Chemoprevention in Kidney Cancer

by

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in the University of Toronto

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THESIS ABSTRACT

Thesis Title: Chemoprevention in kidney cancer
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Background: This thesis is a composition of three studies that explore the role of statins in kidney cancer. Furthermore, I evaluate the potential for different interpretations from the same data depending on the method of classifying medication use.

Methods: The first study was a population-based case-control study evaluating the association of statin use with risk of incident kidney cancer. The second study was a systematic review and meta-analysis reviewing the current evidence relating statins with kidney cancer survival outcomes. The final study was a population-based cohort study evaluating the association of statin use with survival. In the observational studies, I used fractional polynomials for the primary analysis to allow for a non-linear relationship between cumulative exposure and the risk of the outcome. I also compared risk estimates obtained by different methods of classifying medication exposure.

Results: The population-based case-control study included 10,377 incident cases of kidney cancer and 35,939 matched controls. Increasing cumulative use of statins was not associated with kidney cancer risk. I identified 12 studies for inclusion in the systematic review and meta-analysis and found that statin use was significantly associated with markedly improved cancer-specific and overall survival. However, none of these studies evaluated cumulative use. In the population-based cohort study of 9124 patients with incident kidney cancer, increasing cumulative use of statins was associated with minimal improvement in cancer-specific and
overall survival. The association of statin use with kidney cancer risk or survival varied depending on the method of classifying exposure.

**Conclusions:** This thesis does not support the use of statins for the prevention or adjunctive treatment in kidney cancer. Furthermore, risk estimates in pharmacoepidemiology may be sensitive to the method of classifying exposure.
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# TABLE OF CONTENTS

**THESIS ABSTRACT** .................................................................................................................. II

**ACKNOWLEDGEMENTS** ........................................................................................................ IV

**LIST OF FIGURES** ................................................................................................................ IX

**LIST OF TABLES** .................................................................................................................... X

## CHAPTER 1: LITERATURE REVIEW ......................................................................................... 1

- KIDNEY CANCER EPIDEMIOLOGY .......................................................................................... 1
- KIDNEY CANCER RISK FACTORS ......................................................................................... 3
- KIDNEY CANCER PROGNOSIS .............................................................................................. 10
- STATINS AND CANCER-MOLECULAR PATHWAYS ............................................................... 13
- EPIDEMIOLOGIC STUDIES OF STATINS AND CANCER RISK ............................................. 16
- STATINS AND KIDNEY CANCER RISK ............................................................................... 20
- EPIDEMIOLOGIC STUDIES OF STATINS AND CANCER SURVIVAL .................................. 27
- STATINS AND KIDNEY CANCER SURVIVAL .................................................................... 31
- GAPS IN CURRENT LITERATURE ......................................................................................... 34

## CHAPTER 2: METHODS AND DATA SOURCES ....................................................................... 38

- THESIS OVERVIEW ................................................................................................................ 38
- DATA SOURCES .................................................................................................................... 40
- STUDY DESIGN ...................................................................................................................... 42
- STUDY PARTICIPANTS .......................................................................................................... 45
- EXPOSURE CLASSIFICATION ............................................................................................... 48
- POTENTIAL CONFOUNDERS ............................................................................................... 51
- CAUSAL FRAMEWORK ......................................................................................................... 54
- POTENTIAL BIASES ............................................................................................................. 56
- SPECIFIC OBJECTIVES ........................................................................................................ 60
- ETHICS STATEMENT ............................................................................................................ 60
- FIGURES FOR CHAPTER 2 .................................................................................................... 61

## CHAPTER 3: MEDICATION USE AND RISK OF INCIDENT KIDNEY CANCER: A POPULATION-BASED CASE-CONTROL STUDY ........................................................................... 63

- SUMMARY ............................................................................................................................. 63
- INTRODUCTION ..................................................................................................................... 65
CHAPTER 4: STATIN USE AND KIDNEY CANCER SURVIVAL OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

SUMMARY ....................................................................................................................... 88
INTRODUCTION .................................................................................................................. 89
METHODS ........................................................................................................................... 90
DESIGN ............................................................................................................................... 90
SEARCH STRATEGY .......................................................................................................... 90
STUDY SELECTION ........................................................................................................... 90
DATA ABSTRACTION AND RISK OF BIAS ASSESSMENT ............................................. 91
DATA SYNTHESIS AND ANALYSIS ................................................................................ 92
RESULTS ............................................................................................................................ 94
DESCRIPTION OF STUDIES ............................................................................................ 94
RECURRENT-FREE SURVIVAL .......................................................................................... 94
PROGRESSION-FREE SURVIVAL ....................................................................................... 95
CANCER-SPECIFIC SURVIVAL ......................................................................................... 95
OVERALL SURVIVAL ........................................................................................................... 96
DISCUSSION ....................................................................................................................... 97
CONCLUSION .................................................................................................................. 101
FIGURES FOR CHAPTER 4 .............................................................................................. 102
TABLES FOR CHAPTER 4 .............................................................................................. 107

CHAPTER 5: STATIN USE AND KIDNEY CANCER OUTCOMES: A POPULATION—
BASED COHORT STUDY ............................................................................................... 111
SUMMARY ..................................................................................................................... 111
INTRODUCTION ........................................................................................................... 113
METHODS .................................................................................................................... 114
  SETTING ...................................................................................................................... 114
  DATA SOURCES ......................................................................................................... 114
  STUDY PARTICIPANTS ............................................................................................... 114
  EXPOSURE ASSESSMENT .......................................................................................... 115
  STATISTICAL METHODS ............................................................................................ 116
  SENSITIVITY ANALYSES .......................................................................................... 117
RESULTS ....................................................................................................................... 119
  COHORT CHARACTERISTICS .................................................................................. 119
  KIDNEY CANCER-SPECIFIC SURVIVAL .................................................................. 119
  ALL-CAUSE MORTALITY ......................................................................................... 120
  SENSITIVITY ANALYSES .......................................................................................... 121
DISCUSSION ................................................................................................................ 122
CONCLUSION .............................................................................................................. 127
FIGURES FOR CHAPTER 5 ............................................................................................. 128
TABLES FOR CHAPTER 5 ............................................................................................. 133

CHAPTER 6: DISCUSSION AND CONCLUSIONS .............................................................. 142
THESIS SUMMARY ..................................................................................................... 142
IMPLICATIONS AND RECOMMENDATIONS ............................................................... 147
  CLINICAL IMPLICATIONS ......................................................................................... 147
  METHODOLOGICAL IMPLICATIONS ...................................................................... 149
  HEALTH POLICY IMPLICATIONS .......................................................................... 151
THESIS LIMITATIONS ................................................................................................. 152
FUTURE STUDIES ....................................................................................................... 154
CONCLUSIONS ............................................................................................................ 156
LIST OF FIGURES

Figure 2.1: Directed acyclic graph displaying relationship between statin exposure and kidney cancer risk, in relation to other variables.................................................................61

Figure 2.2: Directed acyclic graph displaying relationship between statin exposure and survival outcomes, in relation to other variables.................................................................62

Figure 3.1: Relationship between cumulative exposure to medications on risk of incident kidney cancer................................................................................................................79

Figure 4.1: Flowchart of study selection.................................................................................102

Figure 4.2: Meta-analysis of the effect of statin use on recurrence-free survival in patients with locoregional kidney cancer..................................................................................103

Figure 4.3: Meta-analysis of the effect of statin use on progression-free survival in patients with locoregional kidney cancer..................................................................................104

Figure 4.4: Meta-analysis of the effect of statin use on cancer-specific survival in patients with kidney cancer.......................................................................................................105

Figure 4.5: Meta-analysis of the effect of statin use on overall survival in patients with kidney cancer....................................................................................................................106

Figure 5.1: Cohort derivation..................................................................................................128

Figure 5.2: Relationship between cumulative exposure to medications after kidney cancer diagnosis and cancer-specific survival.............................................................................129

Figure 5.3: Relationship between cumulative exposure to medications after kidney cancer diagnosis and overall survival.....................................................................................130

Figure 5.4: Comparing continuous cumulative use and binary time varying analyses..............131
LIST OF TABLES

Table 3.1: Characteristics of cases and controls.................................................................80
Table 3.2: Medication exposure among cases and controls...............................................81
Table 3.3: Transformations applied through the use of the multi-variable fractional polynomial algorithm.........................................................................................................................82
Table 3.4: Cumulative use of medication exposure modelled with fractional polynomials on risk of incident kidney cancer..................................................................................................................83
Table 3.5: Comparison of different methods of classifying cumulative medication exposure on risk of incident kidney cancer ................................................................................................................84
Table 3.6: Cumulative use of medication exposure modelled with fractional polynomials on risk of incident kidney cancer, adjusted for screening tests........................................................85
Table 3.7: Cumulative use of medication exposure modelled with fractional polynomials on risk of incident kidney cancer, adjusted for presence of comorbidities........................................86
Table 3.8: Cumulative use of medication exposure modelled with fractional polynomials on risk of incident kidney cancer, adjusted for duration of hypertension...........................................87
Table 4.1: Characteristics of included studies.......................................................................107
Table 4.2: Quality assessment of included studies.................................................................110
Table 5.1: Cohort characteristics of 9124 patients aged 65 or older with incident kidney cancer........................................................................................................................................133
Table 5.2: Medication exposure following kidney cancer diagnosis..................................135
Table 5.3: Transformations applied through the use of the multi-variable fractional polynomial algorithm..........................................................................................................................136
Table 5.4: The association between medication exposure and kidney cancer-specific survival by method of analysis...............................................................................................................................137
Table 5.5: The association between medication exposure and overall survival by method of analysis.................................................................................................................................................138
Table 5.6: The association between cumulative medication exposure and survival, adjusted for screening tests..............................................................................................................................139
Table 5.7: The association between cumulative medication exposure and survival, adjusted for presence of comorbidities ................................................................................................................140
Table 5.8: The association between cumulative medication exposure and kidney cancer-specific survival, adjusted for medication use from age 65 to kidney cancer diagnosis.
CHAPTER 1: LITERATURE REVIEW

KIDNEY CANCER EPIDEMIOLOGY

Kidney cancer is the 15th most common malignancy worldwide, with an estimated 337,860 new cases in 2012(1). The crude incidence of kidney cancer is higher in more developed countries compared to less developed countries, with the highest crude incidence reported to be in Europe and the lowest in Africa(1). In Canada, kidney cancer accounts for approximately 2.9% of all incident cancers, making it the 9th most common cancer, with an estimated 6,200 new cases in 2015(2). Kidney cancer may be more common in Canada and other developed countries due to variations in screening patterns, diet, social habits, and competing risks of death(3). The majority of incident cases are in men aged 65 or older(1).

The incidence of kidney cancer is increasing in most countries, including Canada(1, 2, 4). It is estimated that in 2035, there will be 557,934 new cases of kidney cancer in the world(1). This change in crude incidence may be attributable to increased life expectancy, and decreased mortality from competing risks such as infection(3).

Worldwide and in Canada, kidney cancer is the third most common urological malignancy, after prostate and bladder cancer(1, 2). However, kidney cancer has the highest fatality rate of all urological malignancies accounting for approximately 143,406 deaths worldwide in 2012(1), and 1,790 deaths in Canada in 2015(2). In many malignancies, such as prostate cancer and colorectal cancer, cancer-specific mortality trends in the world population have decreased over time (1, 2). In kidney cancer, however, mortality trends have been stable in most countries(4). In Canada, survival rates in kidney cancer have improved, but only marginally; in 1992-1994, the age-standardized five-year relative survival was 59.5% (95%
confidence interval 58.1 to 60.9%) and in 2006-2008, the corresponding survival ratio was 67% (95% confidence interval 65.9 to 68.1%(2).
KIDNEY CANCER RISK FACTORS

Established risk factors for incident kidney cancer include cigarette smoking, hypertension, obesity, and familial cancer syndromes (5). Other factors that have been proposed to modulate kidney cancer risk include diabetes, end-stage renal disease, physical activity, parity in women, alcohol consumption, exposure to trichloroethylene, use of anti-hypertensive drugs, and family history (5). In this section, I review the literature in the context of these risk factors.

Established Risk Factors

Hypertension has been shown to be associated with increased risk of incident kidney cancer in a dose-response relationship. A multi-center, international, prospective cohort study of 296,638 men and women enrolled in the European Prospective Investigation into Cancer and Nutrition evaluated the association of blood pressure measured at baseline with the risk of incident kidney cancer (6). This study included 250 cases of kidney cancer and found a trend for increasing systolic and diastolic pressure with the risk of cancer, though only reaching statistical significance at systolic and diastolic blood pressures > 160 (relative risk 2.48, 95% confidence interval 1.53 to 4.02) and 100 millimetres of mercury (relative risk 2.34, 95% confidence interval 1.54 to 3.55), respectively (6). While this study used the baseline blood pressure measurement to categorize patients, a previous larger cohort study involving 363,992 male participants from the construction industry in Sweden also evaluated whether changes in diastolic blood pressure over time modulated cancer risk (7). This study, in which 759 participants developed kidney cancer, found that there was a dose-response relationship between change in diastolic blood pressure over time and risk of kidney cancer compared to those with no change; those that had diastolic blood pressure reduced over time had a lower risk of kidney cancer (relative risk 0.6 for -14mm
Hg change from baseline, 95% confidence interval 0.3 to 1.3) while those that had diastolic blood pressure increased over time (relative risk 2.3 for +14mm Hg change from baseline, 95% confidence interval 1.4 to 3.7) had a higher risk of kidney cancer(7). While the severity of hypertension appears to be important, there is conflicting evidence on the association of duration of hypertension with kidney cancer risk(8-10), These findings emphasize the importance of adequate control of blood pressure to reduce the risk of kidney cancer.

**Cigarette smoking** is associated with an increased risk of developing several cancers, including kidney cancer(11). Two meta-analyses found that both former and current smokers had, on average, significantly increased risks of developing incident kidney cancer(11, 12). Compared to other malignancies, however, the magnitude of the association of smoking status with incident cancer was lower for kidney cancer (pooled relative risk 1.52 for current smokers, 95% confidence interval 1.33 to 1.74 and pooled relative risk 1.25 for former smokers, 95% confidence interval 1.14 to 1.37)(11). This association did not vary appreciably in sensitivity analyses adjusted for body mass index or stratified by gender, though the risk was higher among men(11, 12). While there was evidence for publication bias in one of these meta-analyses(11), the association remained in a sensitivity analysis accounting for potential hypothetical missing studies. A positive dose-response relationship was also observed based on number of cigarettes consumed daily, while an inverse relationship was observed based on years since quitting smoking(12). These studies highlight the importance of smoking cessation counselling to reduce the risk of incident kidney cancer.

**Obesity**, similar to smoking, has been implicated as a risk factor for several cancers, including kidney cancer(13). A recent meta-analysis of 21 cohort studies involving 9,080,052 participants with 15,144 cases of kidney cancer found that when based on categories of body
mass index, those who were overweight (body mass index 25.0 to 29.99) or obese (body mass index ≥ 30.0) had, on average, significantly increased risks of incident kidney cancer with relative risk estimates of 1.28 (95% confidence interval 1.24 to 1.33) and 1.77 (95% confidence interval 1.68 to 1.87), respectively, when compared to those with a normal weight (body mass index 18.5 to 24.99)(14). These risk estimates were relatively consistent across gender, duration of follow-up, and whether risk estimates were adjusted for age, smoking, and hypertension. This meta-analysis also evaluated for a potential non-linear relationship between body mass index and kidney cancer risk using cubic splines and indeed found evidence supporting a non-linear relationship; relative to a linear relationship, the risk was lower under a body mass index of 30 and greater thereafter.

The association between obesity and kidney cancer risk is lower than the risk associating obesity and cancers of the esophagus and uterus, higher than the risk associated with cancers of the breast, colon, and rectum, and similar to the risk associated with cancers of the liver and gastric cardia(13).

To date, no study has evaluated whether a change in body mass index can modulate kidney cancer risk. However, a prospective cohort study evaluating the association between adult weight change, defined as the weight change from the age of 18 to the onset of menopause, and the risk of invasive breast cancer found that those that gained weight had an increased risk of compared to women who maintained their weight, while those that reduced and kept their reduced weight had a lower risk(15).

**Familial cancer syndromes** associated with increased kidney cancer risk include von Hippel-Lindau, hereditary papillary renal cell carcinoma, familial leiomyomatosis and renal cell
carcinoma, and Burt-Hogg-Dube(5). All of these syndromes are transmitted in an autosomal-dominant manner, though the degree of penetrance is variable. They are relatively rare, with germline mutations in the von Hippel-Lindau gene being the most common, occurring in approximately 1 per 36,000 births(16).

Suspected Risk Factors

A meta-analysis of 7 case-control and 11 cohort studies evaluating the association between diabetes and kidney cancer found that, on average, diabetes was associated with a significantly increased risk of incident kidney cancer (relative risk 1.40, 95% CI 1.16 to 1.69)(17). However, only two of the studies included in this meta-analysis simultaneously controlled for obesity, smoking, and history of hypertension, one of which was performed only in women and found a significantly increased risk associated with diabetes(18) while the other included men and women and found no association in either gender(19). As such, the independent role of diabetes in the etiology of kidney cancer is controversial(16).

An Australian population-based cohort study compared the risk of developing kidney cancer among 28,855 patients requiring renal replacement therapy for end-stage renal disease to the general population. Among patients requiring renal replacement therapy, 82 on dialysis and 30 undergoing renal transplantation developed kidney cancer which conferred a 5.4 (95% CI 4.3 to 6.7) and 5.0 (95% CI 3.4 to 7.1) times increased risk of incident kidney cancer, respectively(20). It is important to note that while end-stage renal disease appears to be associated with an increased risk, the population attributable risk is likely small. Furthermore, the increased risk may be partly due to increased observation resulting in detection bias. Supporting
this notion is that in patients with end-stage renal disease, kidney cancer tends to be diagnosed at an earlier age (21).

**Physical activity** has been shown to have an inverse relationship with incident cancer risk for several malignancies (22). The data in kidney cancer, however, are limited; a review on the association of physical activity with cancer risk concluded that no clear pattern can be drawn from the studies in kidney cancer (22). Further complicating this evaluation is the possibility of confounding from smoking and obesity.

**Alcohol consumption** has been associated with increased risk of several cancers including cancers of the oral cavity, pharynx, oesophagus, liver, colon, rectum, and breast (23). Some cancers, however, show no association with alcohol including cancers of the prostate and bladder, and some cancers such as ovarian and kidney cancer, demonstrate an inverse relationship (23). The studies in kidney cancer have been limited in number and no strong conclusion can be made.

A recent meta-analysis evaluated the association of **parity** with kidney cancer risk (24). This meta-analysis of 5 cohort studies and 9 case-control studies included 5,389 cases and 651,072 non-cases. Compared to nulliparous, ever parity was associated with, on average, a significant increased risk of kidney cancer (relative risk 1.23, 95% confidence interval 1.10 to 1.36). In an evaluation for a dose-response relationship, they found that for each live birth, the risk of kidney cancer increased by 8% (95% confidence interval 5 to 10%). In a subgroup analysis of 4 studies that controlled for obesity, smoking, and hypertension, the association between ever parity vs. nulliparity was extinguished (relative risk 1.14, 95% confidence interval
0.90 to 1.46). A similar subgroup analysis was not performed for the dose-response relationship. Therefore, it remains unclear whether parity is an independent risk factor for kidney cancer.

