# Renal cell cancer

## Impact paragraph

In this chapter I will discuss the scientific and social impact that the research described in this dissertation has provided in the short-term and could provide in the long-term. Furthermore, we will detail how the results were disseminated during the PhD trajectory. Additionally, we put the results of this thesis into a broader perspective by highlighting the potential impact of this dissertation for researchers, clinicians and policymakers in a public health setting and patient care.

**The dissemination of results during the PhD trajectory**

During the PhD trajectory various means were employed to disseminate the study results to a broad audience, including researchers and clinicians from multiple disciplines.

Firstly, study findings were published in various international scientific journals, as detailed in the beginning of each chapter of this dissertation. Secondly, our scientific findings were presented at various conferences and symposia for audiences with a broad background. For example, in 2017 and 2019, our scientific results were presented at the Dutch Epidemiological Conference (WEON), which is generally attended by epidemiologists from various research backgrounds. In addition, our research was presented at science days and research meetings in Maastricht thereby sharing the results to multidisciplinary audiences with a broad clinical and/or healthcare background. Thirdly, scientific results were presented targeted to specific audiences relevant to the scientific work. For instance, considerations regarding the feasibility of the use of formalin-fixed paraffin embedded (FFPE) tumour material were presented at the 4$^{th}$ International Molecular Pathological Epidemiology (MPE) Meeting (Boston, USA) in 2018. At this conference, an international audience from diverse fields gathered for discussions on the topic of MPE. This event proved to be a key opportunity to discuss our insights into factors affecting the quality of sequencing when using routinely archived FFPE material with experts in the field of DNA sequencing. During this meeting, we realized that the use of FFPE tissue for sequencing wasn't as clear-cut as we expected and that various research groups were experiencing similar difficulties in maintaining a high sequencing quality needed in research. By sharing our first-hand experiences from the Netherlands Cohort Study on diet and cancer (NLCS), we hopefully gave other researchers insights on what to account for when using routinely archived FFPE tumour material that has been stored for extended periods of time. Hopefully, this may lead to a reduction in research waste, as researchers may be more inclined to account for sample characteristics (*i.e.* storage duration and DNA concentration) during DNA isolation and work-up that could lead to reduced sequencing yields. To further the dissemination of these insights, appendix 2 has been added to **chapter 5** in this dissertation. Moreover, factors influencing the quality of sequencing were presented to pathologists at the Maastricht Pathology Meeting (Maastricht, the Netherlands) in 2018, which was a joint effort from the British Division of the International Academy of Pathology (BDIAP), the Pathological Society of Great Britain & Ireland and the Dutch Society for Pathology (NVVP). During this meeting questions were addressed on what factors pathologists, among others, should be aware of to maintain sufficient data quality for sequencing. Sharing these insights could be useful for expectations management in the case researchers want to use routinely archived FFPE tumour material which has been stored in suboptimal conditions for a prolonged period of time. Lastly, these insights could also provide helpful information for the initiation of future projects to enable researchers to

optimize the collection and storage of (FFPE) tumour tissue.
Lastly, our research on the association between kidney stones and renal cell carcinoma (RCC) and upper tract urothelial carcinoma (UTUC) was picked up by international press, which enabled our research to reach a broad audience beyond the scientific community. Furthermore, the article was featured on online websites specialized in clinical research, which may hopefully have led to additional awareness around the potential link between kidney stones and RCC and UTUC and its subtypes in clinicians and other health care professionals.

**Future impact of the generated knowledge**
The findings presented in this dissertation may also have various scientific and social implications in the (nearby) future. In addition, several challenges for research are brought up by the research presented in this dissertation that researchers should be aware of in the field of RCC research.

