## **Characterizing Kidney Cancer in Denmark 1991-2021: Kidney-Epi (a DaRenCa-study)**

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### **Study aim**

The purpose is to conduct an epidemiological study of kidney cancer in Denmark from 1991 to 2021. Fundamentally, we aim to characterize the current landscape of kidney cancer in Denmark and how it has changed over the past 30 years.

1. Risk of recurrence based on differences in patient, tumor, and treatment-related characteristics.
2. Mortality rates stratified by UICC stage and recurrence status adjusted for comorbidity and expected remaining lifespan.

We aim to describe the patients diagnosed with kidney cancer, including factors such as age at diagnosis, comorbidities, and socio-economic status. We intend to correlate this information with tumor-related data such as stage (TNM) at diagnosis, tumor grade, and recurrence. Additionally, we will assess survival rates and whether there have been significant changes over the past 30 years. We will investigate the risk of recurrence by examining the proportion of patients experiencing relapse within the three Leibovich risk score groups (‘low’, 'intermediate', and ‘high’ risk) used in Denmark, and assess patient response to treatment. We have chosen the period from 1991 to 2021 as our study period to obtain 30 years of data with a minimum of two years of follow-up.

### **Background**

Kidney cancer is the 7th most diagnosed malignancy, and the number of new cases has increased in recent years, likely due to the widespread use of diagnostic CT scans. As a result, more than half of all new kidney cancer cases are now incidental findings in asymptomatic patients. This has led to stage migration; currently, approximately 85% of patients have localized disease, although the number of patients diagnosed with metastatic disease remains unchanged [1].

The average age at diagnosis is 64 years, and the male-to-female ratio is 2.5:1 [2]. The incidence varies between countries, with the highest rates observed in Europe, North America, and Australia [3]. Cigarette smoking, obesity, and hypertension are well-established risk factors for RCC [4].

It is now almost 30 years since the last assessment of the risk factors associated with the development of kidney cancer in Denmark. At that time, 368 cases and 396 age- and gender-matched controls were interviewed and it was reported that low socioeconomic status correlated with the risk of kidney cancer. At the same time, cigarette smoking was only significantly correlated with the development of kidney cancer in men [5]. However, no analysis of how the factors correlated with outcome data such as survival was performed.

In a more recent study from 2016, 367 patients diagnosed with kidney cancer at Roskilde Hospital in the period from January 2005 to December 2013 were studied to determine recurrence rates and survival in a Danish cohort with renal cell carcinoma. 78 patients (21%) had metastatic disease at the time of diagnosis, while the remaining 289 patients had localized or locally advanced kidney cancer. The average age was 64 years (range: 37-88 years); men accounted for 65% of the cohort. They found in this relatively small cohort that the recurrence rate within five years after surgery for non-metastatic kidney cancer was 22%. For high-risk patients, the recurrence rate was 52.9%. Overall, the three- and five-year survival rates for all patients with RCC regardless of treatment modality were 75% and 66%, respectively [6]. An epidemiological study from 2016, with results from the first 5 years of the Danish Kidney Cancer Group (DaRenCa) database, which as of July 31, 2015, had 3,977 patients, showed that one-year survival after diagnosis had increased from 81.3% in 2010-2011 to 84.1% in 2014–2015 [7].

The first of the two studies was conducted with few patients, considering that approximately 1000 patients are diagnosed with kidney cancer in Denmark annually. The more recent epidemiological study covers a short period, but it clearly shows that significant changes occur in the Danish kidney cancer landscape. Therefore, we aim to characterize the kidney cancer landscape in Denmark in more detail. This is important for understanding the challenges within kidney cancer and for appropriately addressing them, both in terms of research and treatment.

### **Data and data analysis**

*Study population*

The study is based on a population consisting of all Danish patients over 18 years of age diagnosed with renal cancer, with ICD-10 diagnosis codes DC64, DC649, or ICD-7 diagnosis code 1800 from January 1, 1991, to December 31, 2021.