**Trichloroethylene** is a commercial solvent that is primarily used in the vapour degreasing process of metal parts. Occupational exposure can also occur in the textile, health services, electronic, leather processing, food, dry-cleaning, and chemical industries. A meta-analysis of 10 cohort and 10 case-control studies evaluating the association of trichloroethylene exposure with kidney cancer risk found that it conferred, on average, a 48% (95% confidence interval 19 to 83%) increased risk (25). This meta-analysis, however, did not describe whether pertinent confounders were accounted for in the separate studies.

Previous studies examining the association between anti-hypertensive drugs and incident kidney cancer have demonstrated mixed results (26-29). However, these studies have been limited in size, are subject to selection and recall bias, and it is difficult to disentangle the effect of hypertension, thereby limiting their interpretation. A recent review of marketed anti-hypertensive drugs found that fewer than half had results on both genotoxicity and carcinogenicity assays (30); however, among those with data available, many were associated with some degree of genotoxicity or carcinogenicity.

A meta-analysis of 8 case-control and 6 cohort studies found that a **family history** of kidney cancer was associated with a markedly increased risk of kidney cancer (relative risk 2.43, 95% confidence interval 1.73 to 3.12) (31). Similar to previous meta-analyses evaluating kidney cancer risk, however, few studies controlled for the established risk factors of kidney cancer. Furthermore, the studies did not exclude cases that may have had familial cancer syndromes. Therefore, it is difficult to interpret the independent risk conferred by family history of kidney
cancer outside of the context of familial cancer syndromes. The authors of the meta-analysis argue, however, that the familial cancer syndromes are rare and therefore the most of the risk related to family history of kidney cancer is unlikely to be attributable to familial cancer syndromes(31).

In summary, established independent risk factors for kidney cancer are hypertension, obesity, smoking, and familial cancer syndromes. The causal relationship between diabetes, end-stage renal disease, physical activity, alcohol consumption, parity, exposure to trichloroethylene, use of anti-hypertensive drugs, or family history, and kidney cancer risk may be small or confounded by other factors.
KIDNEY CANCER PROGNOSIS

In clinically localized kidney cancer, nephrectomy remains the mainstay of treatment. However, despite treatment, approximately 20% to 30% of those with localized disease experience disease recurrence after nephrectomy, and the majority of those progress to advanced disease and die of the cancer (32, 33). Therefore, predicting survival in kidney cancer is important for patient counselling, tailoring follow-up protocols, and treatment planning. Several studies have evaluated which factors are independently associated with survival outcomes in localized and advanced kidney cancer and have developed nomograms to aid decision making. In this section, I review the most commonly used prognostic models to predict survival in kidney cancer.

Localized kidney cancer

In localized kidney cancer, three separate nomograms have been developed to predict survival and include the Stage, Size, Grade, and Necrosis (SSIGN) score, the University of California Los Angeles Integrated Staging System (UISS), and the Karakiewicz nomogram.

The SSIGN score was developed in patients undergoing radical nephrectomy for clear cell renal cell carcinoma, the most common subtype of kidney cancer (34), at a single institution (35). This study evaluated numerous factors and after applying stepwise selection found that variables most predictive of cancer-specific survival were tumour stage, tumour size (5 centimeters or greater), tumour grade, and presence of necrosis. The model’s predictive ability, as determined by the concordance index, was found to be 0.841. The same group found that these factors were also predictive of progression to metastatic disease (32).

While clear cell renal cell carcinoma is associated with worse survival in univariate analysis, the prognostic information from histology is lost in a multivariate analysis taking into
account tumour stage(34). As such, the UISS was developed in a multi-institutional, international cohort of patients with localized kidney cancer of any histology. This study found that stratifying patients on tumour stage, grade, and Eastern Cooperative Oncology Group performance status into low-, intermediate-, and high-risk categories was able to predict overall survival with reasonable accuracy(36). The concordance index of this model ranged from 0.79 to 0.86, depending on the institution that the model was applied to. Similar predictive ability was found when this system was applied to patients with advanced kidney cancer(37).

More recently, Karakiewicz et al. sought to improve the prediction of cancer-specific survival in a multi-institutional, international cohort(38). This study evaluated numerous factors and after utilizing stepwise selection, they found that a model consisting of tumour stage, tumour grade, and symptom classification (systemic vs. local vs. no symptoms at diagnosis) was the most parsimonious and accurate in predicting cancer-specific survival. The concordance index of this model was 0.863.

Despite the development of these nomograms, clinical guidelines have not adopted them for routine use. Rather, guidelines recommend that follow-up after treatment of localized disease should be based on tumour stage(39-41), and that these nomograms be used to provide rationale for enrolling patients in clinical trials(41).

Advanced kidney cancer

In advanced kidney cancer, two prognostic models are commonly used to predict survival, namely the Motzer criteria and the Heng criteria. The Motzer criteria were developed in 463 patients with advanced kidney cancer of any histology treated with interferon-alpha as the first-line systematic therapy(42). After applying stepwise selection, five variables were found to be most significantly associated with overall survival and included hemoglobin, lactate
dehydrogenase, corrected calcium, Karanofsky performance status, and the interval from diagnosis to treatment. This study did not report the concordance index of this model. They then assigned three risk groups based on the number of risk factors present: favourable risk with zero risk factors, intermediate risk with one or two risk factors, and poor risk with three or more risk factors. Stratification based into these three categories demonstrated significant differences in survival between groups with a median survival of 30, 14, and 5 months in the favourable, intermediate, and poor risk group, respectively(42).

The advent of targeted therapy for advanced kidney cancer has displaced immunotherapy as the first-line systemic treatment due to improved survival and better tolerability(43). Heng et al. subsequently developed a prognostic model for overall survival in 645 patients with advanced kidney cancer of any histology that had received treatment with targeted (anti-vascular endothelial growth factor) therapy(44). After applying stepwise selection, they found that the same 4 Motzer criteria, except for lactate dehydrogenase, were significantly predictive of overall survival, as well as 2 additional predictors, namely absolute neutrophil count and platelets. The concordance index of this model was 0.73. Similar to the Motzer risk stratification, patients in this study were stratified into favourable, intermediate, and poor risk if they had zero, one or two, or three to six risk factors, respectively. Stratification by risk category was significantly predictive of overall survival. In this study, median survival was not reached in the favorable risk group and was 27 and 8.8 months in the intermediate and poor risk group, respectively.(44).

Contrary to localized disease, risk stratification is recommended by clinical guidelines to guide treatment decision making(41, 45).
STATINS AND CANCER-MOLECULAR PATHWAYS

3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, commonly referred to as statins, are among several types of lipid altering agents, and are primarily prescribed in the context of dyslipidemia for both primary and secondary prevention of coronary heart disease(46).

HMG CoA reductase is an enzyme involved in the rate-limiting step of the cholesterol synthesis pathway, known as the mevalonate pathway. Inhibition of this enzyme by statins results in reduced intrahepatic cholesterol which leads to increased low density lipid receptor turnover, increased hepatic low density lipid cholesterol uptake, and ultimately reduced levels of plasma low density lipid cholesterol. Statins also result in reduced levels of very low density lipids, increased levels of high density lipid cholesterol, and reduced levels of triglycerides(46, 47).

Recently, statins have gained interest in the oncology community as studies have shown that their use may be associated with decreased cancer risk and improved cancer survival(48-50). Though the exact mechanism by which statins may exert their putative anti-neoplastic effects is unknown, evidence suggests there are both HMG CoA-dependent and HMG CoA-independent mechanisms.

In the mevalonate pathway, inhibition of HMG-CoA reductase not only inhibits cholesterol synthesis but also the formation of downstream lipid isoprenoid intermediates such as geranylgeranyl pyrophosphate and farnesyl pyrophosphate. These intermediates are added to various proteins during post-translational modification and are essential for them to function. Without these functioning proteins, several downstream pathways are affected and cells
experience increased apoptosis and decreased growth, proliferation, migration, adhesion, and invasion (47, 51).

Statins also exert many pleiotropic effects independent of HMG CoA reductase inhibition. Through interactions with proteasomes, cellular matrix metalloproteinases, and transcription factors, statins regulate cell-adhesion, invasion, proliferation, and inflammation (51, 52).

The first laboratory study to evaluate statins in kidney cancer was published in 2004 (53). This study found that compared to a control medium, murine kidney cancer cells cultured in fluvastatin experienced decreased proliferation, angiogenesis, and invasion, and increased cell cycle arrest and apoptosis. They also performed an in vivo study and found that mice treated with daily oral fluvastatin for 12 days had fewer metastatic nodules compared to mice treated with control medium. However, this benefit was only observed in mice treated with doses of 1 or 10 mg/kg/day while there was no significant difference in the number of metastatic nodules between mice treated at 0.1 mg/kg/day and those treated with control medium (53).

While this previous study used animal kidney cancer cells, another study in human kidney cancer cells also found that fluvastatin significantly inhibited cell proliferation in a dose-dependent manner (54). The doses at which significant growth inhibition was observed were 2 and 3 µmol per litre, concentrations that are achievable when statins are administered to humans. Apoptosis was also induced with the maximum effect seen after 72 to 96 hours of treatment of the cells. This study also evaluated whether statins may exert their anti-neoplastic effects through inhibition of the mammalian target of rapamycin (mTOR) pathway, one of the many downstream pathways affected by inhibition of HMG-CoA reductase. The mTOR pathway is thought to play an important role in survival and growth of kidney cancer cells and several effective targeted
therapies have been developed specifically to inhibit this pathway. Indeed, this study demonstrated that cells exposed to statins had suppressed mTOR activity (54).

Although the previous two studies used fluvastatin, a more recent study evaluated simvastatin against human kidney cancer cells (55). This study found that simvastatin significantly inhibited cell proliferation, induced apoptosis, inhibited cell migration and invasion in a dose-dependent manner. Kidney cancer cells treated with simvastatin had higher expression of pro-apoptotic proteins and lower expression of anti-apoptotic proteins. Studies into the molecular mechanisms of statins on kidney cancer cells found that several pathways were affected, including downregulation of the mTOR pathway. In an animal model from the same study, mice treated with simvastatin at 5mg/kg/day for 5 weeks had significantly reduced tumour volumes at weeks 6 and 7 compared to mice treated with control medium (55).

In summary, the mechanisms by which statins may exert their anti-neoplastic effects is not completely understood. However, several studies suggest that they work through HMG-CoA dependent and independent mechanisms, including downregulation of the mTOR pathway which is believed to be important for kidney cancer growth and survival.
EPIDEMIOLOGIC STUDIES OF STATINS AND CANCER RISK

Interest in statins as potential anti-neoplastic agents has increased significantly over the years with numerous studies evaluating their potential to decrease the risk of cancer. In this section, I review some of these studies with a focus on population-based studies and completed clinical trials.

Graaf et al. performed a population-based, nested, case-control study of individuals from eight cities in the Netherlands(48). The base study population consisted of all patients with one or more prescription for cardiovascular drugs (lipid-lowering agents, beta-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, nitrates, and digoxin). Cases were identified through hospital discharge records indicating a diagnosis of any cancer. For every case, four to six controls were matched on sex, year of birth (within two and a half years), geographic region, index date, and duration of follow-up (within 20%, defined by the time of entry into the prescription database and the index date). Information on statin exposure was obtained through drug dispensing records, which are estimated to be complete. After matching 3,129 cases to 16,976 controls with a mean duration of observation of 7.2 years, they found that compared to no use, statin use over 6 months was associated with a significantly reduced risk of any incident cancer (adjusted odds ratio 0.80, 95% confidence interval 0.66 to 0.96). They also found that increasing total of duration of use, modelled as an ordinal variable, conferred decreasing risk with increasing exposure(48).

Another population-based case-control study evaluating the association between statin use and cancer risk was performed in northern Israel(49). This study identified cases as those with an incident diagnosis of colorectal cancer, while controls were selected from the same source population using a database from a large health care provider. Matching criteria were year
of birth, sex, primary clinic location, and ethnicity. Exposure history to statins was obtained by interview; prescriptions records within one year of diagnosis and one year of study enrollment for cases and controls, respectively, were validated against the participant’s reports. This study included 1651 matched pairs and found that statin use >5 years reduced the risk of incident colorectal cancer by 43% (adjusted odds ratio 0.57, 95% confidence interval 0.44 to 0.73). This association remained after adjustment for use of acetylsalicylic acid and non-steroidal anti-inflammatory drugs, other putative anti-neoplastic medications in colorectal cancer(49).

Using computerised medical records from the General Practice Research Database, Kaye et. al matched 3,244 cancer cases to 14,844 controls on year of birth, sex, general practice affiliation, year of entry into the database and index date(56), presumed to be the date of cancer diagnosis among the cases. Subjects were considered current statin users if they received a prescription for a statin within the year before their index date and their first prescription was more than a year before the index date. They found that current statin use was not significantly associated with overall incidence of cancer (odds ratio 1.0, 95% confidence interval 0.9 – 1.2)(56).

A systematic review and meta-analysis of secondary data from 26 randomized controlled trials and 12 observational studies, including the three studies described above, found that statin use was, on average, not associated with incident cancer risk in pooled estimates from randomized trials (pooled risk ratio 1.00, 95% confidence interval 0.95 to 1.05) while there was a modest association among observational studies (pooled risk ratio 0.92, 95% confidence interval 0.85 to 0.99)(57).

A randomized controlled trial evaluating whether statins can modulate cancer risk in otherwise healthy individuals would be very resource intensive, owing partly to the large number
of patients and extended follow-up that would be required. As such, a prospective short-term study in 50 women at high risk of developing a new breast cancer, deemed by a history of contralateral breast cancer, evaluated whether exposure to simvastatin for 24 – 28 weeks could demonstrate chemopreventative activity as measured by surrogate biomarkers correlated with the risk of developing a new breast cancer(58). This study found that estrone sulfate was significantly decreased at the end of the study, while none of the other biomarkers had significantly changed compared to baseline. This study concluded that better biomarkers for chemopreventative activity are needed and larger studies may be needed for adequate statistical power(58).

A recent randomized, investigator and patient blinded, placebo-controlled phase II clinical trial evaluated whether lovastatin could modulate various biomarkers for melanoma progression in patients with atypical nevi, a precancerous lesion(59). Subjects were randomized 1:1 to placebo or lovastatin for total treatment duration of 6 months. After randomizing 66 subjects, 49 of whom completed the study, there was no significant difference in the primary endpoint between groups, which was histopathologic regression of atypical nevi. This study, which did not meet planned accrual, concluded that if statins were to lower the incidence of melanoma, it would work through other mechanisms than reversing the atypia of atypical nevi. Conversely, this trial also noted that 6 months of treatment may not be adequate for an effect to be noticed.

In summary, meta-analyses of observational studies suggest that the use of statins may be associated with a modest decrease in incident cancer; however, this associated did not bear out in meta-analyses of randomized controlled trials, though these trials were not designed to evaluate cancer risk as a main endpoint. Few prospective studies have been performed to evaluate
whether statins can modulate various biomarkers associated with cancer progression and these studies have not demonstrated efficacy possibly due to sample size, limited duration of exposure, or inadequate biomarkers.
STATINS AND KIDNEY CANCER RISK

A recently published systematic review and meta-analysis evaluated the association of statin use on kidney cancer risk (60). This analysis included 12 studies, of which two were secondary analyses of randomized controlled trials, five were cohort studies, and five were case-control studies. In this section, I briefly review these individual studies, and describe an additional study that has been published thereafter.

The two secondary analyses of randomized controlled trials were from the Air Force/Texas Coronary Atherosclerosis Prevention Study and the Heart Protection Study. The Air Force/Texas Coronary Atherosclerosis Prevention Study was a randomized controlled trial evaluating whether lovastatin could reduce the risk of fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death compared to placebo (61). A total of 6,605 men and women were randomized and followed for an average of 5.2 years. This study described the results in women only and found that among the 997 women randomized, 1 patient developed kidney cancer in the placebo group while there were no kidney cancer cases in the treatment group. Compliance with treatment was not described in this study. Though this trial later published combined cancer rates in men and women, and found no significant difference in the overall incidence of cancer between groups, this combined report did not provide details on kidney cancer incidence (62).

In the Heart Protection Study, 20,536 individuals aged 40 to 80 years with a vascular disease or diabetes were randomized to simvastatin or placebo and followed for approximately 5 years to determine incidence of all-cause mortality and deaths from all coronary and non-coronary causes (63). A secondary endpoint included incidence of cancer between groups. Compliance with the allocated treatment, defined as at least 80% of scheduled tablets taken since
last follow-up, was 85% in the statin group, but only 17% in the placebo group as many patients in this group were eventually on a non-study statin. A total of 814 cancers developed in the statin group and 803 in the placebo group, which was non-statistically significantly different in an intention-to-treat analysis \((p=0.9)\). Of these cancers, 45 were kidney cancer, 23 in the statin group and 22 in the placebo group; this also was not statistically significantly different (rate ratio 1.04, 95% confidence interval 0.58 to 1.86). The results of this trial should be interpreted with caution, however, given the high level of contamination in the placebo group and the small number of incident kidney cancers.

Of the five case-control studies, one was the study by Graaf et. al described above, which used prescription claims in Netherlands to determine exposure\(48\). In the 101 cases of kidney cancer from this study, statin use over 6 months was associated with a significantly reduced risk of incident kidney cancer (adjusted odds ratio 0.27, 95% confidence interval 0.08 to 0.95). Another case-control study by Kaye et al., also described above, included 3 cases of kidney cancer and also found no significant association between statin use and kidney cancer risk (relative risk 1.0, 95% confidence interval 0.3 to 4.2)\(56\).

Coogan et al. performed a case-control study of patients admitted to hospitals in three different U.S. cities\(64\). Cases were identified through interview and were those whose cancer was first diagnosed the year before the hospital admission at which the patient was interviewed. Controls were those with no history of cancer admitted to a hospital for diagnoses judged to be unrelated to statin use. Medication use was also identified through interview. Regular statin use was defined as use at least 4 times per week for at least 3 continuous months, beginning at least 12 months before hospitalization. This study included 221 cases of kidney cancer and found that
regular use of statins was not associated with kidney cancer risk (adjusted odds ratio 1.1, 95% confidence interval 0.6 to 1.9)(64).

Using a database maintained by the South Central Veterans Affairs Health Care Network, Khurana et al. performed a case-control study of 483,733 patients in the database(65). Cases and controls were identified through review of medical records. It is unclear how stain use was defined in this study, though the authors mention that patients taking a statin after cancer diagnosis were excluded from the statin use group. This study included 1,446 cases of kidney cancer and found that statin use was associated with a 48% reduced risk of kidney cancer (adjusted odds ratio 0.52, 95% confidence interval 0.45 to 0.60)(65).