*Determinants for renal cell carcinoma*
One of the primary aims of this dissertation was to assess risk factors for RCC and its subtypes. Two potential risk factors which are highly prevalent in the population, namely type 2 diabetes mellitus and kidney stones, which as of yet are not considered established risk factors for RCC, were observed to be associated with an increased risk of RCC in the Netherlands Cohort Study on diet and cancer.
The study on type 2 diabetes mellitus described in this dissertation reinforces recent evidence from the Nurses' Health Study and the Health Professionals Follow Up Study that diabetes mellitus is associated with RCC specifically in women, but not in men[1]. From a scientific perspective, this observation could be of great importance for finding clues for unravelling factors that contribute to the development of RCC. In a similar vein, the observed association between anti-diabetic medication use and the risk of RCC may prove to be an interesting observation for future research. Anti-diabetic medication has often been a source for heated debate in the scientific community. This is, in part, due to the inconsistent associations between anti-diabetic medication and the risk of various cancers[2, 3]. The information regarding the effect of these types of medication on the risk of kidney cancer remains limited from observational studies[2]. Hopefully, other largescale prospective cohorts will find opportunities to look into replication of these findings, as these observed results in our study do not yet suffice as conclusive evidence due to underlying methodological constraints.
The current evidence on the association between kidney stones and RCC is slightly stronger, although mainly supported by evidence from retrospective cohort studies or case-control studies. As a result of a meta-analysis by Cheungpasitporn *et al.*, kidney stones have been featured on Wolters Kluwer UpToDate as a risk factor for RCC, enabling physicians to easily access information on the role of this risk factor in RCC[4, 5]. Interestingly, the majority of studies featured in the aforementioned meta-analysis were published between 1984-1997[4]. Resultingly, no evidence is available regarding associations between kidney stones and specific RCC tumor entities. Therefore, if clinicians are inclined to look for more information on kidney stones and the relationship with RCC subtypes, they are likely to end up with the data from our study, being the first to report on the heterogeneity of associations regarding kidney stones across ccRCC and pRCC risk. This heterogeneity of associations is of particular interest, as the relationship cannot be explained by the occurrence of kidney stones due to a

disconnect between the location where kidney stones form and the location where ccRCC and pRCC develop. This finding may therefore provide a lead for delving deeper into the characteristics and mechanisms resulting in the association between kidney stones and RCC subtypes for future research.
An increased awareness by both clinicians, policy makers and patients for (lesser known) risk factors for RCC and its subtypes may contribute to improved individual healthcare in the future. With increased awareness clinicians may be better equipped to provide advice targeted to the characteristics of the patient. As many of the risk factors for RCC are shared with other important comorbidities that tend to severely effect the quality of life, these advices may improve the overall health of patients. Furthermore, policy makers and health professionals may include these risk factors in guidelines and factsheets to aid in the education of clinicians, patients and researchers.

*Heterogeneous associations for histologic subtypes of RCC*
In recent years more attention has been brought to the associations between risk factors and the risk of specific histological subtypes of RCC. These histological subtypes may be differentially associated to risk factors due to their distinct clinical, pathological and genetic makeup. Information on the association between risk factors and specific subtypes of RCC is crucial as potential differences in association can add noise when trying to assess aetiological relationships. For instance, if a risk factor is only associated to a specific histologic subtype of RCC, no clear or conclusive evidence may be found if studies are performed in a population with varying tumour histologic subtypes. Therefore, the observed differences across the risk of ccRCC and pRCC regarding the history of kidney stones and body mass index (BMI) may help elucidate differences in aetiology and differences in aetiological mechanisms involved between subtypes. At present, new entities are continuously described and incorporated in the WHO classification for tumours. Therefore, more research is needed to establish whether different entities possess different aetiologic mechanisms.

Even though established risk factors convey additional risks for RCC it remains hard to translate these findings into direct changes in prevention strategies for health policy makers. Population screening, for instance, is not a feasible strategy at this point in time. One of the primary barriers to population screening for RCC is the relatively low prevalence of RCC. It is estimated that by screening 1,000 asymptomatic individuals from the general population using ultrasound only one or two cases of RCC will be detected[6]. An employable strategy to resolve this problem is by creating prediction models for targeted screening of high-risk populations. However, as (modifiable) risk factors for RCC, including smoking, obesity, hypertension, kidney stones and diabetes mellitus, only translate into moderate risk increases and since they are not specific for RCC, these factors are unlikely to be suitable for use in risk prediction models[6]. Resultingly, more evidence is needed on the aetiology of RCC to make risk estimations more accurate. Hopefully, this will enable us to detect RCC in earlier stages in future times and, in turn, reduce mortality rates of RCC.

