk-biobank. GWAS summary statistics for other risk factors were obtained from: GIANT: https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium. Meta-analysis of GSCAN and UK Biobank: https://genome.psych.umn.edu/index.php/GSCAN, DIAGRAM: https://diagram-consortium.org/index.html, MAGIC: http://magicinvestigators.org/downloads/, CKDGEN: https://ckdgen.imbi.uni-freiburg.de/. The summary statistics were last accessed in April 2024.

Abbreviations.

2HrGlu	2 hour glucose test
BMI	body mass index
CKD	chronic kidney disease
DBP	diastolic blood pressure
eGFR	estimated glomerular filtration rate
eQTL	expression quantitative trait locus
GWAS	genome-wide association study
HbA1c	glycated hemoglobin
LTL	leukocyte telomere length
PP	pulse pressure
RBC	red blood cells
RCC	renal cell carcinoma
SBP	systolic blood pressure
WBC	white blood cells
WHR	waist-hip circumference

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Key Messages:

- We investigated the effects of risk factors on renal cell carcinoma (RCC) and its major histologic subtypes along with differences in effects of risk factors across the subtypes clear cell (ccRCC) and papillary (papRCC).
- We found substantial heterogeneity in the effects of risk factors across histologic subtypes, with anthropometric factors and red blood cell counts showing stronger effects on ccRCC, while telomere length and kidney biomarkers showed stronger effects on papRCC.
- Our findings advance our understanding of the etiology of RCC and its complexity across different disease subtypes, underscoring the need for more widespread exploration of etiologic heterogeneity in epidemiologic studies.

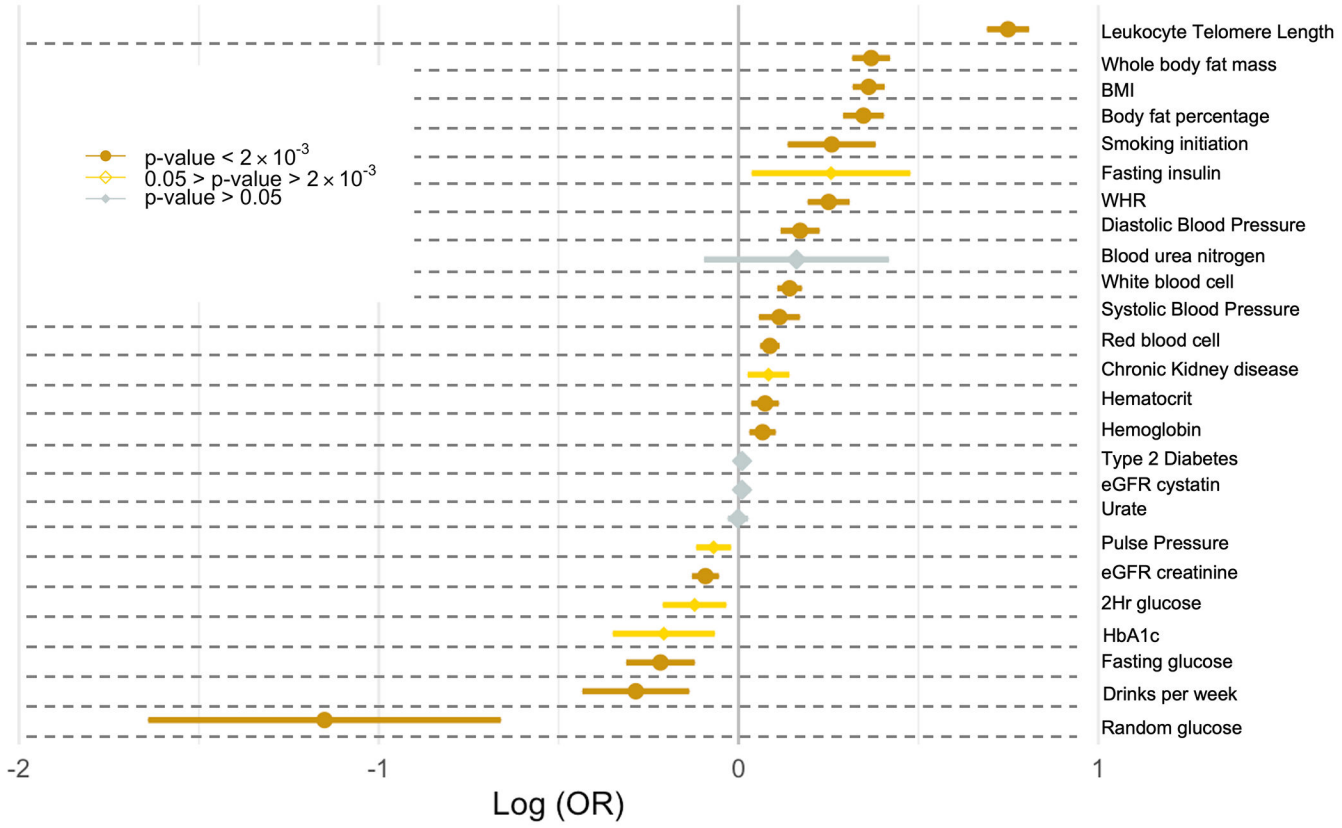

Figure 1: Effects of risk factors on RCC.