Only one case-control study included in the meta-analysis evaluated different durations of cumulative exposure(66). This population-based case control study from Taiwan used data from a random sample of 1,000,000 people from covered by the universal National Health Insurance program. Cases were identified through database review as those with an incident diagnosis of kidney cancer. Controls were those admitted to the hospital with a diagnosis that was unrelated to statin use. Use of statins was also obtained through database review and cumulative use was obtained based on dates of prescriptions and number of days supplied. This study included 177 cases matched to 708 controls on age, sex, and index date, and found that any use of statin was not significantly associated with kidney cancer risk (adjusted odds ratio 1.08, 95% confidence interval 0.70 to 1.67). When comparing cumulative use based on median exposure among the controls, those below (adjusted odds ratio 0.91, 95% confidence interval 0.50 – 1.53) or above (adjusted odds ratio 1.28, 95% confidence interval 0.73 to 2.23) the median had no significant change in kidney cancer risk compared to those with no statin use(66).
One of the five cohort studies included in the meta-analysis was a study from Japan that included 263 patients with coronary heart disease(67). This study compared pravastatin to no treatment on the progression and regression of coronary atherosclerosis. As a secondary endpoint, they evaluated cancer incidence and after following patients for approximately 5 years, there was 1 case of kidney cancer in the non-treated group and 0 in the treated group, yielding an observed/expected ratio of 15.97 (95% confidence interval 0.21 to 88.85) in the non-treated group compared to the reference population. However, the treated group consisted of two heterogeneous subgroups, one that took the statins for \( \geq 75\% \) of the study period and another that took the statins for \( > 25\% \) of the time. Moreover, the study states that patients with malignant disease were not eligible for the study, yet their analysis of incident cancer included 8 cases of cancer that were diagnosed prior to study entry. As such, the results from this study are difficult to interpret.

Another cohort study by Friedman et al. used data from the Kaiser Permanente Medical Care Program which contains comprehensive data on cancer diagnoses and pharmacy records(68). This study used a time varying analysis whereby patients contributed to the unexposed group until their first prescription. However, after the first prescription, patients contributed survival time to the exposed group regardless of whether or not they had any further prescriptions. They were also able to tabulate cumulative use based on dates and duration of prescriptions. Cumulative use was divided into four categories: no use, less than 3 years, 3-5 years, or over 5 years. Median follow-up was 4.91 years. This study provided a combined analysis for kidney, renal pelvis, and ureteral cancers and only described the number of cancer cases among statin users, which was 135 amongst those with any use. This study found that compared to no use of statin, any use was associated with a 23\% increased risk (adjusted hazard
ratio 1.23, 95% confidence interval 1.02 to 1.48), while use of more than 5 years (adjusted hazard ratio 1.19, 95% confidence interval 0.79 to 1.79) was not significantly associated with kidney, renal pelvis, or ureteral cancer risk. This study did not provide data on the other durations of cumulative use.

Using data from a general practitioner research database in England and Wales, Hippisley-Cox et al. performed a population-based prospective cohort study evaluating the intended and unintended effects of statins in over two million subjects(69). A statin user was considered as an individual with a new prescription of statin during the study period, while all remaining patients were classified as non-users. A total of 2,996 cases of kidney cancer were diagnosed in this cohort, though information on duration of follow-up is not provided. This study found that statin use was not significantly associated with risk of incident kidney cancer, though they did not provide a specific risk estimate; rather they provided risk estimates by individual statin subtypes(69). This study is prone to immortal-time bias as ‘users’ would have had to have sufficient follow-up to receive a prescription(70). Furthermore, as some statins are available over-the-counter in this population(71), there is the possibility of misclassification bias with some users being falsely labeled as non-users.

Jacobs et al. used data from the Cancer Prevention Study-II Nutrition Cohort to evaluate the association of statin use on the risk of 10 cancers(72). Participants were mailed a self-administered questionnaire at periodic intervals that obtained information on medication use and medical history, including information on the use of cholesterol-lowering drugs. This study is subject to misclassification bias as use of any cholesterol-lowering drug, including fibrates and bile-acid binding resins, were considered users of statins, though the authors argued that the majority of subjects using this class of medication would be using statins. Based on the responses
from subsequent questionnaires, the analysis used a time varying method to classify patients as never, former, or current users. In this fashion, the authors also attempted to account for cumulative use. The analysis included 133,255 subjects, of whom 396 developed kidney cancer, and found that compared to never users, neither former use (adjusted hazard ratio 0.81, 95% confidence interval 0.47 to 1.38), current use less than 5 years (adjusted hazard ratio 1.07, 95% confidence interval 0.80 to 1.42) or current use over 5 years (adjusted hazard ratio 0.94, 95% confidence interval 0.68 to 1.31) were significantly associated with risk of incidence kidney cancer.

In a similar study design, Liu et al. used data obtained from self-administered questionnaires from the Nurses’ Health Study and the Health Professionals Follow-Up Study(73). This study involved 118,651 participants of whom 277 developed kidney cancer, though duration of follow-up is not clearly described. As with the Jacobs et al. study, the baseline and early questionnaires did not distinguish between type of cholesterol-lowering drug and the authors attributed any use of a cholesterol-lowering drug during a certain period of follow-up to statins. Participants who reported regular use of statins (≥ 2 times per week) at each biennial questionnaire were considered current users for the subsequent 2-year follow-up period. Current non-users were those that did not report use during that questionnaire cycle. Though not explicitly stated, it is plausible that this study used a time varying analysis comparing current users vs. non-users. This study reported that current use of statins was not associated with kidney cancer risk in men (adjusted hazard ratio 1.17 (95% confidence interval 0.75 to 1.81) or women (adjusted hazard ratio 0.68, 95% confidence interval 0.46 to 1.00). This study also compared ever vs. never use and durations of use ≥4 years vs. <4 years, neither of which found a significant association.
When pooling the data from the above 12 studies, Zhang et al. found that statin use was, on average, not significantly associated with kidney cancer risk (pooled relative risk 0.92, 95% confidence interval 0.71 to 1.19)(60). It is notable that this meta-analysis made recognition of the poor quality of studies on the association of statin use with kidney cancer risk to date and emphasized the need for further high-quality studies.

Since the publication of that meta-analysis, a population-based case-control study involving 4,606 cases of kidney cancer, the largest study to date, has been recently published(74). This study from Denmark utilized multiple nationwide registries, including a prescription database with information on dates of prescriptions and number of tablets dispensed. In the primary analysis, the authors assumed a daily intake of one tablet while adding 25% additional days to the duration to allow for minor noncompliance and irregular refill patterns. As such, estimated duration of exposure is higher than actual duration of exposure as patients may be taking more than one tablet per day, and compliant patients would have artificially inflated estimated durations. In the primary analysis, cumulative duration of use was dichotomized to ≥5 vs. <5 years and secondary analyses included ever vs. never analyses and multiple categories for cumulative duration of use (<1 year, 1 – 4.99 years, 5 – 9.99 years, and ≥10 years). Compared to no statin use, use ≥5 years was not significantly associated with kidney cancer risk (adjusted odds ratio 1.06, 95% confidence interval 0.91 to 1.23). Similar results were found in the secondary analyses.

In summary, several studies have evaluated the association between statin use and kidney cancer risk. However, these studies had a limited number of kidney cancer cases and are prone to several biases, making it difficult to interpret the association of statin use with kidney cancer risk. As noted by the meta-analysis on this topic(60), further research is needed in this area.
EPIDEMIOLOGIC STUDIES OF STATINS AND CANCER SURVIVAL

Similar to cancer risk, there are several studies in the literature evaluating the association of statin use on survival outcomes in various malignancies. In this section, I review some of these studies with a focus on population-based studies. Furthermore, I review some of the completed randomized controlled trials evaluating statins to improve survival in cancer.

Nielsen et al. performed a population-based retrospective cohort study of 245,925 individuals utilizing data from various registries in Denmark (50). Their primary analysis compared regular statin users, defined as those that had statin prescriptions filled within 6 months before the date of cancer diagnosis and within 2 years before the date of cancer diagnosis, to patients that had never received a statin prescription. Irregular stain users were excluded from the study. With a median follow-up of 2.6 years, this study found that regular statin use was associated with a 15% reduced risk of death from any cause (adjusted hazard ratio 0.85, 95% confidence interval 0.83 to 0.87) and 15% reduced risk of cancer-specific mortality (adjusted hazard ratio 0.85, 95% confidence interval 0.82 to 0.87). This study also performed a dose-response analysis based on estimated daily dose and found that the benefits were relatively similar across various cut points. Analysis by cancer subtype also found a trend towards benefit in cancer-specific mortality for regular statin users among 5942 cases of kidney cancer, though statistical significance was not reached (adjusted hazard ratio 0.85, 95% confidence interval 0.71 to 1.01) (50).

Using data from the United Kingdom Clinical Practice Research Database, which covers approximately 7% of the United Kingdom population, Cardwell et. al. performed a population-based retrospective cohort study evaluating the association of post-diagnostic statin use on survival outcomes in patients with colorectal cancer (71). Statin use was determined from general
practitioners’ prescribing records and use was categorized based on the number of prescriptions during follow-up: non-user, short-term user (1-11 prescriptions), and long-term user (≥12 prescriptions). To avoid immortal-time bias, whereby an individual would have to survive a minimum period of time to accumulate more prescriptions(70, 75), this study performed a time varying analysis based on the dates of the prescriptions. In this study of 7,657 patients with colorectal cancer, short-term (adjusted hazard ratio 0.71, 95% confidence interval 0.61 to 0.84) and long-term users (adjusted hazard ratio 0.73, 95% confidence interval 0.60 to 0.88) had similar improvements in cause-specific survival. Similar results were noted for overall survival. Ever vs. never analyses demonstrated similar results, including after adjustment for pre-diagnostic statin use(71). An important limitation of relying on the number of prescriptions is that different physicians may use varying durations of prescriptions and a patient with three 30 day prescriptions would be noted as having higher use than a patient with one 90 day prescription.

Using the same databases from the United Kingdom, Yu et al. performed a similar analysis in prostate cancer(76). This study of 11,772 patients also found that any use of a statin conferred a cancer-specific (adjusted hazard ratio 0.76, 95% confidence interval 0.66 to 0.88) and overall survival (adjusted hazard ratio 0.86, 95% confidence interval 0.78 to 0.95) advantage compared to no use. In contrast to the previous study in colorectal cancer, however, there was a trend towards improved survival for both outcomes with increasing cumulative duration of use, based on four defined categories (less than 12 months, 12 to 24 months, 24 to 36 months, and ≥36 months). Notably, simvastatin has been available in the United Kingdom over-the-counter since 2004(71) and this exposure cannot be accounted for in these studies.
Promising results from laboratory and observational studies have led to randomized controlled trials evaluating statins as a stand-alone or in combination therapy in the neoadjuvant and adjuvant setting for various malignancies. A few of these completed trials are described below.

A randomized, open-label, phase II study in 106 statin-naïve patients who failed at least 1 platinum-based chemotherapy for locally advanced or metastatic non-small cell lung cancer compared gefitinib vs. gefitinib and simvastatin(77). Treatment continued until disease progression, unacceptable toxicity, consent withdrawal, loss to follow-up, death, major protocol violation, or noncompliance. The primary endpoint was tumour response rate and secondary endpoints included progression-free survival, overall survival, and safety. In an intention-to-treat analysis, this study found no significant difference between treatment arms for any of the outcomes evaluated. However, this trial did not report the number of treatment cycles in either group or compliance, and it is therefore unknown whether study subjects received adequate exposure to statins.

In patients with metastatic colorectal cancer that had failed prior oxaliplatin-containing chemotherapy, a recent randomized, double-blind, placebo-controlled, phase III trial compared Xeliri (irinotecan and capecitabine) or Folfiri (leucovorin, 5-fluorouracil and irinotecan) in combination with simvastatin or placebo(78). Treatment cycles were repeated until evidence of disease progression, unacceptable toxicity, or patient refusal. A total of 269 patients were randomized and the median number of cycles administered was 6 in the simvastatin group and 7 in the placebo group. This study found no significant difference in progression-free survival, which was the primary end point, or response rate, duration of tumour response, overall survival,
time to progression, or safety profile, which were the secondary endpoints. This trial also did not describe compliance with treatment.

Finally, a randomized, open-label, trial in patients with unresectable advanced hepatocellular carcinoma treated with transcatheter arterial embolization compared adjuvant 5-fluorouracil vs. 5-fluorouracil and pravastatin(79). Compliance was assessed by detecting pravastatin in urine. With a median follow-up of 11 months, all 83 patients randomized died due to cancer progression and/or hepatic failure. This study found that those randomized to 5-fluorouracil and pravastatin had significantly improved median survival (18 months vs. 9 months, p=0.006). Maximal tumour diameter was also significantly reduced in the statin group at 6 and 12 months. Median duration of pravastatin administration was 16.5 months and this study described that pravastatin was detected in all urine samples, though it is unclear to what degree this corresponds with prescribed compliance.

In summary, the population-based observational studies described above have supported a protective association of statins with cancer survival. However, this has not borne out in some of the randomized trials to date. This discordance may be due to bias in the observational studies or limitations such as lack of power or compliance in the randomized trials.
STATINS AND KIDNEY CANCER SURVIVAL

A meta-analysis published in 2015 evaluated the association of statin use with prognosis in prostate, bladder, and kidney cancer (80). When pooling the risk estimates from four studies involving 5,746 patients with kidney cancer, this meta-analysis found that, on average, statin use was not significantly associated with progression-free survival (pooled hazard ratio 0.91, 95% confidence interval 0.54 to 1.55) or cancer-specific survival (pooled hazard ratio 0.72, 95% confidence interval 0.35 to 1.50); however, there was an improvement in overall survival (pooled hazard ratio 0.81, 95% confidence interval 0.69 to 0.96) (80). In this section, I briefly review the four cohort studies in this meta-analysis with regards to kidney cancer. At the time of writing, there were no active trials evaluating statins as part of treatment for kidney cancer.

Choi et al. evaluated the association between exposure to statins before cancer diagnosis and relapse-free survival and progression-free survival in 115 patients undergoing nephrectomy for kidney cancer (81). The look-back period for exposure to statins before cancer diagnosis, however, is not specified. Although this study provides separate Kaplan-Meier curves for each outcome, a hazard ratio for what seems to be a composite outcome of relapse and progression is presented. Neither analysis demonstrated any significant difference for statin users compared to non-users.

Another study by Viers et al. defined the look-back period as within 3 months before surgery (82). This study of 2,357 patients undergoing nephrectomy for kidney cancer evaluated progression-free, cancer-specific, and overall survival. This study found higher risks of progression (adjusted hazard ratio 1.22, 95% confidence interval 0.95 to 1.57) and cancer-specific mortality (adjusted hazard ratio 1.02, 95% confidence interval 0.74 to 1.39) and lower
risk of all-cause mortality (adjusted hazard ratio 0.84, 95% confidence interval 0.69 to 1.00) in the statin group, though none reached statistical significance.

While neither of the two previous studies found a benefit favouring statin use, another study found a significant improvement in cancer-specific and overall survival when comparing statin use vs. non-use at the time of nephrectomy for kidney cancer(83). The analyses by Kaffenberger et al. included 666 patients and found that statin use at the time of nephrectomy was associated with a 52% reduction in cancer-specific mortality (adjusted hazard ratio 0.48, 95% confidence interval 0.28 to 0.83) and a 38% reduction in all-cause mortality (adjusted hazard ratio 0.62, 95% confidence interval 0.43 to 0.90).

Although Kaffenberger et al. did not evaluate progression-free survival, another study of 2,608 patients undergoing nephrectomy found that statin use at the time of surgery was associated with a 33% improvement in progression-free survival (adjusted hazard ratio 0.67, 95% confidence interval 0.47 to 0.96) but no significant improvement in overall survival (adjusted hazard ratio 0.89, 95% confidence interval 0.71 to 1.13)(84). While this analysis also compared use vs. non-use at the time of surgery, they performed time varying analyses in which current use of statin was associated with a 29% reduction in all-cause mortality (adjusted hazard ratio 0.71, 95% confidence interval 0.58 to 0.88), but progression-free survival (adjusted hazard ratio 0.77, 95% confidence interval 0.56 to 1.07) was no longer significant. In their time varying analyses, patients who started a statin after surgery contributed person-time to the non-user group until starting the statin, after which they contributed to the user group.

The previously published meta-analysis evaluating the association of statin use with kidney cancer survival did not include the study by Nielsen et al.(50), described above, even
though an estimate for kidney cancer-specific survival among statin users was provided. Furthermore, a secondary analysis of the Global Advanced Renal Cell Carcinoma Trial also provided a risk estimate for the association of statin use with overall survival, and was not included in the meta-analysis despite its publication date falling within the literature search window(85).

Since the publication of the previous meta-analysis, 6 additional studies have evaluated the association of statin use on survival outcomes in kidney cancer. I elaborate on these studies in Chapter 4. Given the relatively limited number of pooled subjects included in the prior meta-analysis, an updated meta-analysis may be able to provide further insight on the association between statin use and kidney cancer survival outcomes.
GAPS IN CURRENT LITERATURE

Several studies have evaluated the association of statin use on kidney cancer risk and survival outcomes. However, these studies have had several limitations and further research is needed to evaluate whether statins may have a therapeutic role in kidney cancer. In this section, I elaborate on these limitations.

Study population

Studies in the literature on this topic have been generally limited by sample size. Indeed, the majority of studies evaluating statin use on kidney cancer risk or survival have included fewer than 1,000 kidney cancer patients. Furthermore, very few population-based studies exist in the literature, limiting their generalizability. As such, there is a need for large, population-based studies on this topic.

Accuracy of exposure measurement

Many of the studies evaluating statin use and kidney cancer risk relied on interview or questionnaire data, which are prone to recall bias. Additionally, some of the studies considered use of a non-statin cholesterol lowering medications as statin use. Although these studies argued that cholesterol lowering medications used by the respective populations were primarily statins, this is prone to misclassification bias. As this assumption is a differential misclassification bias, since it can only apply to those that used cholesterol lowering medications, the direction of bias is generally unpredictable(86, 87); however, assuming that non-statin cholesterol medications are not associated with kidney cancer risk and that statins are protective, the direction of bias would be towards the null. In studies evaluating statin use and kidney cancer survival, the majority of studies relied medical chart review to obtain history of statin use. Overall, very few studies have used a comprehensive, validated database to obtain information on statin exposure.
Definition of a user

An important limitation to many studies in chemoprevention is the definition of a ‘user’ and this has been quite heterogeneous across studies. Additionally, very few studies on this topic have accounted for intermittent or cumulative use, as their data are difficult to obtain outside of databases where the population is eligible for prescription coverage. This is particularly problematic if only use at a specific time is considered; for example, in studies evaluating statins and kidney cancer survival, all but one study (84) considered use around the time of diagnosis or surgery, but did not consider change in use after diagnosis or surgery. This is prone to misclassification bias as a subject considered a ‘user’ may subsequently become a non-user and vice-versa. This can be mitigated by using a time varying analysis where a patient contributes survival time to the exposed or unexposed category, depending on their exposure status during follow-up.