For clinicians and general practitioners it remains of great importance to actively promote healthy lifestyles as the reduction of the prevalence of obesity, smoking and hypertension in the general population may pose viable strategies to the reduction of the burden of RCC. For instance, information from GLOBOCAN (Global Cancer Incidence, Mortality and

Prevalence) indicates that more than 20% of the RCC cases in Europe can be attributed to obesity[7]. Furthermore, tobacco smoking also heavily contributes to the burden of kidney cancer[8]. More information is needed to get more accurate estimations on the burden of RCC attributed to hypertension, diabetes mellitus and kidney stones. To this end, more information is needed on the direct mechanisms by which these risk factors are associated to RCC. An example is inconclusive evidence regarding the role of anti-hypertensive medication on the risk of RCC. Insights in such factors may then open new avenues for prevention strategies against renal cancer in the general population.

In the past, strategies have been made to create risk profiles of patients who developed (cc) RCC[9]. In general, the focus in these methods relies on clinical characteristics to create a prognostic index. Based on the predicted prognosis of these patients, different systemic therapies are recommended. These models could also benefit from additional prognostic variables such as molecular testing. For instance, in this dissertation **(chapter 6)** we reported that patients with ccRCC had a better prognosis if they had *VHL* or *PBRM1* mutations, when compared to patients without these mutations. Insights like these, combined with detailed clinical information may be used in the future to predict the prognosis of (cc)RCC in patients or to recommend treatments with higher rates of success.
One important sidenote regarding this observed association is that the analyses in this dissertation were based on a mostly treatment-naïve population. This may provide indications of how ccRCC progresses without the effect of interventions beyond surgical resection. Nowadays, this information is hard to obtain, as patients tend to receive various forms of treatment (a.o surgical resection, targeted therapy and/or immunotherapy). Hopefully, the information on gene profiles described in this thesis may provide useful information for researchers and clinicians who are looking to further incorporate mutational profiles in prognostic indices. Hopefully, in the future extensive tailored treatment strategies will become available for the treatment of RCC depending on the genotypic and phenotypic features of the tumour. Having clearer information regarding more optimal treatment strategies for patients by incorporating prognostic features may aid clinicians in providing better patient care in the future, which may reduce the health care burden of RCC.

**Conclusion**
In this dissertation we have included several studies that highlight aetiological and prognostic mechanisms for the risk of RCC and its subtypes. To disseminate this evidence to the right audiences and to increase the impact of this work, several strategies were employed to share these results with researchers, clinicians and general audiences. While most results are not directly suited for inclusion in adjustments to current healthcare, they may provide crucial insights and leads for future studies into the aetiology of RCC and its subtypes.

## References


1. Graff RE, Sanchez A, Tobias DK, et al. Type 2 Diabetes in Relation to the Risk of Renal Cell Carcinoma Among Men and Women in Two Large Prospective Cohort Studies. Diabetes Care. 2018;41: 1432-1437.
2. Karlstad O, Starup-Linde J, Vestergaard P, et al. Use of insulin and insulin analogs and risk of cancer - systematic review and meta-analysis of observational studies. Curr Drug Saf. 2013;8: 333-348.
3. Zhang K, Bai P, Dai H, Deng Z. Metformin and risk of cancer among patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Prim Care Diabetes. 2020.
4. Cheungpasitporn W, Thongprayoon C, O'Corragain OA, et al. The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis. Qjm. 2015;108: 205-212.
5. Atkins MB, Choueiri TK. Epidemiology, pathology, and pathogenesis of renal cell carcinoma. In: Richie JP, editor. UpToDate. Waltham, MA, 2020.
6. Rossi SH, Klatte T, Usher-Smith J, Stewart GD. Epidemiology and screening for renal cancer. World J Urol. 2018;36: 1341-1353.
7. Arnold M, Lam F, Ervik M, Soerjomataram I. Cancer and Obesity: Global burden of cancer attributable to excess weight. Available from URL: http://gco.iarc.fr/obesity [accessed November 25, 2020].
8. Safiri S, Kolahi A-A, Mansournia MA, et al. The burden of kidney cancer and its attributable risk factors in 195 countries and territories, 1990–2017. Scientific Reports. 2020;10: 13862.
9. Achermann C, Stenner F, Rothschild SI. Treatment, Outcome and Prognostic Factors in Renal Cell Carcinoma - A Single Center Study (2000-2010). J Cancer. 2016;7: 921-927.