Forest Plot (OR and 95% CI) showing the effects of 25 risk factors on RCC ordered by the magnitudes of the ORs. The ORs and confidence intervals are colored by respective levels of significance. See Methods and Supplementary Table S3 for more details. [Abbreviations: 2Hr glucose, 2 hour glucose test; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; OR, odds ratio; WHR, waist to hip ratio.

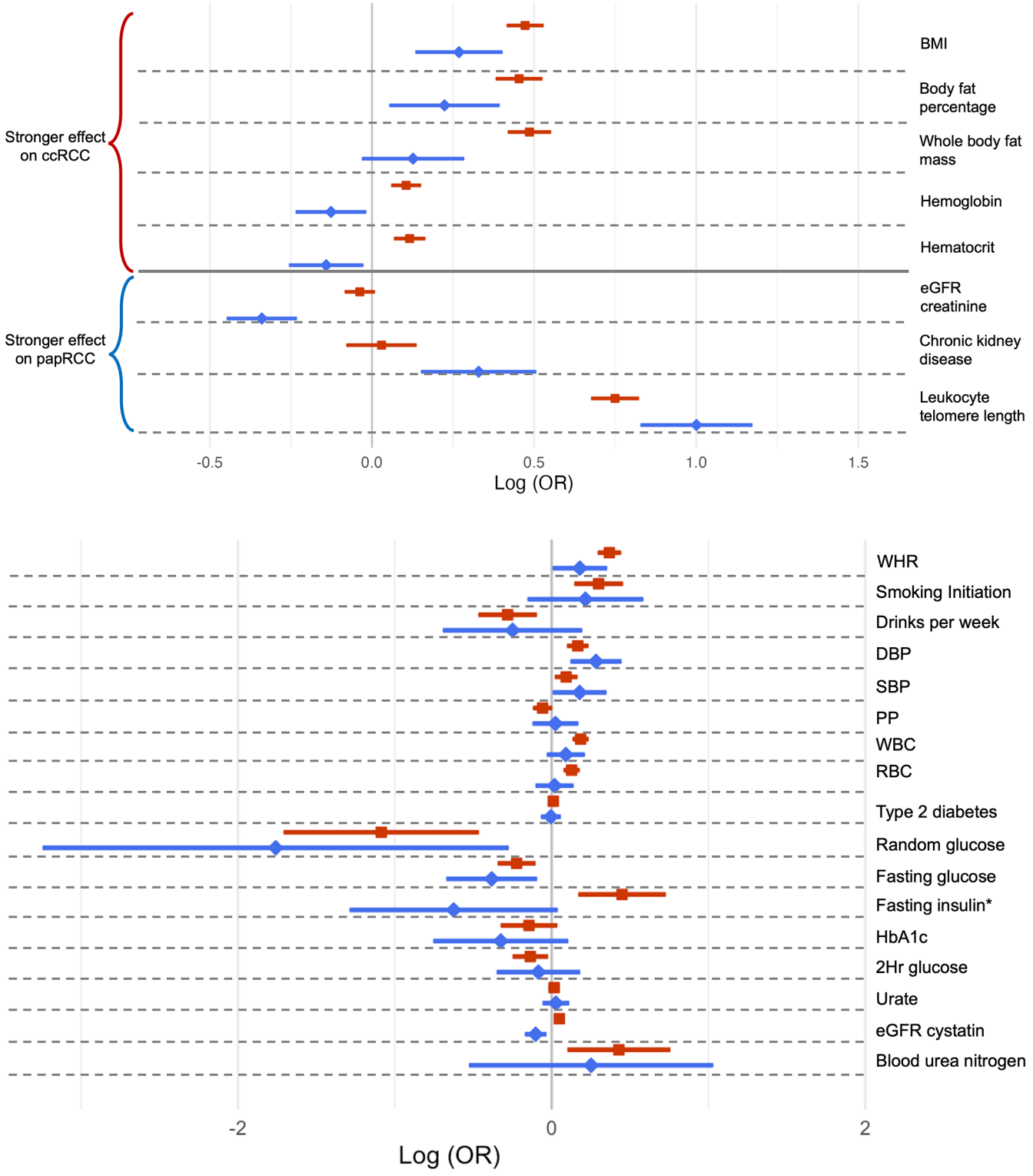

Figure 2: Effects of risk factors on subtypes of RCC.