Dose-response relationship

Cumulative use analyses can help determine whether a dose-response relationship exists between increasing medication exposure and risk of outcomes, supporting causality for chemoprevention (88). While cumulative use has not yet been evaluated in kidney cancer survival studies, in kidney cancer risk studies the cut-points for cumulative use are often chosen arbitrarily. Although cumulative use can be modelled as a linear term, there is no biological rationale to assume that the relationship between medication use and cancer risk or survival follows a linear one. As such, studies in pharmacoepidemiology should account for cumulative use and allow for a non-linear relationship between exposure and the risk of outcome.

Use of concomitant medications
The majority of studies to date evaluating statins in kidney cancer have not controlled for exposure to other putative anti-neoplastic medications. In addition to statins, several other commonly prescribed medications, including angiotensin-converting enzyme inhibitors(89, 90), angiotensin II receptor blockers(89, 90), acetylsalicylic acid(91-93), non-steroidal anti-inflammatory drugs(93-96), beta blockers(97, 98), calcium channel blockers(99), selective serotonin reuptake inhibitors(100-102), statins(50), and proton pump inhibitors (PPIs)(103, 104) have been associated with cancer risk and survival outcomes for various malignancies. Because statin users are often on other concomitant medications, understanding the independent association of statins with cancer risk and survival outcomes requires controlling for exposure to other putative anti-neoplastic medications, which has not been adequately done to date.

**Summary**

Statins represent an ideal medication for chemoprevention as they are inexpensive and generally well tolerated. However, the evidence to date has several limitations and it is unclear whether they are associated with reduced risk and improved survival in kidney cancer. Given the number of studies that have been published since the previous meta-analysis evaluating statins and kidney cancer outcomes, an update is also necessary to review the current evidence. Finally, although randomized controlled trials provide the highest quality of evidence, a trial in chemoprevention would be costly and resource intensive given the number of patients and duration of follow-up that would be required. A hypothetical randomized trial evaluating statins to reduce the risk of cancer-specific mortality in patients undergoing nephrectomy for intermediate risk, defined by UISS(37), localized kidney cancer, with a type I error rate of 0.05, power of 0.9, 5-year accrual and follow-up periods, would require 970 patients in each arm to detect a hazard ratio of 0.80. Furthermore, trials tend to be restricted to healthier individuals and
the findings may not be generalizable to other populations. As such, population-based research that utilizes analytical methods that account for intermittent and cumulative use and controls for some of the biases in previous cohort studies can provide insight on the therapeutic role of statins in kidney cancer.
CHAPTER 2: METHODS AND DATA SOURCES

THESIS OVERVIEW

This thesis further explores the association of statin exposure with kidney cancer risk and survival outcomes. A recent meta-analysis has recently summarized this topic for kidney cancer risk (105), with only one new study since its publication (74). However, several studies evaluating statins in kidney cancer survival have been published since the meta-analysis by Luo et al. (80) and an update is warranted. Furthermore, I used population-based administrative data to account for several of the limitations that studies on this topic have been prone to. I further explored how methods of classifying exposure can influence the estimates of benefit of statin use on outcomes in chemoprevention. Therefore, the thesis comprises the following three studies:

1. A population-based case-control study evaluating the association between exposure to several commonly-prescribed putative anti-neoplastic medications, including statins, and the risk of incident kidney cancer.

2. A systematic review and meta-analysis evaluating the association between statin use and survival outcomes in kidney cancer.

3. A population-based cohort study evaluating the association between exposure to several commonly-prescribed putative anti-neoplastic medications, including statins, and survival in patients with kidney cancer.

The methods used for the systematic review and meta-analysis were in accordance with the Cochrane Handbook for Systematic Reviews (106). Further details for this study are provided.
in Chapter 4. In the subsequent subsections, I focus on the details pertaining to the population-based studies.
DATA SOURCES

To perform the population based studies, I linked various health administrative databases. In this section, I describe these databases and provide a description of validation studies where available.

Canadian Institute for Health Information (CIHI) - Discharge Abstracts Database (DAD)

The CIHI-DAD contains information on demographic and administrative data for hospital admissions and day surgeries throughout Canada. This database has been previously validated and was shown to have a high degree of accuracy for demographic data and procedures, whereas the diagnosis coding accuracy was variable(107).

National Ambulatory Care Reporting System (NACRS)

The NACRS database contains information on patient visits to hospital and community-based ambulatory care facilities. Encounters that are captured include day surgery, emergency department visits, and outpatient clinic visits(108).

Ontario Health Insurance Plan (OHIP)

The OHIP database contains all claims made by physicians and other health care providers for insured services provided to the residents in Ontario. Each record is unique for a specific service provided to a specific person on a specific day. The record contains information on the date and type of service provided, diagnosis, provider and patient identification, the associated fee code, and the total fee paid to the provider(108).

Ontario Cancer Registry (OCR)

The OCR is a population based tumour registry maintained by Cancer Care Ontario. The OCR was started in 1964 and contains data on all cancers diagnosed in Ontario with the exception of non-melanoma skin cancers. The registry passively obtains data from pathology
reports on all cases where there is a diagnosis of cancer, patient records from designated cancer-
specialty treatment centers, hospital discharge records from CIHI on all Ontario hospital
admissions and day surgery cases with a diagnosis of cancer, and reports of deaths from the
Registrar General in Ontario(109). The OCR is estimated to capture over 95% of all cancer
cases(110), and has been validated for its data in breast(111) and head and neck cancers(109).
Cause of death has been shown to have 95% sensitivity, 86% specificity, 86% positive predictive
value, and 95% negative predictive value(111).

**Ontario Drug Benefit (ODB)**

The ODB database includes prescriptions dispensed to all Ontarians aged 65 years or
older and individuals living in long-term care facilities, on disability and social assistance(112).
Levy et al. evaluated the reliability of the coding of the Drug Identification Number, and the
date, quantity and duration of the dispensation of 5,155 claims sent to the ODB and found that
the overall error rate was 0.7%(113).

**Registered Persons Database (RPDB)**

The RPDB is a registry maintained by the Ministry of Health and Long-Term Care in
Ontario. This database has demographic information on all residents of Ontario including date of
birth, gender, address, and date of death (if applicable)(108). This database is also used to derive
a patient’s socioeconomic and rurality statuses based on address recorded. Socioeconomic status
is estimated by linking an individual’s postal code data with Canadian census data on median
household income levels by neighbourhood of residence(114).
STUDY DESIGN

To evaluate the association between exposure to medications and kidney cancer risk, I chose nested a case-control study design. To evaluate the association between exposure to medications and survival outcomes in kidney cancer, I chose a cohort study design. These study designs are particularly suitable for their respective questions and in this section I review some of these reasons.

Nested case-control study (medication use and cancer risk)

In a case-control study, individuals are selected based on whether or not they developed the outcome of interest. Exposure history is then determined retrospectively from cases, those who develop the outcome, and compared to exposure history of controls, those who do not develop the outcome. A nested case-control study is a variant of the classic case-control design in which the cases and controls are selected from a well-defined cohort. In my study, this cohort is Ontario population aged greater than 66(115).

This study design is ideal when the proportion of the study population with the disease of interest is lower than the proportion exposed(116). This is true in our study as the proportion of patients on statins in the general population far exceeds the proportion with kidney cancer(50). Case-control studies are also preferred when the objective is to study several possible risk factors for a single disease(116). Indeed, in my study I evaluated multiple putative anti-neoplastic medications. Finally, the nested case-control study is more efficient than the classic case-control study as the comparison group is not the entire population but a random selection of controls.

There are also some disadvantages to case-control studies. Identifying all cases is an issue with many case-control studies, and incomplete case ascertainment can lead to bias if the
exposure of interest is related to the probability of being identified as a case(116). This was not an issue in my case-control study as the OCR captures over 95% of cancer cases in Ontario(110) and being captured by the registry is independent of medication exposure. Exposure history can also lead to bias if the outcome is known and exposure history is obtained retrospectively. This can lead to recall bias whereby being diagnosed with a disease may lead cases to remember or report their exposures differently from controls(117). However, this bias was offset in my study as I used a nested case-control design and medication exposure data was recorded systematically for administrative purposes, before the outcome occurred.

**Cohort study (medication use and kidney cancer survival)**

In a cohort study, individuals with a common characteristic are followed over time for the development of an outcome. In contrast to the classic case-control study design, a cohort is assembled independent of outcome status. Cohort studies are subcategorized into retrospective or prospective cohort studies, depending on the timing of data collection in relation to the development of the outcome.

An advantage of cohort studies compared to case-control studies is that they allow for the evaluation of multiple outcomes. Indeed, my study evaluating the association of medication exposure with survival outcomes included both cancer-specific and overall survival. Another advantage is that cohort studies follow the temporal sequence of events and can be easier to understand for clinicians and patients.

Attrition bias is a possible disadvantage in cohort studies whereby subjects may be lost to follow-up and hence their outcome cannot be ascertained. This is particularly problematic if there is differential loss to follow-up related to exposure status. This bias is mitigated if the
analysis controls for person-time at risk, as is done with survival analyses. Prospective cohort studies can also be expensive and time-consuming as such studies often require a large number of patients to be followed for a sufficiently long-period of time to have an adequately powered statistical analysis. This was not an issue for my study since the Institute of Clinical and Evaluative Sciences already had the required data on the Ontario population spanning several years. While prospective cohort studies can be more costly and time-consuming than retrospective ones, the latter may suffer from their dependence on previously collected records which may be limited by missing or poorly collected information(87). In my study, certain variables of interest were not collected by the administrative databases; however, the advantages of the retrospective cohort design outweigh those of the prospective design for my particular study.
STUDY PARTICIPANTS

Population-based case control study

In a case-control study, cases and controls should ideally be identified from the same base population. That is, the study base population comprises all individuals who are risk of the outcome and those that would develop the outcome would be identified as cases, whereas those without the outcome could serve as potential controls (116). For the purpose of my study, the study base was the Ontario population aged 66 or greater.

As mentioned above, complete case ascertainment strengthens the validity of a case-control study (116) and the OCR is estimated to be over 95% complete (110), facilitating this aspect. Therefore, the OCR was used to identify individuals with an incidence diagnosis of kidney cancer. Cases were restricted to those aged \( \geq 66 \) at the time of diagnosis, herein referred to as the index date, to allow for at least one year’s history of medication exposure to be captured through the ODB.

Appropriate selection of controls is more complex, and Wacholder et al. proposed three principles for control selection, namely the study-base principle, the comparable accuracy principle, and the deconfounding principle (116).

The first principle is the study-base principle where controls constitute a random sample of non-diseased subjects within the study base. Given the relative completeness of the OCR, controls can be assumed to be those without a diagnosis of kidney cancer in the OCR. The comparable accuracy principle, as implied by the name, stipulates that the accuracy of information from cases and controls should be equally reliable. The accuracy of the data collected through administrative databases is expected to be independent of outcome status and
therefore my study satisfies this principle. Finally, the deconfounding principle suggests that controls can be selected to reduce the possibility for confounding. I describe in detail the potential for confounding and its implications on selecting controls in a subsequent section. Briefly, to reduce confounding controls were matched to cases on age within one year, sex, comorbidity score, geographic location, determined by the first three characters of the postal code, and history of hypertension.

Population-based cohort study

A cohort should consist of individuals that have the potential to develop the outcomes of interest. That is, they should be at risk and have sufficient follow-up to develop the outcome. Furthermore, the cohort should sufficiently resemble the population to which the results will be generalized(117).

The cohort for my study comprised of patients with an incident diagnosis of kidney cancer in the OCR. Since all patients included in the study have kidney cancer, they were all at risk of having the outcomes of interest, namely kidney cancer-specific mortality and all-cause mortality. Although sufficient follow-up is a relative term and there is no established minimum in kidney cancer, all patients had at least one year follow-up for overall survival given that incident cases of cancer are updated in the OCR with at least one year’s lag behind vital status. I restricted my cohort to patients aged 65 or older at the time of diagnosis, as comprehensive prescription claims data are restricted to this age group.

Since the underlying clinical relevance of these study results are to improve survival by applying modifiable pharmacological interventions to patients presenting with incident kidney cancer, I excluded those patients with a previous diagnosis of malignancy (other than non-
melanoma skin cancer). This was done to exclude patients who may have worse outcomes due to their pre-existing malignancy, rather than being an effect of kidney cancer or of putative anti-neoplastic medications. I also excluded patients whose histology indicated a primary malignancy other than kidney cancer. These may be patients with metastatic disease to the kidney and are therefore not representative of the patient of interest with incident primary kidney cancer.
EXPOSURE CLASSIFICATION

I obtained prescription claims data for all study participants using the ODB. Based on the dates of prescriptions and the days supplied field, I was able to estimate cumulative duration of exposure as a continuous measure for each medication. This method accounts for intermittent use since by using the dates and durations of prescriptions, I was able to estimate periods without exposure in which the cumulative exposure up to and during that time remained constant. However, when the patient obtained a subsequent prescription, they continued to accumulate exposure.

As described above, many studies in chemoprevention for kidney cancer to date have not used cumulative exposure, and the few that have did not model it as a continuous measure. Several studies have compared any use vs. no use (also referred to as ever vs. never) and this is subject to misclassification bias, which is described in further detail below. Other studies have categorized cumulative exposure into two or more groups. This method of classifying exposure has some advantage and disadvantages. This method is relatively simple to perform from an analytical perspective and the results are easily interpreted(118). However, there are important disadvantages. First, from a biological perspective it does not make sense that individuals close to but at opposite sides of a chosen cut point have different rather than similar risks of the outcome. Second, these cut points are chosen arbitrarily or are driven by the data, which increases the probability of observing a false positive association. Finally, categorization can lead to over-parameterization resulting in loss of efficiency, yielding large standard error estimates(118, 119).

When cumulative use is modelled as a continuous term, it is often done assuming a linear relationship. However, this assumption of linearity may not be appropriate and is often not
evaluated. This can result in a misspecified final model in which a relevant predictor may not be included (because the true relationship with the outcome is non-linear) or inclusion of a predictor whose true functional form differs from a linear one(118, 119). An alternative approach is to use restricted cubic splines. While this allows for some non-linearity, the range of functional forms evaluated with these methods are limited(119).

For my studies, I used fractional polynomials for the primary analysis. Fractional polynomials were proposed by Royston and Altman in which a rich class of possible functional forms are evaluated(120). In this method, an exponent from a predefined set of integer and non-integer values are applied to one or two terms of the continuous variable. A total of 44 functional forms are evaluated, 1 of which is linear, 7 of which are first degree transformations, and 36 of which are second degree transformations(120). To choose the best transformation for a continuous predictor, the closed test procedure, also known as RA2, is applied(120). Briefly, this procedure determines whether increasing complexity of the model yields a better fit.

Although fractional polynomials were initially proposed for a single predictor, they have since been applied to allow for multiple continuous predictors to have transformations. This is known as the multivariable fractional polynomial algorithm(120). In the first step, all continuous predictors are entered into the model as linear terms. The predictors are then arranged according to their degree of association, determined by the p-value, and the predictor with the strongest degree of association (lowest p-value) is evaluated first. The deviance of the model from each of the 44 transformations of the first predictor is estimated, with all other predictors being treated as linear terms. After applying the RA2 procedure, the best functional form is selected, or the predictor may be excluded. The predictor with the second strongest degree of association is then evaluated, while maintaining the transformation selected for the first predictor, if the predictor
was not excluded. These steps are repeated until all continuous predictors have been evaluated, which denotes the completion of the first cycle. In the second cycle, continuous predictors that were excluded in the first cycle are re-evaluated while maintaining the transformations selected for included predictors in the first cycle, in the sequence of the degree of association as done in the first cycle(120).
POTENTIAL CONFOUNDERS

Confounding is an important concept in epidemiological research and can be described as a distortion of an association between an exposure and outcome by an extraneous factor. More formally, a variable is considered a potential confounder if it fulfils the following three criteria: 1) the variable must be associated with the outcome, 2) it must be associated with the exposure, that is, it must be unequally distributed between the exposed and unexposed groups, and 3) it must not be an effect of the exposure and not be a factor in the causal pathway for the outcome(121). The use of directed acyclic graphs (Figures 2.1 and 2.2) can help understand which variables fulfill these criteria(122). In this section, I review the potential for confounding and the methods by which I attempted to mitigate them.

Confounding by indication is an important consideration in pharmacoepidemiology. For example, patients on statins tend to have a greater comorbidity burden than patients not using statins(74, 123), and are therefore more likely to interact more with the health care system. Regular medication use may also be a marker of interactions with the health care system as patients may need to see their physicians for continued assessment of the indication for medication use. As many kidney cancers are detected incidentally, more interactions with the health care system increases the possibility of abdominal imaging and subsequent diagnosis of kidney cancer. Statin exposure itself, however, does not affect comorbidity burden and is therefore not in the intermediate pathway between statin exposure and cancer risk or survival. While statin use may be associated with a small increased risk of diabetes(124), this would not be expected to substantially increase the frequency of interactions with health care services beyond the baseline health care needs of statin users. Therefore, in this context, comorbidity burden represents a confounder as it fulfills the three criteria described above. In the study

51
evaluating cancer risk, adjusting for this confounder is likely to decrease the unadjusted association of statin therapy on cancer risk to a moderate degree. Similarly, statin users are more likely to have decreased life expectancy due a greater comorbidity burden; adjusting for this confounder in the study evaluating survival is likely to decrease the unadjusted association to a moderate degree. Comorbidity burden can be adjusted for through the use of a comorbidity score.

For our studies, comorbidity score was assessed using the John Hopkins Aggregated Diagnostic Groups. This method of determining comorbidity burden was designed to predict health care utilization and considers the duration, severity, and intensity of service use related to both inpatient and outpatient claims(125). This information was estimated from data using the OHIP, CIHI, and NACRS databases, described above, and has been shown to be superior at predicting mortality in Ontario administrative databases compared to the Charlson Comorbidity Index and Elixhauser comorbidities(125).

To further address confounding by indication, I performed sensitivity analyses directly controlling for the presence of diabetes, congestive heart failure, myocardial infarction, end stage renal disease, stroke, coronary artery angioplasty or coronary artery bypass graft surgery, and abdominal aortic aneurysm repair and aortic bypass.

Similarly, though not directly indicated for hypertension, statin users are more likely to have hypertension(74), an established risk factor for kidney cancer. Therefore, I controlled for history of hypertension in the study evaluating cancer risk. For my studies, I used the Ontario Hypertension Database which is a validated registry that uses data from physician claims and hospitalizations(126).
Although smoking and obesity are established risk factors for kidney cancer, this information is not available in administrative data. As these factors relate to cardiovascular disease, is it possible that they are more frequent among statin users. Being unable to account for these confounders may result in an overestimation of the association of statins on kidney cancer risk to a moderate degree.

Year of cohort entry is another potential confounder given the temporal changes in prescriptions for some of the medications as well as increasing incidence of kidney cancer and improvements to treatments(127, 128).