*Exclusion criteria*

To reduce the level of noise in the data and the following results, we will exclude patient who have been diagnosed with other cancers than RCC before curative RCC surgery.

Patients will also be excluded if they have emigrated, died, or were diagnosed with a new primary cancer other than RCC or metastasis of unspecified origin within 180 days of the initial index RCC surgery.

*Shifts in Renal Cancer Diagnosis and Survival Patterns Over Time*

We will use statistical methods to examine the distribution of age and TNM stages at diagnosis, examining trends over time in 5-year intervals. To analyze survival and recurrence, we will utilize Kaplan-Meier curves and Cox proportional hazard regression.

We aim to explore and characterize whether there has been a stage migration in renal cancer over the last three decades in Denmark. With advancements in diagnostic technologies, we anticipate detecting more tumors at earlier stages due to increased incidental findings.

Furthermore, we will investigate the trend in survival after a renal cancer diagnosis over time to determine if the general survival time has improved. This analysis will incorporate the TNM stage as a covariate, considering the disease's aggressiveness as a significant determinant of survival outcomes. In this analysis, we will also assess the effect of the new treatment regimens introduced in renal cancer patient management in Denmark, such as the use of immunotherapy and the start of the Danish “Cancer packages”, ensuring prompt treatment initiation within 14 days of diagnosis. As part of this analysis, we will also examine recurrence rates over time.

*Comorbidities*

We will be investigating comorbidities. Leveraging comprehensive hospital records pre-and post-diagnosis, we aim to discern the interplay between renal cancer and other medical conditions. Our goal is not only to identify conditions following renal cancer but also to identify those predisposing individuals to the disease. This could potentially facilitate earlier detection strategies. Employing a machine learning framework, we will construct models delineating the comorbidities preceding renal cancer, subsequently validating these findings in an age- and comorbidity-matched non-renal dataset.

*Sex differences*

Given the skewed sex distribution in renal cancer patients (2:1 male-to-female ratio), we want to investigate what other differences there are between the sexes in renal cancer. This will cover survival, residual disease, stage differences, and comorbidities. Importantly, these analyses will be conducted longitudinally to assess temporal trends.

All analyses will be performed using R.

### **Data availability**

### Due to data protective law, data will only be available upon application to The Danish Health Data Authority. The code used for data analysis will be published.

### **Publication policy**

### Positive, negative, and undefined results from this study will be published in peer-reviewed scientific journals. This study will not publish personally identifiable data in any way.

**References**

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018. doi:10.3322/caac.21442

2. Motzer RJ, Jonasch E, Agarwal N, et al. Kidney Cancer, Version 3.2015. *J Natl Compr Cancer Netw*. 2015. doi:10.6004/jnccn.2015.0022

3. Cho E, Adami HO, Lindblad P. Epidemiology of renal cell cancer. *Hematol Oncol Clin North Am*. 2011. doi:10.1016/j.hoc.2011.04.002

4. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. *Nat Rev Urol*. 2010. doi:10.1038/nrurol.2010.46

5. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH. Risk factors for renal cell carcinoma in Denmark. I. Role of socioeconomic status, tobacco use, beverages, and family history. Cancer Causes Control. 1994;5: 105–113.

6. Azawi NH, Tesfalem H, Mosholt KSS, Høyerup P, Jensen ES, Malchau E, et al. Recurrence rates and survival in a Danish cohort with renal cell carcinoma. Dan Med J. 2016;63. Available: https://www.ncbi.nlm.nih.gov/pubmed/27034180

7. Petersen AC, Søgaard M, Mehnert F, Larsen EH, Donskov F, Azawi NH, Kromann-Andersen B. The database of the Danish Renal Cancer Group. Clin Epidemiol. 2016;8:725-729. <https://doi.org/10.2147/CLEP.S106042>