Forest Plot (OR and 95% CI) showing the effects of (A) any risk factor with significant evidence of heterogeneity in effects across subtypes ($P_{heterogeneity} < 0.05$), as determined

from the case-only analysis including anthropometric traits, blood cell types, kidney functions and telomere length risk factors on ccRCC (in red and boxes) and papRCC (in blue and diamonds) and (B) effects of the remaining factors on ccRCC and papRCC. See Methods and Table 1 for details. [Abbreviations: 2Hr glucose, 2 hour glucose test; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; OR, odds ratio; PP, pulse pressure; RBC, red blood cells; SBP, systolic blood pressure; WBC, white blood cells; WHR, waist to hip ratio.

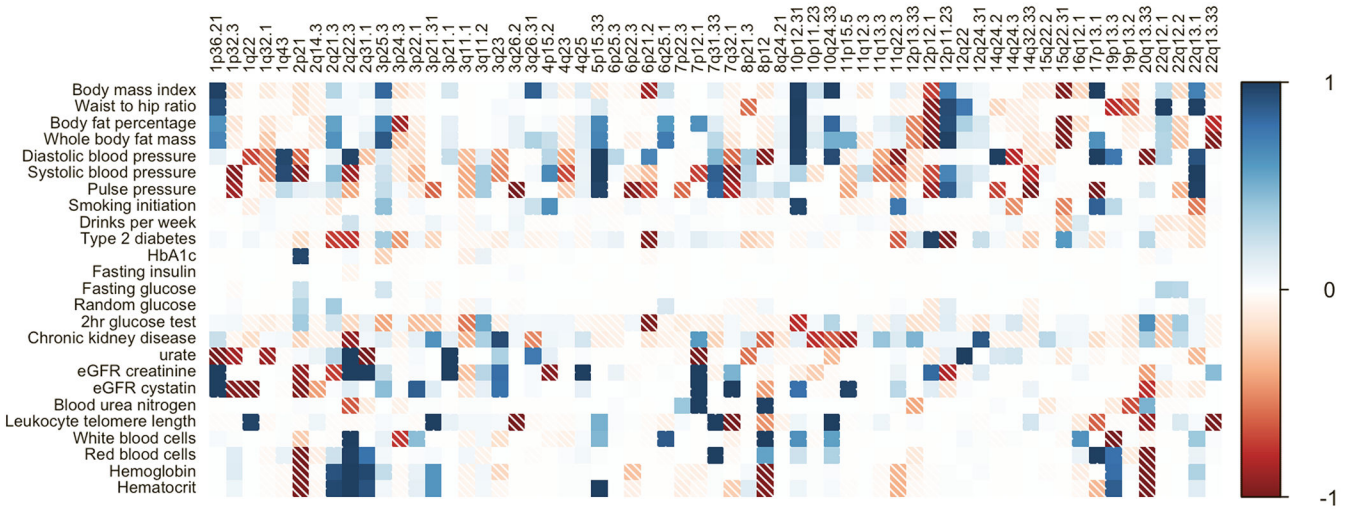

Figure 3: Colocalization of RCC loci with risk factors.

Heatmap showing the maximum colocalization probabilities (PP.H4) of GWAS significant RCC region with risk factors analyzed. The intensity of the colors are proportional to the colocalization probabilities while the direction/sign denotes the concordance of direction of the risk factor SNP variant with RCC lead variant in the loci (positive[+] if concordant and negative[−] and diagonally shaded if discordant). Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; hr, hour.

Table 1.

Odds ratios and 95% confidence intervals (CI) from mendelian randomization analyses for risk factors on ccRCC and papRCC as well the test of heterogeneity in effects using case-only analysis ($P_{Heterogeneity}$; See Methods). Source for the genome-wide summary statistics and number of instruments corresponding to each risk factor is mentioned. The associations achieving Bonferroni-corrected statistical significance ($P<2\times10^{-3}$) are in bold.