Finally, despite Ontario being a publicly funded health care system, those with lower socioeconomic status may not have similar access to health care providers and therefore fewer opportunities to be prescribed medication or undergo diagnostic imaging(129). Furthermore, socioeconomic status may also related to survival(130). Although individual socioeconomic status is not available in administrative data, geographic location was used as a surrogate, as has been done routinely in studies utilizing administrative data in Ontario(131, 132).

While there are other aspects that relate to whether or not patients will be exposed to statins, such as physician preference, or experience all-cause or kidney cancer-specific mortality, such as tumour characteristics, these do not represent confounders as they are not associated with both exposure and outcome. As such, controlling for these factors will not improve the estimation of the exposure-outcome relationship; rather, it would reduce statistical precision.
CAUSAL FRAMEWORK

In the counterfactual model of causation, patients with exposure cannot be observed and evaluated on outcomes as if they had not had the exposure, and patients without exposure cannot be evaluated on outcomes as if they had the exposure. This model occurs in both randomized trials and observational studies. However, in trials with proper randomization, causal effects are obtained due to the concept of exchangeability, which means that the observed risk of the outcome in the unexposed group would have been the same as the observed risk of the outcome in the exposed group, had the unexposed group received the exposure, and vice-versa (133). In other words, proper randomization ensures that, independent of the exposure, the groups being compared are at equal risk of the outcome. In contrast, causal effect measures cannot be directly obtained from observational studies as the underlying risk of the outcome often differs between groups that are compared; rather, measures of association are obtained from observational studies (133).

In this context, comparisons between unexposed and exposed groups in observational studies are only valid if the frequency of outcomes observed in the unexposed group would be similar to the frequency of outcomes in the exposed group, had they actually been unexposed (and vice-versa). As is shown in the directed acyclic graphs in Figures 2.1 and 2.2, the measured factors that are expected to alter the frequency of kidney cancer risk in the groups, independent of medication exposure, are comorbidity, history of hypertension, socioeconomic status, and year of diagnosis. Similarly, the measured factors expected to alter the frequency of mortality in the groups, independent of medication exposure, are comorbidity, socioeconomic status, year of diagnosis, and disease stage. Controlling for these directly, or through the use of surrogates,
therefore, should provide the best measure of association between exposure to putative anti-neoplastic medications and survival outcomes.
POTENTIAL BIASES

Bias is another important concept in epidemiological research and can be thought of as a systematic error that reduces the internal validity of a study(86). Bias can lead to over or underestimation of the association between an exposure and an outcome. In this section, I review the potential for selection and information bias in the proposed studies.

Selection Bias

Selection bias can occur in case-control studies if participants are selected based on knowledge of exposure history. However, my study identified cases and controls independent of exposure history.

Another form of selection bias, known as immortal-time bias, can occur in studies evaluating the association between medication exposure and survival outcomes. This occurs when a patient must be alive for a defined period of time in order to be exposed to a medication(70); consequently, patients with longer durations of exposure are those who survive longer(75). Furthermore, naively classifying medication exposure as a dichotomous comparison (use vs. non-use over a given period) does not take into account the intermittent nature of the exposure; a patient that started their prescription one month after cancer diagnosis would have accumulated one month of immortal-time. Indeed, a recent systematic review and meta-analysis evaluating the association of beta-blockers on cancer survival outcomes found that when including all relevant studies, beta-blockers were significantly associated with improved overall (pooled hazard ratio 0.88, 95% confidence interval 0.79 to 0.97) and cancer-specific survival (pooled hazard ratio 0.75, 95% confidence interval 0.64 to 0.88)(134). However, when excluding studies at unclear or high risk of immortal-time bias, the association between beta-blockers and
overall survival was extinguished (pooled hazard ratio 1.00, 95% confidence interval 0.93 to 1.07), and approached the null for cancer-specific survival (pooled hazard ratio 0.90, 95% confidence interval 0.83 to 0.98). To avoid this bias in the case-control study, cases and controls were matched on age, and the index date in controls was assigned to ensure identical duration of follow-up to allow equal exposure periods. In the cohort study, medication exposure was modeled as a time varying covariate using the dates and days supplied for each prescription.

The healthy-user bias is another form of selection bias. In this bias, the health status of individual determines the opportunity for exposure and outcome. This can occur in our studies whereby statin users are those seeking preventative treatments and they may therefore be more likely to interact with health-care services and be compliant with treatment and follow-up for cancer. In my studies, I attempted to mitigate this bias by obtaining the frequency of tests that would be expected to occur more frequently in healthy-users, namely colonoscopies, fecal occult blood tests, and periodic oculo-visual assessments.

Information Bias

Information bias is the systematic distortion of classifying an exposure, outcome, or other relevant variables. They can be classified as non-differential if it affects both groups equally, or differential if one group is affected more than the other. They can be further classified as independent or dependent based on whether the error rate is related to the error rate of another variable(87). The direction of bias on the association between an exposure and an outcome is towards the null in the context of an independent non-differential misclassification when both the exposure and outcome are dichotomous in nature. In other situations, the direction of bias is generally unpredictable(86, 87).
In our studies, since dates of prescriptions and the days supplied field will be used as a surrogate for medication exposure, the actual exposure may not correspond to the estimated exposure if patients are non-compliant with their medication prescriptions. As such, this represents an independent differential exposure misclassification error since it is not dependent on other variables and can only apply to those who are potentially exposed. The direction of this bias in this context is generally unpredictable (87); however, assuming that statins are protective then the direction of bias would be towards the null. While a measurable biomarker would provide a more accurate estimate of exposure, such biomarkers are not readily available for the medications of interest, particularly in administrative data. However, patients that consistently renew their prescriptions are likely compliant and my analyses account for intermittent and cumulative use.

Furthermore, my studies used secondary data with imperfect sensitivity and specificity to determine the exposure, outcome, and information needed to adjust for confounding. For example, the accuracy of the outcome measure cause of death has been evaluated in other malignancies and has shown good, but not perfect, sensitivity and specificity (109, 111). If a similar accuracy is assumed for kidney cancer, the direction of this independent non-differential misclassification error is unpredictable. Ideally, charts from each patient in the study would be obtained to validate the cause of death obtained from administrative data but this is not feasible given the large number of charts required.

Many NSAIDs are available over the counter and it is possible that some exposure will not be captured due to this, thereby representing a misclassification bias. However, considering that patients would not have to pay the full cost for medication had they obtained it by prescription, it is unlikely that over the counter exposure would bias the results to a strong
degree. Furthermore, it has been demonstrated that using administrative data for exposure to over the counter drugs is a reasonable estimate of actual exposure (135). This represents an independent non-differential exposure misclassification error since it is not dependent on other variables and can apply to both with exposure recorded and the unexposed. The direction of this bias is unpredictable given the continuous nature of the exposure variable.

Finally, as alluded to earlier, the primary analysis in many studies of chemoprevention have classified exposure in a dichotomous manner denoting ever vs. never use. This is particularly problematic in cohort studies when exposure is determined during a defined period prior to or at baseline. This method of classifying medication exposure is subject to misclassification bias since patients considered non-users may begin the medication of interest during follow-up and yet be considered a never user in the analysis. Similarly, an “ever user” may be an individual with exposure months before baseline, and no exposure during follow-up, and yet would be analysed as a user when no exposure was received from baseline to end of follow-up. In this context, a survival benefit observed from an ever use may reflect other explanations than exposure of the medication itself. My primary analysis accounted for periods of intermittent use and therefore this was not a concern in my studies. However, I performed secondary analyses using the ever vs. never method to see if the results were consistent with analyses accounting for intermittent and cumulative use.
SPECIFIC OBJECTIVES

- To determine the association between exposure to commonly prescribed medications and the risk of incident kidney cancer.
- To review the current literature and determine the average association between exposure to statins and kidney cancer recurrence-free survival, progression-free survival, cancer-specific survival, and overall survival.
- To determine the association between exposure to commonly prescribed medications and the risk of kidney cancer-specific mortality and all-cause mortality.
- To evaluate how methods of classifying exposure may influence risk estimates.

ETHICS STATEMENT

With the exception of the systematic review and meta-analysis which did not involve individual patient data, all remaining studies obtained approval from Research Ethics Board at the Sunnybrook Health Sciences Center and the University of Toronto. No personal identifying information (such as patient name, OHIP number, or date of birth) were required for these studies. All patients were identified using encoded health card numbers.
FIGURES FOR CHAPTER 2

Figure 2.1 - Directed acyclic graph displaying relationship between statin exposure and kidney cancer risk, in relation to other variables.

Adapted from www.dagitty.net

Figure legend:
- exposure
- outcome
- ancestor of exposure
- ancestor of outcome
- ancestor of exposure and outcome
- unobserved (latent)
- other variable
- causal path
- biasing path
Figure 2.2 - Directed acyclic graph displaying relationship between statin exposure and survival outcomes, in relation to other variables.

Adapted from www.dagitty.net

Figure legend:
- exposure
- outcome
- ancestor of exposure
- ancestor of outcome
- ancestor of exposure and outcome
- unobserved (latent)
- other variable
- causal path
- biasing path
CHAPTER 3: MEDICATION USE AND RISK OF INCIDENT KIDNEY CANCER: A POPULATION-BASED CASE-CONTROL STUDY

SUMMARY

PURPOSE: Exposure to commonly prescribed medications may be associated with cancer risk. However, there are limited data in kidney cancer. Furthermore, methods of classifying cumulative medication exposure in previous studies may be prone to bias.

METHODS: I conducted a population-based nested case-control study utilizing health care databases in Ontario, Canada. Individuals enrolled as cases were aged ≥66 with an incident diagnosis of kidney cancer. For each individual enrolled as a case, I identified up to four individuals as controls matched on age, sex, history of hypertension, comorbidity score, and geographic location. Cumulative exposure to commonly prescribed medications hypothesized to modulate cancer risk were obtained using prescription claims data. I modelled exposure in four different fashions: 1) as continuous exposures using a) fractional polynomials (which allow for a non-linear relationship between an exposure and outcome) or b) assuming a linear relationship; and 2) as dichotomous exposures denoting a) ≥3 vs. < 3 years exposure; or b) ‘ever’ vs. ‘never’ exposure. I used conditional logistic regression to estimate the association of medication exposure on incident kidney cancer.

RESULTS: I studied 10,377 incident cases of kidney cancer and 35,939 matched controls. The directions of association were relatively consistent across analyses; however, the magnitudes were sensitive to the method of analysis. When utilizing fractional polynomials, increasing cumulative exposure to acetylsalicylic acid, selective serotonin reuptake inhibitors, and proton-
pump inhibitors were associated with significantly reduced risk of kidney cancer, while increasing exposure to anti-hypertensive drugs was associated with significantly increased risk.

CONCLUSION: This study provides impetus to further explore the effect of commonly prescribed medications on carcinogenesis to identify modifiable pharmacological interventions to reduce the risk of kidney cancer.
INTRODUCTION

The incidence of kidney cancer is increasing in most countries worldwide (4) with an estimated 337,860 new diagnoses in 2012 (1). The rising incidence is thought to be due to multiple reasons including the increasing use of diagnostic imaging, as well as increasing rates of obesity and hypertension in the population which are known risk factors for incident kidney cancer (7). Despite the majority of tumours detected in the present era being early stage tumours (136), survival rates have only marginally improved over time (128). Other than lifestyle modification, there are currently no approved interventions to reduce the risk of kidney cancer.

Several commonly-prescribed medications, such as acetylsalicylic acid (ASA) (92, 93), non-steroidal anti-inflammatory drugs (NSAIDs) (93, 96), proton-pump inhibitors (PPIs) (104), statins (49), and selective serotonin-reuptake inhibitors (SSRIs) (102), have recently gained interest in the oncology community for their putative anti-neoplastic effects as studies have suggested that their use may be associated with a decreased risk of incident cancer. These medications are relatively inexpensive and well tolerated, making them ideal candidates for chemoprevention in cancer. While some of these medications have been thoroughly investigated in various malignancies, with randomized controlled trials underway (137, 138), there are limited data on the association of exposure to these putative anti-neoplastic medications and the risk of incident kidney cancer (60, 74, 91). Conversely, there is conflicting evidence on whether exposure to several anti-hypertensive medications is associated with increased risk of kidney cancer (26-29). However, to date, there has been no study to evaluate these medications simultaneously, limiting the interpretation of the independent association of each medication class with kidney cancer risk. Determining the risk associated with each medication class may
identify modifiable pharmacological interventions to reduce the risk of a cancer that is common, increasing in incidence, and often lethal.
METHODS

SETTING AND DESIGN

I conducted a population-based nested case-control study of Ontario, Canada residents aged 66 or older from April 1st, 1997 to December 31st, 2014. All patients had universal access to hospital care, physician services, and prescription drug coverage. This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

DATA SOURCES

I identified medication use through prescription claims of the Ontario Drug Benefit database, which contains comprehensive records of prescription drugs dispensed to all Ontario residents aged 65 or older. I chose to include cases aged ≥66 in order to have complete data on at least one year’s history of medication exposure. I used the Ontario Cancer Registry (OCR) to identify patients with incident kidney cancer. I obtained hospitalization data from the Canadian Institute for Health Information Discharge Abstract Database, which contains detailed clinical information regarding all hospital admissions in Ontario. I used the Ontario Health Insurance Plan database to identify claims for physician services, and obtained basic demographic data from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance. These databases were linked in an anonymous fashion using encoded health card numbers, and are routinely used to study drug safety(131, 132, 139). Details regarding all of the databases used and their validity have been provided in Chapter 2.
STUDY PATIENTS

I defined case patients as those with an incident diagnosis of kidney cancer (ICD-9: 189.0; ICD-10: C64) in the OCR. The date of first recorded diagnosis served as the index date for all analyses. For each individual identified as a case, I randomly selected up to four control patients. Control patients were matched to each case according to age (within 1 year), sex, comorbidity score (defined by the Johns Hopkins Adjusted Clinical Groups score(125) in the five years prior to index date), geographical area (defined by the first three characters of the postal code), and history of hypertension. To allow for equal durations of medication exposure among cases and matched controls with varying date of births, the index date among controls was assigned to allow identical duration of follow-up after age 65. To reduce selection bias, I used incidence-density sampling to select controls, thereby allowing cases to also serve as potential controls during the follow-up period that they were without cancer. Additionally, to reduce the potential for detection bias whereby those with medication use are more likely to interact with health services and receive diagnostic imaging, controls had to have had an interaction with the health care system within two years of the assigned index date. Finally, I excluded cases without any matches.

ASSESSMENT OF MEDICATION EXPOSURE

I identified all outpatient prescriptions for angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), ASA, beta-blockers, calcium-channel blockers, PPIs, NSAIDs, statins, and SSRIs. Using the dates of prescriptions and days supplied field, I estimated cumulative exposure to each class of medication.
STATISTICAL ANALYSIS

To account for the matched nature of the data, I used conditional logistic regression analyses to estimate the association of drug exposure with the risk of incident kidney cancer. To allow for a non-linear relationship between cumulative duration of medication exposure and risk of incident kidney cancer, for the primary analysis I used a multivariable fractional polynomial algorithm to select the best transformation for each medication (120, 140). Since the effect of a single day’s incremental increase of medication exposure is clinically negligible, I modelled regression coefficients to represent an increase in increments of 6 months of medication use. The midpoint of each increment was compared to no use (0 months) to estimate the corresponding odds ratio.

To compare fractional polynomial models with other methods of classifying cumulative exposure, I also performed secondary analyses modelling cumulative medication exposure as a linear relationship, dichotomizing exposure to $\geq 3$ vs. $<3$ years of exposure, and “ever” use vs. “never” use. To be considered an ‘ever’ user, the patient had to have filled at least one prescription during follow-up.

All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC) and used a two-sided p value of 0.05 as the threshold for statistical significance.

SENSITIVITY ANALYSES

I conducted several sensitivity analyses of the primary analysis. First, to further reduce detection bias, I adjusted the analysis for screening tests received in the five years prior to index date including fecal occult blood tests, colonoscopies, and periodic oculo-visual assessments.
Second, to minimize confounding by indication, I adjusted the analysis for several comorbidities including history of diabetes, congestive heart failure, myocardial infarction, end stage renal disease, stroke, coronary artery angioplasty or coronary artery bypass graft surgery, and abdominal aortic aneurysm repair and aortic bypass. Finally, it has been suggested that increasing cumulative use of anti-hypertensives may be associated with increased kidney cancer risk(26); however, it is difficult to determine whether this is related to the duration of hypertension or due to increasing medication exposure. I therefore adjusted the analysis for duration of hypertension.
RESULTS

STUDY POPULATION

During the 17-year study period, I identified 10,479 incident cases of kidney cancer. Of these, I successfully matched 10,377 (99%) cases to 35,939 controls. The characteristics of cases and controls are shown in Table 3.1. All characteristics were well balanced between the groups. Medication exposure for cases and controls is shown in Table 3.2. Cases and controls were most commonly exposed to ACEIs and NSAIDs, with 52.8% and 52.2% of cases having any exposure, respectively compared to 49.3% and 54.3% among controls, respectively. The medication class that the lowest proportion of cases and controls were exposed to was SSRIs with 14.7% and 16.2% exposure, respectively.

PRIMARY ANALYSIS

After applying the multivariable fractional polynomial algorithm, statins were excluded from the final model. Cumulative use of ARBs had a linear relationship with the log-odds of the outcome, while non-identity transformations were required for the best functional form for the remaining medications (Figure 3.1 and Table 3.3). Compared to no use, prolonged exposure of 36 – 42 months to any anti-hypertensive (ACEIs, ARBs, calcium-channel blockers, and beta-blockers) was associated with significantly increased risk of incident kidney cancer (Table 3.4). Conversely, prolonged exposure of 36 – 42 months to ASA, SSRIs, and PPIs was associated with significantly reduced risk of incident kidney cancer. Exposure to NSAIDs, regardless of duration, was not associated with kidney cancer risk.
SECONDARY ANALYSES

In modelling cumulative exposure to medications as a linear relationship (Table 3.5), increasing exposure to ACEIs, ARBs, and calcium-channel blockers were significantly associated with increased risk of incident kidney cancer, while only PPIs was associated with decreased risk of kidney cancer. ASA, beta-blockers, NSAIDs, SSRIs, and statins were not significantly associated with kidney cancer risk.

When dichotomizing exposure, exposure ≥3 years to ACEIs, ARBs, beta-blockers, and calcium-channel blockers was significantly associated with increased kidney cancer risk (Table 3.5), while ASA and PPIs were associated with decreased risk. In this analysis, NSAIDs, SSRIs, and statins were not significantly associated with kidney cancer risk.

Evaluating whether ‘ever’ exposure was associated with kidney cancer risk demonstrated that ACEIs, ARBs, beta blockers, and calcium-channel blockers were associated with significantly increased risk (Table 3.5), while any exposure to ASA, NSAIDs, and SSRIs were associated with significantly decreased risk. Any exposure to statins or PPIs was not significantly associated with kidney cancer risk.

SENSITIVITY ANALYSES

Analyses controlling for screening tests, comorbidities, or duration of hypertension demonstrated similar results to the primary analysis (Tables 3.6, 3.7, and 3.8).
DISCUSSION

This population-based study evaluating the association of commonly prescribed medications with the risk of incident kidney cancer found that increasing cumulative exposure to ASA, SSRIs, or PPIs were associated with significantly reduced risk of kidney cancer, while increasing exposure to anti-hypertensive medications was associated with significantly increased risk of kidney cancer. These results were consistent across several sensitivity analyses. However, the magnitude and significance of association varied depending on the method of classifying cumulative exposure. These findings have important implications for future studies in pharmacoepidemiology and the management of patients at high risk for kidney cancer.

I used fractional polynomials for my primary analysis to allow for a non-linear relationship between cumulative medication exposure and risk of kidney cancer. Several of the previous studies evaluating medication exposure and cancer risk, however, have categorized cumulative exposure at different cut points (26-29, 49, 74, 91, 96, 104). The advantage of this method is that the results are relatively easy to understand in terms of low, medium, and high risk groups but there are also several disadvantages including arbitrary selected cut points, loss of efficiency, and overestimation of effect sizes (119, 140). An alternative approach is to model medication exposure as a continuous linear term; however, the assumption of linearity may be incorrect resulting in a misspecified final model in which a relevant predictor may have a null association because the true relationship differs substantially from a linear one (120, 140). While transformations such as quadratic or cubic polynomials have been proposed, the range of transformations evaluated is often limited (120). Conversely, fractional polynomials as proposed by Royston and Altman make few assumptions and evaluate 44 different functions allowing for considerable flexibility on the relationship between a continuous predictor and an outcome (120).
I explored how different methods of classifying medication exposure may influence the results and found that the associations between cumulative medication exposure and kidney cancer risk were sensitive to the method of analysis. For some medications, such as ACEIs and calcium channel blockers, the direction of the association was consistent across all analyses; however, the magnitude of the association was markedly increased when dichotomizing exposure. Conversely, prolonged exposure to ASA or SSRIs demonstrated substantial reduction in kidney cancer risk in the primary analysis employing fractional polynomials, but the degree of association was modest or even non-significant when dichotomizing or assuming a linear relationship for medication exposure. Indeed, similar results have been observed by others(119, 120). Taken together, fractional polynomials may be the most robust method to evaluate the association between cumulative medication exposure and cancer risk and should be the preferred method of classifying medication exposure in pharmacoepidemiology studies.

Using fractional polynomials, I found that increasing exposure to ASA, SSRIs, or PPIs was significantly associated with decreased kidney cancer risk. The results were consistent across several sensitivity analyses. The association I observed with ASA is contrary to a recent meta-analysis of 6,640 cases of kidney cancer that found that exposure to ASA was associated with a non-significant increased risk of kidney cancer(141). However, it is difficult to interpret the results of this meta-analysis as all of the included studies categorized exposure in a dichotomous manner, and several relied on interview or questionnaire data and are therefore prone to recall bias. While to date neither PPIs nor SSRIs have been evaluated in relation to kidney cancer risk, in-vitro and observational studies in other malignancies suggest that these medications have anti-neoplastic properties(102, 104, 142, 143). The results of our study provide
impetus to further study ASA, SSRIs, and PPIs for their potential to reduce the risk of incident kidney cancer.

Conversely, I found that increasing exposure to all anti-hypertensives was associated with significantly increased cancer risk. While there is conflicting evidence on the association of duration of hypertension with kidney cancer risk(8-10), our results were consistent even after controlling for duration of hypertension. Previous studies examining this association have demonstrated mixed results(26-29), but these studies have been limited in size, subject to selection and recall bias, and have dichotomized medication exposure, thereby limiting their interpretation. A recent review of marketed anti-hypertensive drugs found that fewer than half had results on both genotoxicity and carcinogenicity assays(30); however, among those with data available, many were associated with some degree of genotoxicity or carcinogenicity. Taken together, these findings emphasize the need to further evaluate anti-hypertensive medications on kidney cancer risk to identify modifiable pharmacological factors to reduce cancer risk.

This study has several strengths. First, the population-based approach allowed me to study a relatively large population and reduced the potential for selection bias. Second, I had access to comprehensive prescription data, allowing me to estimate cumulative exposure to each medication over the study period. Third, I used fractional polynomials to allow for a non-linear relationship between medication exposure and kidney cancer risk, the advantages of which have been described above. Fourth, I performed several sensitivity analyses to reduce detection and confounding by indication biases; these analyses demonstrated consistent results, supporting the strength of the results. Finally, I evaluated multiple medications hypothesized to modulate cancer risk, allowing me to ascertain the independent association of each medication.
This study also has limitations. First, I was unable to account for smoking habits or obesity, established risk factors for kidney cancer (5), as this information is not available in administrative databases. However, I attempted to control for these potential confounders by matching on several predictors of these factors such as age, gender, and geographic area. Indeed, a population-based study in Ontario found that these factors were predictive of body mass index, including neighbourhood characteristics associated with each geographical area determined by the first the three characters of the postal code (144), as was used in this study. While there is no similar data on predicting smoking habits in Ontario, several other studies have found age, gender, and neighbourhood characteristics to be predictive of smoking status (145-147). Furthermore, both smoking and obesity relate to an individual’s health status (148) and matching on the comorbidity score may have further reduced the potential for selection bias between cases and controls. Second, given that comprehensive prescription data are only available for those aged 65 or older, the results of this study do not apply to younger populations; further studies are needed to confirm whether these medications are associated with kidney cancer risk in younger patients. Similarly, I did not have access to medication exposure prior to age 65. However, this is not expected to strongly bias the results as this applies to both cases and controls. Furthermore, my method of analysis compares not only users and non-users, but also different durations of exposure within users. Third, I estimated medication exposure through prescription data; the actual exposure may not correspond to the estimated exposure if patients are non-compliant with their medication prescriptions. However, patients that consistently renew their prescriptions are likely compliant. Fourth, secondary data with imperfect sensitivity and specificity were used for the study. However, several of the databases have been validated (139). Last, ASA and many NSAIDs are available over the counter and it is possible that some exposure was not captured.
due to this. However, considering that patients would not have to pay the full cost for medication had they obtained it by prescription, it is unlikely that over the counter exposure would bias the results to a strong degree. Furthermore, it has been previously shown that using administrative data for exposure to drugs available over the counter is a reasonable estimate of actual exposure(135). Despite these limitations, this large population-based study used comprehensive prescription data and robust statistical modelling to identify several potential modifiable pharmacological interventions to reduce kidney cancer risk.
CONCLUSION

This study evaluating the association of exposure to commonly prescribed medications hypothesized to modulate cancer risk found that increasing cumulative exposure to acetylsalicylic acid, selective serotonin reuptake inhibitors, and proton-pump inhibitors was associated with significantly reduced risk of incident kidney cancer. Conversely, increasing exposure to several anti-hypertensive medications was associated with significantly increased risk. These results provide impetus to further explore the effect of these medications on carcinogenesis to identify potential modifiable pharmacological interventions to reduce the risk of incident kidney cancer.
Figure 3.1: Relationship between cumulative exposure to medications on risk of incident kidney cancer.
Table 3.1: Characteristics of cases and controls.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case patients (n=10377)</th>
<th>Control patients (n=35939)</th>
<th>Absolute Standardized difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (n (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65 – 66</td>
<td>632 (6.1)</td>
<td>2335 (6.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>67 – 68</td>
<td>1249 (12.0)</td>
<td>4536 (12.6)</td>
<td></td>
</tr>
<tr>
<td>69 – 70</td>
<td>1181 (11.4)</td>
<td>4252 (11.8)</td>
<td></td>
</tr>
<tr>
<td>71 – 72</td>
<td>1225 (11.8)</td>
<td>4424 (12.3)</td>
<td></td>
</tr>
<tr>
<td>73 – 74</td>
<td>1135 (10.9)</td>
<td>4012 (11.2)</td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td>4955 (47.8)</td>
<td>16380 (45.6)</td>
<td></td>
</tr>
<tr>
<td>Male gender (n (%))</td>
<td>6019 (58.0)</td>
<td>20539 (57.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Urban* (n (%))</td>
<td>1520 (14.6)</td>
<td>5230 (14.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>Income quintile† (n (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 1 (lowest)</td>
<td>2112 (20.4)</td>
<td>7108 (19.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>2163 (20.8)</td>
<td>7633 (21.2)</td>
<td></td>
</tr>
<tr>
<td>Quintile 3</td>
<td>2040 (19.7)</td>
<td>7007 (19.5)</td>
<td></td>
</tr>
<tr>
<td>Quintile 4</td>
<td>2010 (19.4)</td>
<td>7049 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Quintile 5 (highest)</td>
<td>2009 (19.4)</td>
<td>7024 (19.5)</td>
<td></td>
</tr>
<tr>
<td>Comorbidity score‡ (median (IQR))</td>
<td>13 (10 – 15)</td>
<td>13 (10 – 15)</td>
<td>0.03</td>
</tr>
<tr>
<td>History of hypertension (n (%))</td>
<td>8172 (78.8)</td>
<td>28989 (80.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>History of diabetes (n (%))</td>
<td>3226 (31.1)</td>
<td>9897 (27.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>History of congestive heart failure (n (%))</td>
<td>1624 (15.6)</td>
<td>4242 (11.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>History of myocardial infarction (n (%))</td>
<td>622 (6.0)</td>
<td>2313 (6.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>History of end stage renal disease (n (%))</td>
<td>275 (2.6)</td>
<td>324 (0.90)</td>
<td>0.13</td>
</tr>
<tr>
<td>History of stroke (n (%))</td>
<td>480 (4.6)</td>
<td>1633 (4.5)</td>
<td>0.00</td>
</tr>
<tr>
<td>History of coronary artery angioplasty or coronary artery bypass graft surgery (n (%))</td>
<td>966 (9.3)</td>
<td>3529 (9.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>History of and abdominal aortic aneurysm repair and aortic bypass (n (%))</td>
<td>147 (1.4)</td>
<td>521 (1.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Number of colonoscopies in 5 years prior to index date (median (IQR))</td>
<td>0 (0 – 0)</td>
<td>0 (0 – 1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of fecal occult blood tests in 5 years prior to index date (median (IQR))</td>
<td>0 (0 – 1)</td>
<td>0 (0 – 1)</td>
<td>0.00</td>
</tr>
<tr>
<td>Number of oculo-visual tests in 5 years prior to index date (median (IQR))</td>
<td>0 (0 – 0)</td>
<td>0 (0 – 0)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviations: IQR: interquartile range
*Data missing in 16 patients (0.03%); †Income quintiles from median income in neighborhoods from 1 (low) to 5 (high), data missing in 161 patients (0.35%); ‡Comorbidity scores were calculated by using Johns Hopkins Adjusted Clinical Groups Case-Mix System assigning a specific weight to each adjusted diagnostic group (low, weighted adjusted diagnostic group score 5 or lower; intermediate, 6-9; high, 10 or higher).
Table 3.2: Medication exposure among cases and controls.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Case patients (n=10377)</th>
<th>Control patients (n=35939)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with any exposure (n (%))</td>
<td>Cumulative exposure in months of patients with any exposure (median (IQR))</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>5480 (52.8)</td>
<td>30.2 (9.9 – 65.8)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>1941 (18.7)</td>
<td>27.1 (9.4 – 55.6)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>2425 (23.4)</td>
<td>14.7 (3.6 – 40.7)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>4087 (39.4)</td>
<td>29.7 (9.1 – 67.4)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>4284 (41.3)</td>
<td>32.6 (11.2 – 66.3)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>5419 (52.2)</td>
<td>3.3 (1.0 – 13.4)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>1522 (14.7)</td>
<td>9.8 (2.4 – 34.2)</td>
</tr>
<tr>
<td>Statins</td>
<td>4957 (47.8)</td>
<td>37.7 (15.0 – 71.5)</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>3440 (33.2)</td>
<td>9.2 (2.0 – 34.4)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs
Table 3.3: Transformations applied through the use of the multi-variable fractional polynomial algorithm.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Transformation (power(s))</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>FP2 (-1, 2)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>Linear</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>FP2 (1, 1)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>FP2 (-2, -0.5)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>FP2 (-2, 2)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>FP1 (-0.5)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>FP2 (1, 1)</td>
</tr>
<tr>
<td>Statins</td>
<td>Excluded</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>FP2 (-2, 0)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE: angiotensin converting enzyme; FP: fractional polynomial; NSAIDs: non-steroidal anti-inflammatory drugs
Table 3.4: Cumulative use of medication exposure modelled with fractional polynomials on risk of incident kidney cancer.

<table>
<thead>
<tr>
<th></th>
<th>Cumulative use (OR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 – 6 months</td>
</tr>
<tr>
<td><strong>Angiotensin converting enzyme inhibitors</strong></td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td><strong>Angiotensin II receptor blockers</strong></td>
<td>1.01 (1.01 to 1.02)</td>
</tr>
<tr>
<td><strong>Acetylsalicylic acid</strong></td>
<td>0.96 (0.94 to 0.98)</td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
<td>1.13 (1.07 to 1.20)</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td>0.93 (0.91 to 0.96)</td>
</tr>
<tr>
<td><strong>Proton-pump inhibitors</strong></td>
<td>1.03 (1.02 to 1.04)</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs; OR: odds ratio
Table 3.5: Comparison of different methods of classifying cumulative medication exposure on risk of incident kidney cancer.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Linear for each increasing 6 months of exposure (OR (95% CI))</th>
<th>≥3 years vs. &lt;3 years (OR (95% CI))</th>
<th>Ever vs. never exposure (OR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>1.02 (1.02 to 1.03)</td>
<td>1.21 (1.14 to 1.29)</td>
<td>1.20 (1.14 to 1.26)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>1.03 (1.02 to 1.04)</td>
<td>1.27 (1.16 to 1.40)</td>
<td>1.12 (1.05 to 1.19)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>0.99 (0.98 to 1.00)</td>
<td>0.90 (0.82 to 0.99)</td>
<td>0.93 (0.88 to 0.98)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>1.01 (1.00 to 1.01)</td>
<td>1.08 (1.01 to 1.15)</td>
<td>1.09 (1.04 to 1.15)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1.02 (1.01 to 1.02)</td>
<td>1.26 (1.18 to 1.34)</td>
<td>1.27 (1.21 to 1.34)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1.00 (0.99 to 1.01)</td>
<td>1.04 (0.94 to 1.15)</td>
<td>0.92 (0.87 to 0.96)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>0.99 (0.98 to 1.00)</td>
<td>0.88 (0.78 to 1.00)</td>
<td>0.85 (0.80 to 0.91)</td>
</tr>
<tr>
<td>Statins</td>
<td>1.00 (0.99 to 1.00)</td>
<td>0.98 (0.92 to 1.04)</td>
<td>0.95 (0.90 to 1.00)</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>0.98 (0.98 to 0.99)</td>
<td>0.86 (0.78 to 0.93)</td>
<td>0.99 (0.94 to 1.04)</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs; OR: odds ratio
Table 3.6: Cumulative use of medication exposure modelled with fractional polynomials on risk of incident kidney cancer, adjusted for screening tests.

<table>
<thead>
<tr>
<th>Medication category</th>
<th>0 – 6 months</th>
<th>6 – 12 months</th>
<th>12 – 18 months</th>
<th>18 – 24 months</th>
<th>24 – 30 months</th>
<th>30 – 36 months</th>
<th>36 – 42 months</th>
<th>42 – 48 months</th>
<th>48 – 54 months</th>
<th>54 – 60 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiotensin converting enzyme inhibitors</strong></td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.01)</td>
<td>1.01 (1.01 to 1.01)</td>
<td>1.01 (1.01 to 1.02)</td>
<td>1.02 (1.01 to 1.03)</td>
<td>1.03 (1.02 to 1.04)</td>
<td>1.04 (1.03 to 1.05)</td>
<td>1.05 (1.04 to 1.07)</td>
<td>1.06 (1.04 to 1.09)</td>
</tr>
<tr>
<td><strong>Angiotensin II receptor blockers</strong></td>
<td>1.01 (1.01 to 1.02)</td>
<td>1.04 (1.03 to 1.05)</td>
<td>1.06 (1.04 to 1.08)</td>
<td>1.09 (1.06 to 1.12)</td>
<td>1.12 (1.08 to 1.15)</td>
<td>1.14 (1.10 to 1.19)</td>
<td>1.17 (1.11 to 1.23)</td>
<td>1.20 (1.13 to 1.27)</td>
<td>1.23 (1.15 to 1.31)</td>
<td>1.26 (1.17 to 1.35)</td>
</tr>
<tr>
<td><strong>Acetylsalicylic acid</strong></td>
<td>0.96 (0.94 to 0.98)</td>
<td>0.91 (0.86 to 0.95)</td>
<td>0.86 (0.79 to 0.93)</td>
<td>0.82 (0.74 to 0.90)</td>
<td>0.78 (0.69 to 0.88)</td>
<td>0.75 (0.65 to 0.86)</td>
<td>0.72 (0.61 to 0.84)</td>
<td>0.69 (0.57 to 0.83)</td>
<td>0.66 (0.54 to 0.81)</td>
<td>0.64 (0.51 to 0.79)</td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
<td>1.13 (1.07 to 1.20)</td>
<td>1.07 (1.04 to 1.11)</td>
<td>1.06 (1.03 to 1.09)</td>
<td>1.05 (1.02 to 1.06)</td>
<td>1.04 (1.02 to 1.06)</td>
<td>1.04 (1.02 to 1.05)</td>
<td>1.03 (1.02 to 1.05)</td>
<td>1.03 (1.02 to 1.05)</td>
<td>1.03 (1.02 to 1.05)</td>
<td>1.03 (1.02 to 1.04)</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td>0.93 (0.91 to 0.96)</td>
<td>0.84 (0.79 to 0.89)</td>
<td>0.76 (0.69 to 0.84)</td>
<td>0.70 (0.62 to 0.80)</td>
<td>0.65 (0.56 to 0.76)</td>
<td>0.60 (0.50 to 0.69)</td>
<td>0.56 (0.46 to 0.66)</td>
<td>0.52 (0.41 to 0.63)</td>
<td>0.49 (0.38 to 0.55)</td>
<td>0.46 (0.35 to 0.60)</td>
</tr>
<tr>
<td><strong>Proton-pump inhibitors</strong></td>
<td>1.03 (1.02 to 1.04)</td>
<td>0.98 (0.98 to 0.99)</td>
<td>0.96 (0.95 to 0.97)</td>
<td>0.95 (0.94 to 0.96)</td>
<td>0.94 (0.93 to 0.96)</td>
<td>0.93 (0.92 to 0.95)</td>
<td>0.93 (0.91 to 0.95)</td>
<td>0.92 (0.90 to 0.94)</td>
<td>0.92 (0.90 to 0.94)</td>
<td>0.91 (0.89 to 0.94)</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs; OR: odds ratio

Cumulative use (OR (95% CI))
Table 3.7: Cumulative use of medication exposure modelled with fractional polynomials on risk of incident kidney cancer, adjusted for presence of comorbidities.