	Risk Factor	Number of instruments	ccRCC			papRCC			$P_{Heterogeneity}$
			OR	95% CI	P	OR	95% CI	P	
Significant heterogeneity Stronger effect on ccRCC	Body Mass Index *a	734	**1.58**	**1.50 – 1.68**	**1.13×10^{-59}**	**1.24**	**1.07 – 1.42**	**9.07×10^{-05}**	2.74×10^{-04}
	Body fat percentage *a	817	**1.57**	**1.46 – 1.69**	**4.14×10^{-35}**	1.25	1.05 – 1.48	9.88×10^{-03}	6.34×10^{-04}
	Whole body fat mass *a	661	**1.63**	**1.52 – 1.74**	**3.89×10^{-46}**	1.13	0.97 – 1.32	0.116	1.47×10^{-04}
	Hemoglobin a	1238	**1.09**	**1.05 – 1.13**	**1.99×10^{-7}**	0.88	0.79 – 0.98	0.023	7.33×10^{-4}
	Hematocrit a	1145	**1.12**	**1.07 – 1.17**	**3.63×10^{-6}**	0.87	0.77 – 0.97	0.016	5.33×10^{-5}
Significant heterogeneity Stronger effect on papRCC	eGFR creatinine f	1357	0.96	0.92 – 1.01	0.113	**0.71**	**0.64 – 0.79**	**5.59×10^{-10}**	7.76×10^{-5}
	Chronic Kidney Disease f	25	1.07	0.99 – 1.15	0.071	**1.39**	**1.16 – 1.66**	**2.89×10^{-4}**	5.42×10^{-5}
	Leukocyte Telomere length a	255	**1.99**	**1.93 – 2.06**	**5.56×10^{-92}**	**2.50**	**2.28 – 2.72**	**6.51×10^{-30}**	6.24×10^{-03}
Nominal heterogeneity	Fasting insulin e	45	**1.59**	**1.10 – 2.23**	**1.56×10^{-3}**	0.51	0.21 – 1.01	0.053	0.033
No significant heterogeneity	Systolic Blood Pressure *a	608	1.04	0.97 – 1.12	0.277	1.20	1.01 – 1.42	0.041	0.076
	Smoking Initiation c	261	**1.31**	**1.12 – 1.53**	**7.37×10^{-4}**	1.20	0.82 – 1.74	0.252	0.086
	Waist to Hip Ratio b	817	**1.45**	**1.34 – 1.56**	**1.05×10^{-34}**	**1.20**	**1.02 – 1.42**	**1.53×10^{-03}**	0.339
	Diastolic Blood Pressure *a	604	1.11	1.04 – 1.19	3.15×10^{-3}	**1.30**	**1.11 – 1.52**	**1.38×10^{-3}**	0.853
	Pulse Pressure *a	783	0.92	0.87 – 0.98	0.014	1.05	0.91 – 1.20	0.493	0.827
	Drinks per week c	107	0.87	0.72 – 1.03	0.141	0.77	0.50 – 1.18	0.236	0.723
	Type 2 Diabetes d	376	1.01	1.00 – 1.04	0.071	1.00	0.93 – 1.06	0.881	0.155
	Fasting glucose e	152	0.85	0.75 – 0.96	0.011	0.73	0.56 – 0.98	0.036	0.392
	Random glucose e	208	0.46	0.27 – 0.87	0.016	0.19	0.04 – 0.84	0.027	0.997
	HbA1c e	144	0.87	0.69 – 0.92	0.141	0.76	0.49 – 1.17	0.209	0.317
	2-hour Glucose test e	16	0.87	0.77 – 0.97	0.017	0.90	0.68 – 1.18	0.438	0.932

	Risk Factor	Number of instruments	ccRCC			papRCC			$P_{Heterogeneity}$
			OR	95% CI	P	OR	95% CI	P	
	Urate [f]	265	1.02	0.96 – 1.02	0.501	1.03	0.94 – 1.12	0.531	0.773
	Blood urea nitrogen [f]	340	1.54	0.78 – 1.35	0.841	1.29	0.59 – 2.80	0.526	0.337
	eGFR Cystatin [f]	1517	1.05	0.99 – 1.03	0.414	0.90	0.84 – 0.96	0.119	0.135
	White Blood Cell count [a]	1238	**1.17**	**1.12 – 1.22**	**2.58×10^{-13}**	1.09	0.97 – 1.23	0.065	0.627
	Red Blood Cell count [a]	1841	**1.10**	**1.07 – 1.14**	**2.11×10^{-8}**	1.02	0.90 – 1.15	0.652	0.665

*: ORs for corresponding risk factors are normalized by standard deviation and reported as OR_{SD}.

Source studies for GWAS of risk factors:

a: UK Biobank

b: GIANT + UK Biobank

c: GSCAN + UK Biobank

d: DIAGRAM

e: MAGIC

f: CKDGen.

See Supplementary Table 1 for details on the studies

'+' denotes meta-analysis . For source of the summary statistic see Data availability

Abbreviations: ccRCC, clear cell; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; OR, odds ratio; P, p-value; papRCC, papillary; SD, standard deviation.