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Cumulative use (OR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 – 6 months</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>1.01 (1.01 to 1.02)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>0.96 (0.94 to 0.98)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>1.13 (1.07 to 1.20)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>0.93 (0.91 to 0.95)</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>1.03 (1.02 to 1.04)</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs; OR: odds ratio
Table 3.8: Cumulative use of medication exposure modelled with fractional polynomials on risk of incident kidney cancer, adjusted for duration of hypertension.

<table>
<thead>
<tr>
<th></th>
<th>Cumulative use (OR (95% CI))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 – 6 months</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>1.01 (1.01 to 1.02)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>0.96 (0.94 to 0.98)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>1.13 (1.07 to 1.20)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td>Selective serotonin uptake inhibitors</td>
<td>0.93 (0.91 to 0.96)</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>1.03 (1.02 to 1.04)</td>
</tr>
</tbody>
</table>

Abbreviations: CI: confidence interval; NSAIDs: non-steroidal anti-inflammatory drugs; OR: odds ratio
CHAPTER 4: STATIN USE AND KIDNEY CANCER SURVIVAL OUTCOMES: A SYSTEMATIC REVIEW AND META-ANALYSIS

SUMMARY

BACKGROUND: Statin use has been associated with improved survival outcomes in various malignancies. Randomized controlled trials are currently underway evaluating their utility as adjunctive cancer therapies. However, studies evaluating the association between statin use and outcomes in kidney cancer yield conflicting results.

METHODS: Medline and EMBASE were searched to identify studies evaluating the association between statin use and kidney cancer survival outcomes. Risk of bias was evaluated with the Newcastle-Ottawa scale. I pooled hazard ratios for recurrence-free survival, progression-free survival, cancer-specific survival, and overall survival using random-effects models. Publication bias was evaluated through Begg’s and Egger’s tests, and the trim and fill procedure.

RESULTS: I identified 12 studies meeting inclusion criteria and summarized data from 18,105 patients. No study was considered to be at high risk of bias. Statin use was not significantly associated with recurrence-free survival (pooled hazard ratio (HR) 0.97, 95% CI 0.89 to 1.06) or progression-free survival (pooled HR 0.92, 95% CI 0.51 to 1.65); however, statin use was associated with marked improvements in cancer-specific survival (pooled HR 0.67, 95% CI 0.47 to 0.94) and overall survival (pooled HR 0.74, 95% CI 0.63 to 0.88). There was no strong evidence of publication bias for any outcome.

CONCLUSIONS: These results demonstrate that statin use among patients with kidney cancer is associated with significantly improved cancer-specific and overall survival. Further studies are needed to confirm the therapeutic role of statins in kidney cancer therapy.

A journal article pertaining to this chapter can be found at doi: 10.1016/j.ctrv.2016.11.009.
INTRODUCTION

Kidney cancer is the third most common urological malignancy and the most lethal of all urological cancers (1). Moreover, the number of incident cases has been rising worldwide (1). Although the majority of kidney cancers currently detected are at an early stage (136), survival rates have only marginally improved (128). Nephrectomy remains the mainstay of treatment in clinically localized disease, but despite treatment 20% to 30% of those with localized disease experience recurrence after nephrectomy, and the majority of those patients die of the disease (32, 33). Unfortunately, there are no currently approved therapies to reduce the risk of recurrence, progression or death from kidney cancer after primary treatment of localized disease. While targeted therapies have been shown to prolong survival in patients with metastases, the survival advantage is on the order of months (149). Trials exploring the role of adjuvant targeted therapies have thus far proven negative (150). Furthermore, the financial burden of targeted therapy in kidney cancer is significant (151).

Studies evaluating the association between statin use and kidney cancer survival outcomes have provided conflicting results (50, 81-85, 123, 152-156). Reviewing the available evidence may provide insight on areas of further research required to understand the potential role of statins in kidney cancer therapy. I conducted a systematic review to examine whether use of statins was associated with differential survival outcomes in adults diagnosed with kidney cancer.
METHODS

DESIGN

This study was designed and conducted following the Cochrane Handbook for Systematic Reviews(106). The results are reported in conformity with Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines(157).

SEARCH STRATEGY

With the assistance of a professional librarian, I searched OVID MEDLINE and EMBASE from inception to October 2016. I used both subject headings and textword terms related to statins AND (kidney cancer OR cancer mortality). The detailed search strategy is shown in the appendix. I also searched the first 200 hits on Google scholar with the search terms “statin kidney cancer survival” and “statin cancer survival”. Electronic searches were supplemented by manual searches of references of electronically-identified included articles.

STUDY SELECTION

I included published abstracts and manuscripts that were either randomized controlled trials or observational studies (prospective and retrospective cohort studies), regardless of language or year of publication, that explored the association between statin use and survival outcomes in kidney cancer. I excluded studies if the publication was a commentary, case report, case series, editorial, or letter to the editor.

The outcomes of interest were recurrence-free survival (RFS), progression-free survival (PFS), cancer-specific survival (CSS), and overall survival (OS). Because definitions for RFS and PFS vary, for the purpose of this review I defined RFS as time from curative treatment to
development of local or distant recurrence. In patients with locoregional disease, I defined PFS as time from curative treatment to metastases or death from kidney cancer, while in patients with metastatic disease I defined it as time from treatment to progression or death from any cause. I included studies evaluating the association between statin use and survival outcomes in cancer in general if data specific to kidney cancer were available. I required that articles report a risk estimate relating statin use to RFS, PFS, CSS, or OS using survival analysis, along with an estimate of precision, such as a standard error, p-value or 95% confidence interval (CI).

Participants included all adults aged 18 or older diagnosed with kidney cancer of any clinical stage. I included studies that compared statin use, regardless of type, dosage, or frequency, to no statin use or placebo.

To avoid including overlapping patient populations, all included studies were evaluated for authorship, recruitment years, data sources, and geographic location. If patient populations were found to overlap, I preferentially included full articles over abstracts, and articles with the most comprehensive population.

DATA ABSTRACTION AND RISK OF BIAS ASSESSMENT

Titles, abstracts, articles reviews, and data extractions were performed independently by myself and another reviewer with formal training in clinical epidemiology. The extracted data included information on authorship, year of publication, study country of origin, study design, sample size, number of patients on statins, treatment for kidney cancer, follow-up period, covariates included in the analysis, and risk estimates. If pertinent data were missing from a study, I contacted authors for further details. Disagreements at any stage were resolved by discussion and consensus, with residual disagreement adjudicated by a third author.
If the same article reported several estimates, the most fully adjusted estimate was chosen (multivariate regression was selected over univariate regression, which was selected over Kaplan-Meier survival estimates), as has been done previously(105, 158).

The risk of bias at the individual study level was assessed according to the Newcastle-Ottawa Scale for observational studies(159). Risk of bias was considered to be low (total score 7-9), moderate (total score 4-6), or high (total score 1-3).

DATA SYNTHESIS AND ANALYSIS

In the primary analysis, I pooled natural log-transformed risk estimates for each outcome. When only a Kaplan-Meier curve or the probability of survival to a specific time-point was given, survival probabilities were converted to a relative risk and confidence intervals were constructed accordingly(160, 161).

Heterogeneity among studies was assessed using the Cochran Q ($\chi^2$) statistic and quantified using the $I^2$ statistic, with $I^2>50\%$ indicative of substantial heterogeneity(162). Where data were sufficiently homogenous, a fixed-effects model was used to estimate the pooled hazard ratios (HR); in the presence of substantial heterogeneity, pooled HRs were calculated using a random-effects model(163). To properly interpret random-effects models, prediction intervals (PI) were estimated for each pooled HR using the estimate of between-study variance ($\tau^2$) when 3 or more studies were available in the analysis. While the pooled HR provides an estimate of the average study-specific effect, prediction intervals account for the heterogeneity between studies and provide an estimate of the range of effects that can plausibly be expected in a new study examining the same association(164).
Publication bias was evaluated using Begg’s and Egger’s tests. Egger’s test was only applied when 3 or more studies were available in the analysis. Duval and Tweedie nonparametric trim and fill procedures were then used to further evaluate publication bias. This method estimates the number and risk estimates of potentially unpublished studies that, if included in the primary analyses, may mitigate publication bias (165).

For CSS and OS, I performed subgroup analyses based on disease stage (metastatic vs. locoregional disease). Additionally, I planned two sensitivity analyses *a priori*: to explore the impact of study quality, I conducted sensitivity analyses by excluding studies considered at high risk of bias. I also recalculated a pooled hazard ratio by excluding studies that were only available in abstract form.

For all analyses, a two-sided p-value of <0.05 was considered statistically significant. STATA (v. 13.0, College Station, TX) was used for statistical analyses.
RESULTS

DESCRIPTION OF STUDIES

The flow diagram describing study selection is shown in Figure 4.1. A total of 12 studies (50, 81-85, 123, 152-156) comprising of 18,105 patients met inclusion criteria, of which two were only available in abstract form (152, 154) (Table 4.1). Two studies were secondary analyses of trials (85, 155), while the remaining ten were observational cohort studies (50, 81-84, 123, 152-154, 156), one of which was population-based (50); there were no randomized controlled trials with the primary objective evaluating whether statin use is associated with survival outcomes in kidney cancer. The majority (58%) of included studies were from the USA. In the studies where details were available, median follow-up ranged from 1.5 to 7.8 years and the proportion of patients on statins ranged from 6.0% to 59.4%.

The results of the assessment of risk of bias among the 12 included studies is provided in Table 4.2. The majority (75%) of studies were considered to be at low risk of bias.

RECURRENCE-FREE SURVIVAL

There was significant heterogeneity among the 4 studies evaluating RFS (Q=6.7, degrees of freedom (df) = 3, p=0.08, $\Gamma^2$=55.2%). When I pooled the results of these 4 studies using a random-effects model, statin use was associated with a 3% average reduction in the risk for kidney cancer recurrence (HR 0.97, 95% CI 0.89 to 1.06; 95% PI 0.71 to 1.33, Figure 4.2). There was no evidence of publication bias according to Begg’s test (p=0.73) or Egger’s tests (p=0.33). However, based on the distribution of the estimates between included studies, the trim and fill procedure estimated one theoretical missing study; incorporating this study into the pooled estimate demonstrated similar results (HR 0.97, 95% CI 0.90 to 1.05).
None of the studies evaluating RFS were at high risk of bias or were in abstract form.

PROGRESSION-FREE SURVIVAL

While two studies described PFS in patients with metastatic disease, one of these did not provide a risk estimate and could not be included in the meta-analysis for PFS.(85)

Among the 2 studies evaluating PFS in locoregional disease, there was significant heterogeneity ($Q=7.2$, df=1, $p=0.007$, $I^2=86.2\%$). When I pooled the results of these 2 studies using a random-effects model, statin use was, on average, associated with an 8% reduced risk of cancer progression (HR 0.92, 95% CI 0.51 to 1.65; Figure 4.3). There was no evidence of publication bias according to Begg’s test ($p=1.0$). The trim and fill procedure did not identify any theoretical missing studies.

None of the studies evaluating PFS were at high risk of bias or in abstract form.

CANCER-SPECIFIC SURVIVAL

There was significant heterogeneity among the 6 studies evaluating CSS ($Q=15.1$, df=5, $p=0.010$, $I^2=67.0\%$). When I pooled the results of these 6 studies using a random-effects model, statin use was, on average, associated with a 33% reduced risk of death due to kidney cancer (HR 0.67, 95% CI 0.47 to 0.94; 95% PI 0.24 to 1.82, Figure 4.4). There was no evidence of publication bias according to Begg’s test ($p=0.13$) or Egger’s tests ($p=0.12$). The trim and fill procedure did not identify any theoretical missing studies.

Only one study evaluated CSS in metastatic patients exclusively(85). When evaluating 5 studies with data for patients with locoregional disease only, the association between statin use and CSS was similar (HR 0.71, 95% CI 0.36 to 1.40).
None of the studies evaluating CSS were at high risk of bias. When excluding abstracts, the association between statin use and CSS was also similar (HR 0.83, 95% CI 0.64 to 1.06).

OVERALL SURVIVAL

There was significant heterogeneity among the 7 studies evaluating OS (Q=12.5, df=6, p=0.052, \( \hat{I}^2=51.8\%\)). When I pooled the results of these studies using a random-effects model, statin use was, on average, associated with a 26% reduced risk of death from any cause (HR 0.74, 95% CI 0.63 to 0.88; 95% PI 0.47 to 1.17, Figure 4.5). There was no evidence of publication bias according to Begg’s test (p=0.23) or Egger’s test (p=0.056). The trim and fill procedure did not identify any theoretical missing studies.

The association between statin use and OS was similar in 2 studies evaluating metastatic patients exclusively (HR 0.61, 95% CI 0.30 to 1.23), and in those 5 studies with data for patients with locoregional disease (HR 0.75, 95% CI 0.61 to 0.92).

None of the studies evaluating OS were at high risk of bias. When excluding abstracts, the association between statin use and OS was also similar (HR 0.74, 95% CI 0.63 to 0.88).
DISCUSSION

In this meta-analysis involving 18,105 kidney cancer patients, I found that statin use was associated with, on average, a 33% reduced risk of cancer-specific mortality and 26% reduced risk of all-cause mortality. However, there was no appreciable reduction in the risk of cancer recurrence or progression associated with statin use.

While the majority of studies included in this study were at low risk of bias, overall there were a relatively limited number of studies evaluating statins and kidney cancer survival outcomes. However, the number of included studies was similar to recent meta-analyses evaluating statins and survival outcomes in other malignancies such as breast(166) and colorectal(167) cancer, which included 5 and 12 studies, respectively. Consistent with the results of this study, these meta-analyses also found that statin use was associated with significantly improved with CSS and OS(166, 167). Although the direction and magnitude of associations in the present study for CSS and OS were similar across subgroup analyses, they were not always statistically significant which may reflect reduced statistical power.

While these earlier meta-analyses did not include prediction intervals, in this study the prediction intervals for CSS and OS crossed 1.0, indicating that while statin use around the time of diagnosis is associated with, on average, improved CSS and OS in kidney cancer (all pooled HRs <1), in some future studies there may be no association(164).

Furthermore, although earlier meta-analyses involving breast and colorectal cancer did not include recurrence or progression as outcomes, in our study there was a non-statistically significant association towards reduced risk of cancer recurrence or progression that did not reach statistical significance. Indeed, there were few studies evaluating these outcomes with
discrepant results; for recurrence-free survival, two of the four studies included provided only unadjusted estimates and these studies trended towards the null(81, 156).

Taken together, the findings of the meta-analysis have important implications in kidney cancer. First, further research is needed to evaluate whether statins may reduce the risk of recurrence or progression. Given that 20% to 30% of patients experience recurrence or progression after nephrectomy(32, 33) and costs associated with targeted therapy are upwards of $30,000US(151), if statins are found to be protective against recurrence or progression they may confer significant cost savings as they are relatively inexpensive. Second, the prediction intervals in this study suggest that there may be subgroups of kidney cancer patients that may benefit from statin use while others that do not; research on identifying these subgroups will allow for individual-directed treatment. Third, the results from this meta-analysis suggest that patients with indications for lipid-lowering therapy and concurrent kidney cancer should be preferentially treated with statins. Finally, further studies are needed to evaluate the role of statins in improving CSS and OS in patients with kidney cancer.

The strengths of this meta-analysis include a comprehensive search strategy devised with the assistance of a professional librarian experienced in systematic reviews and meta-analyses. Although a previous meta-analysis evaluating statin use and kidney cancer outcomes has been published that included four studies(80), that study may have missed some of the earlier studies identified in this study by using a selective list of search terms. Another strength of this study is that all titles, abstracts, and articles were independently reviewed by two individuals with formal training in clinical epidemiology. Finally, while previous meta-analyses have been conducted in various malignancies evaluating statin use and cancer outcomes, to the best of my knowledge the present study is one of few in the literature to include predication intervals, an important aspect
for the proper interpretation of random-effects models and directly applicable to the translation of the results of a meta-analysis to clinical practice(164).

Several limitations of this analysis warrant emphasis. First, there was significant heterogeneity in the studies among all outcomes assessed, which may reflect differences in durations of follow-up, proportions of patients on statins, and factors adjusted for in the statistical models. I attempted to control for the heterogeneity by using random-effects models and several sensitivity analyses which demonstrated relatively consistent results. Second, I included abstracts without a full text available and it is difficult to properly appraise their methods and results. However, I took a more inclusive approach to avoid publication bias; indeed, exclusion of the abstracts demonstrated similar results. Third, studies included in this meta-analysis classified statin use as a binary exposure. Classifying exposure in this manner does not account for intermittent use and can therefore lead to bias because medication use can change over time. Only one study included in this analysis performed a time varying analysis to account for intermittent use and found that the association between statin use and survival outcomes in kidney cancer differed when comparing use at the time of surgery with the time varying analysis(84). Another study in diabetics with kidney cancer accounted for intermittent and cumulative use and found that current use, but not cumulative use of statins was associated with improved survival outcomes(139); however, the findings of this study may not be generalizable to non-diabetics as a separate study found that the association of statins on survival outcomes varied depending on diabetic status(168). Therefore, future studies evaluating chemoprevention in kidney cancer should attempt to account for intermittent and cumulative use. If such a study demonstrates a protective association of statins on survival outcomes in kidney cancer, a prospective study is warranted to evaluate the role of statins in kidney cancer therapy. Despite
these limitations, the present study has important implications for future research and patient management of kidney cancer patients, and demonstrates findings consistent with reviews in other malignancies.
CONCLUSION

This systematic review and meta-analysis demonstrates that statin use among patients with kidney cancer is associated with significantly improved cancer-specific and overall survival. However, these studies classified exposure in a binary manner and future studies evaluating statin use and survival outcomes in kidney cancer should attempt to account for intermittent and cumulative use.
FIGURES FOR CHAPTER 4

Figure 4.1: Flowchart of study selection.

2725 records identified through search strategy
246 duplicate records removed
2479 titles/abstracts reviewed
2387 excluded by title/abstract review
92 articles reviewed
80 excluded by article review
  • 20 review articles
  • 16 did not evaluate statins as an exposure
  • 19 did not have kidney cancer specific data
  • 10 duplicate/overlapping populations
  • 5 did not evaluate survival outcomes
  • 8 letters to editor/commentaries
  • 2 evaluated diabetic population
12 articles included in meta-analysis

4 articles evaluating RFS
4 articles evaluating PFS
6 articles evaluating CSS
7 articles evaluating OS

Footnote: CSS: cancer-specific survival; OS: overall survival; PFS: progression-free survival; RFS: recurrence-free survival
Figure 4.2: Meta-analysis of the effect of statin use on recurrence-free survival in patients with locoregional kidney cancer.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haddad 2015</td>
<td>0.54 (0.33, 0.86)</td>
</tr>
<tr>
<td>Choi 2013</td>
<td>0.97 (0.91, 1.08)</td>
</tr>
<tr>
<td>Krane 2014</td>
<td>1.00 (0.99, 1.01)</td>
</tr>
<tr>
<td>Nayyar 2016</td>
<td>1.09 (0.65, 1.81)</td>
</tr>
<tr>
<td>Overall (I-squared = 55.2%, p = 0.082)</td>
<td>0.97 (0.69, 1.06)</td>
</tr>
<tr>
<td>with estimated predictive interval</td>
<td>(0.71, 1.33)</td>
</tr>
</tbody>
</table>
Figure 4.3: Meta-analysis of the effect of statin use on progression-free survival in patients with locoregional kidney cancer.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton 2014</td>
<td>0.67 (0.47, 0.96)</td>
</tr>
<tr>
<td>Viere 2015</td>
<td>1.22 (0.95, 1.57)</td>
</tr>
<tr>
<td>Overall (I-squared = 86.2%, p = 0.007)</td>
<td>0.92 (0.51, 1.65)</td>
</tr>
</tbody>
</table>
Figure 4.4: Meta-analysis of the effect of statin use on cancer-specific survival in patients with kidney cancer.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gayed 2014</td>
<td>0.22 (0.06, 0.79)</td>
</tr>
<tr>
<td>Lee 2014</td>
<td>0.32 (0.14, 0.71)</td>
</tr>
<tr>
<td>Kaffenberger 2015</td>
<td>0.48 (0.28, 0.83)</td>
</tr>
<tr>
<td>Nielsen 2012</td>
<td>0.85 (0.72, 1.01)</td>
</tr>
<tr>
<td>Nayan 2016</td>
<td>0.90 (0.40, 2.01)</td>
</tr>
<tr>
<td>Viers 2015</td>
<td>1.02 (0.74, 1.39)</td>
</tr>
<tr>
<td>Overall (I-squared = 67.0%, p = 0.010)</td>
<td>0.67 (0.47, 0.94)</td>
</tr>
</tbody>
</table>

with estimated predictive interval . (0.24, 1.82)
Figure 4.5: Meta-analysis of the effect of statin use on overall survival in patients with kidney cancer.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee 2012</td>
<td>0.38 (0.18, 0.63)</td>
</tr>
<tr>
<td>Haddad 2015</td>
<td>0.45 (0.28, 0.71)</td>
</tr>
<tr>
<td>Kaffenberger 2015</td>
<td>0.62 (0.43, 0.90)</td>
</tr>
<tr>
<td>McKay 2016</td>
<td>0.80 (0.66, 0.97)</td>
</tr>
<tr>
<td>Viers 2015</td>
<td>0.84 (0.69, 1.00)</td>
</tr>
<tr>
<td>Hamilton 2014</td>
<td>0.89 (0.71, 1.13)</td>
</tr>
<tr>
<td>Nayan 2016</td>
<td>0.89 (0.55, 1.44)</td>
</tr>
<tr>
<td>Overall (I-squared = 51.8%, p = 0.052)</td>
<td>0.74 (0.63, 0.88)</td>
</tr>
</tbody>
</table>

with estimated predictive interval

- (0.47, 1.17)
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Population-based?</th>
<th># of patients</th>
<th># of patients on statins (%)</th>
<th>Criteria for labelling statin ‘user’</th>
<th>Initial treatment for kidney cancer</th>
<th>Survival outcomes evaluated</th>
<th>Follow-up</th>
<th>Covariates in multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee at al. 2012</td>
<td>Multinational</td>
<td>Secondary analysis of trial</td>
<td>No</td>
<td>416</td>
<td>25 (6.0)</td>
<td>Treatment with statin at baseline</td>
<td>IFN alpha-2a vs. temsirolimus vs. IFN+temsirolimus</td>
<td>†PFS, OS</td>
<td>Median 17.9 months (range 0.3 - 27.5)</td>
<td>Age, gender, geographic region, nephrectomy status, histology, time from metastasis to randomization, Karnofsky performance score, hemoglobin level, serum lactate dehydrogenase, corrected serum calcium</td>
</tr>
<tr>
<td>Neilson et al. 2012</td>
<td>Denmark</td>
<td>Cohort</td>
<td>Yes</td>
<td>5942</td>
<td>NS</td>
<td>Exposure to statin before cancer diagnosis</td>
<td>NS</td>
<td>CSS</td>
<td>NS</td>
<td>Age, gender, stage, treatment with chemotherapy, treatment with radiation, cardiovascular disease, diabetes, birth year, ethnic descent, highest obtained level of education, size of residential area</td>
</tr>
<tr>
<td>‡Choi et al. 2013</td>
<td>South Korea</td>
<td>Cohort</td>
<td>No</td>
<td>115</td>
<td>21 (18.3)</td>
<td>Exposure to statin before cancer diagnosis</td>
<td>Nephrectomy</td>
<td>RFS</td>
<td>NS</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Gayed et al. 2014</td>
<td>USA</td>
<td>Cohort</td>
<td>No</td>
<td>63</td>
<td>14 (22.2)</td>
<td>On statins at the time of analysis</td>
<td>NS</td>
<td>CSS</td>
<td>Median 22 months (range 1 - 107)</td>
<td>Motzer criteria (Karnofsky performance status, lactate dehydrogenase, haemoglobin, corrected calcium, and presence/absence of nephrectomy)</td>
</tr>
<tr>
<td>Hamilton et al. 2014</td>
<td>USA</td>
<td>Cohort</td>
<td>No</td>
<td>2608</td>
<td>708 (27.1)</td>
<td>Statin use at the time of surgery</td>
<td>Nephrectomy</td>
<td>PFS, OS</td>
<td>Median 3 years</td>
<td>Age, gender, race, surgical approach, Charlson comorbidity index, stage, preoperative glomerular filtration rate, symptoms, year of surgery</td>
</tr>
</tbody>
</table>

TABLES FOR CHAPTER 4

Table 4.1: Characteristics of included studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Type</th>
<th>No</th>
<th>Median Age (IQR)</th>
<th>Preoperative Use of Statin</th>
<th>Surgery Procedure</th>
<th>Follow-up Measure</th>
<th>Unadjusted CSS Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krane et al. 2014</td>
<td>USA</td>
<td>Cohort</td>
<td>339</td>
<td>104 (30.7)</td>
<td>NS</td>
<td>Nephrectomy</td>
<td>RFS</td>
<td>NS</td>
</tr>
<tr>
<td>Lee et al. 2014</td>
<td>USA</td>
<td>Cohort</td>
<td>155</td>
<td>92 (39.4)</td>
<td>NS</td>
<td>Nephrectomy</td>
<td>PFS, CSS, OS</td>
<td>Median 68 months (IQR 50 - 90) NS</td>
</tr>
<tr>
<td>Kaffenberger et al. 2015</td>
<td>USA</td>
<td>Cohort</td>
<td>*666</td>
<td></td>
<td>Statin use at the time of surgery</td>
<td>Nephrectomy</td>
<td>CSS, OS</td>
<td>Median 42.5 months (IQR 19.2 - 67.1) CSS: ASA score, stage, grade, corrected hypercalcemia, anemia, blood group OS: age, ASA score, grade, corrected hypercalcemia, anemia, blood group</td>
</tr>
<tr>
<td>Viers et al. 2015</td>
<td>USA</td>
<td>Cohort</td>
<td>2357</td>
<td>630 (26.7)</td>
<td>Statin use within 3 months before surgery</td>
<td>Nephrectomy</td>
<td>PFS, CSS, OS</td>
<td>Median 7.8 years (IQR 5.3 - 11.2) Age, gender, surgical approach, symptoms, smoking, ECOG performance status, Charlson comorbidity index, body mass index, tumor size, histology, stage, grade, tumor necrosis, sarcomatoid features</td>
</tr>
<tr>
<td>Haddad et al. 2015</td>
<td>USA</td>
<td>Cohort</td>
<td>850</td>
<td>342 (40.2)</td>
<td>On statins at the time of surgery or at any time during follow-up</td>
<td>Nephrectomy</td>
<td>RFS, OS</td>
<td>Median 25.0 months (IQR 7.8 - 52.3) RFS: age, gender, stage, grade, lymphovascular invasion, surgical approach, pre-operative creatinine OS: age, body mass index, ECOG performance status, stage, grade, lymphovascular invasion, surgical approach, pre-operative creatinine</td>
</tr>
<tr>
<td>McKay et al. 2016</td>
<td>Multinational</td>
<td>Secondary analysis of trials</td>
<td>3701</td>
<td>417 (11.3)</td>
<td>Receiving a statin at baseline</td>
<td>Targeted therapy</td>
<td>PFS, OS</td>
<td>NS</td>
</tr>
<tr>
<td>Nayan et al. 2016</td>
<td>Canada</td>
<td>Cohort</td>
<td>No</td>
<td>893</td>
<td>259 (29.0)</td>
<td>Active use of statins at the time of surgery</td>
<td>Nephrectomy</td>
<td>RFS, CSS, OS</td>
</tr>
<tr>
<td>------------------</td>
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</tr>
</tbody>
</table>

*Number of patients included in multivariable analysis
† Study included PFS as an outcome but did not provide a risk estimate
‡ Study included PFS as an outcome but did not define PFS and was therefore not included in the meta-analysis for PFS
α Adjusted for in propensity score

Abbreviations: ASA: American Society of Anesthesiologists; CSS: cancer-specific survival; ECOG: Eastern Cooperative Oncology Group; IQR: interquartile range; NS: not specified; OS: overall survival; PFS: progression-free survival; RFS: recurrence-free survival
## Table 4.2: Quality assessment of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Representativeness of the exposed cohort</th>
<th>Selection of the nonexposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Demonstration that outcome of interest was not present at start of study</th>
<th>Comparability of cohorts on the basis of the design or analysis</th>
<th>Assessment of outcome</th>
<th>Was follow-up long enough for outcomes to occur?</th>
<th>Adequacy of follow up of cohorts</th>
<th>Total number of stars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. 2012</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>8</td>
</tr>
<tr>
<td>Neilson et al. 2012</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
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<td>*</td>
<td>*</td>
<td>8</td>
</tr>
<tr>
<td>Choi et al. 2013</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
<td>*</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>†Gayed et al. 2014</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
<td>*</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Hamilton et al. 2014</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>8</td>
</tr>
<tr>
<td>Krane et al. 2014</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>8</td>
</tr>
<tr>
<td>†Lee et al. 2014</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>7</td>
</tr>
<tr>
<td>Kaffenberger et al. 2015</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>9</td>
</tr>
<tr>
<td>Viers et al. 2015</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>9</td>
</tr>
<tr>
<td>Haddad et al. 2015</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>8</td>
</tr>
<tr>
<td>McKay et al. 2016</td>
<td>*</td>
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<td>*</td>
<td>*</td>
<td>**</td>
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<td>*</td>
<td>8</td>
</tr>
<tr>
<td>Nayan et al. 2016</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>9</td>
</tr>
</tbody>
</table>

†Study only available in abstract form

Footnote: Each asterisk represents one star in the Newcastle-Ottawa Scale system. The maximum number of stars is 2 for comparability and 1 for each of the other categories, for a total of up to 9 stars.
CHAPTER 5: STATIN USE AND KIDNEY CANCER OUTCOMES: A POPULATION—BASED COHORT STUDY

SUMMARY

BACKGROUND: Several observational studies have shown that use of commonly prescribed medications is associated with improved survival in various malignancies. Methods of classifying medication use in many of these studies, however, do not account for intermittent or cumulative use. Moreover, there are limited data on the influence of these medications on kidney cancer survival.

METHODS: I performed a population-based cohort study utilizing multiple healthcare databases. I identified patients aged 65 or older with an incident diagnosis of kidney cancer between 1997 and 2013 and examined use of nine putative anti-neoplastic medications using prescription claims. Multivariable Cox proportional hazard models evaluated the association of medication exposure on cancer-specific and overall survival. I conducted three separate analyses: I modeled the effect of cumulative duration of exposure to the study medications on outcomes, the effect of current exposure (in a binary nature) and the effect of exposure at the time of diagnosis.

RESULTS: During the 16-year study period, I studied 9124 patients. Increasing cumulative use to angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors were associated with markedly improved cancer-specific survival; increasing exposure to NSAIDs was associated with markedly improved overall survival. These results were generally discordant with analyses evaluating the effect of current use and exposure at the time of diagnosis.
CONCLUSION: Pharmacoepidemiology studies may be sensitive to the method of analysis, and cumulative use analysis may be the most robust as it accounts for intermittent use and supports a dose-outcome relationship. Prospective studies are needed to confirm whether patients diagnosed with kidney cancer should be started on an angiotensin-converting enzyme inhibitor, NSAID, or selective serotonin reuptake inhibitor to improve survival.
INTRODUCTION

Several medications have recently gained interest in the oncology community for their putative anti-neoplastic effects, including angiotensin-converting enzyme inhibitors (ACEIs)(89, 90), angiotensin II receptor blockers (ARBs)(89, 90), acetylsalicylic acid (ASA)(91), non-steroidal anti-inflammatory drugs (NSAIDs)(94, 95), beta blockers(97, 98), calcium channel blockers (CCBs)(99), selective serotonin reuptake inhibitors (SSRIs)(100, 101), statins(50), and proton pump inhibitors (PPIs)(103). Randomized controlled trials are currently underway evaluating some of these medications as a stand-alone, or in combination therapy in the adjuvant or neo-adjuvant setting for various malignancies(169, 170). These medications are relatively inexpensive and generally well tolerated, and are therefore ideal candidates for chemoprevention.

However, concerns have been raised about the potential for bias in pharmacoepidemiology studies in chemoprevention, particularly related to the method of classifying medication exposure(70). Indeed, the majority of studies evaluating chemoprevention have not accounted for intermittent or cumulative use, including existing studies in kidney cancer(82-84, 123, 153, 156, 171-177). Therefore, the objectives of this study were two-fold: a) to evaluate the association between use of commonly-prescribed medications with potential anti-neoplastic effects and survival in patients with incident kidney cancer; and b) to compare different methods of classifying exposure to better understand the biases that may arise from pharmacoepidemiology studies.
METHODS

SETTING

I conducted a population-based retrospective cohort study of Ontarians aged 65 or older newly diagnosed with kidney cancer. This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

DATA SOURCES

I used the Ontario Cancer Registry (OCR) to identify patients with incident kidney cancer (ICD-9: 189.0; ICD-10: C64). I identified medication use through prescription claims of the Ontario Drug Benefit database, which contains comprehensive records of prescription drugs dispensed to all Ontario residents aged 65 or older. I obtained hospitalization data from the Canadian Institute for Health Information Discharge Abstract Database, which contains detailed clinical information regarding all hospital admissions in Ontario. I used the Ontario Health Insurance Plan database to identify claims for physician services, and obtained basic demographic data and date of death from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance. These databases were linked in an anonymous fashion using encoded health card numbers. Details regarding all databases used and their validity have been provided in Chapter 2.

STUDY PARTICIPANTS

I accrued patients from April 1st, 1997 until December 31st, 2013, following them until December 31st, 2011 (for cancer-specific mortality) and December 31st, 2014 (for all-cause
mortality). These dates were based on the most recent update of the database used for each outcome. All subjects had universal access to physician services, hospital care and prescription drug coverage.

I deemed study subjects to have localized disease at presentation if they underwent surgery, radiofrequency ablation or cryotherapy as the first treatment following diagnosis of kidney cancer. Other subjects were deemed to have advanced disease if they received immune- or targeted therapy, or no intervention as their first treatment following diagnosis of kidney cancer. This classification is consistent with other studies conducted in Ontario(139, 178, 179).

Patients were excluded if they had a diagnosis of any malignancy (excluding non-melanoma skin cancers) prior to their kidney cancer diagnosis. This was done to exclude patients who may have worse outcomes due to their pre-existing malignancy, rather than being an effect of kidney cancer or of putative anti-neoplastic medications. I also excluded patients whose histology indicated a primary malignancy other than kidney cancer.

EXPOSURE ASSESSMENT

I quantified medication exposure from the diagnosis of kidney cancer to the end of follow-up using prescription dates and the number of days supplied in each, as done previously(139). This allowed for the calculation of the duration of cumulative exposure for each day of follow-up, as well as accounting for periods of intermittent use.
OUTCOME ASSESSMENT

The primary outcome was cancer-specific survival and the secondary outcome was overall survival. For each outcome, patients were followed until their date of last contact with health services, death or the end of the study period, whichever occurred first.

STATISTICAL METHODS

I conducted time-to-event analyses using multivariable Cox proportional hazard regression to estimate the effect of drug exposure on the risk of the primary and secondary outcomes. For cancer-specific survival, I estimated the cause-specific hazard since the focus of my study was to determine whether the use of statins was directly associated with cancer-specific mortality. This method of analysis is considered more applicable for studying the etiology of events, rather than the subdistribution hazard accounting for competing risks which may be more applicable for predicting resource allocation and policy decisions(180).

Covariates in the model were selected a priori and included age at kidney cancer diagnosis, sex, comorbidity (defined by the Johns Hopkins ACG score(125)), year of kidney cancer diagnosis (to account for temporal changes in exposures and outcomes), disease stage (localized vs. advanced), socioeconomic status, rurality, and exposure to each medication after kidney cancer diagnosis.

I evaluated the association between medication exposure and outcomes in three ways. First, I examined cumulative medication use as a continuous time varying covariate. Second, I studied medication use as a binary time varying covariate denoting whether or not the subject was currently receiving the medication of interest. The first two models account for intermittent
use; however, they evaluate different hypotheses. The cumulative use analysis evaluates whether increasing past use is associated with survival. In contrast, the current use analysis examines whether current or active use of a medication, as a binary variable, is associated with survival. Finally, while comprehensive prescription data allowed me to perform the first two analyses, such analyses are often not feasible in institutional data. Therefore, the third method of analysis, used by many observational studies in pharmacoepidemiology, considered use vs. non-use at the time of diagnosis and was performed to evaluate whether results were consistent with methods accounting for intermittent use.

For the analysis of cumulative use, I used the multivariable fractional polynomial algorithm to determine the functional form that best described the relationship between cumulative duration of exposure to each medication and the hazard of mortality. Since each day of incremental use is clinically insignificant, hazard ratios (HR) in this analysis are presented in increments per 6 months of use. The midpoint of each increment was compared to no use (0 months) to estimate the corresponding hazard ratio.

All statistical analyses were performed using SAS (version 9.3; SAS Institute, Cary, NC) and used a two-sided p value of 0.05 as the threshold for statistical significance.

SENSITIVITY ANALYSES

To ensure that the results from the cumulative use analyses were robust, several sensitivity analyses were planned a priori: 1) To minimize healthy user bias, whereby those who are more compliant with prescribed medications are those who are more likely to seek health care services, estimates were adjusted for the number of colonoscopies, fecal-occult blood tests,
and periodic oculo-visual assessments in the first 5 years following kidney cancer diagnosis; 2) To minimize confounding by indication, estimates were adjusted for comorbid conditions prior to kidney cancer diagnosis including history of hypertension, congestive heart failure, myocardial infarction, end stage renal disease, and stroke; and lastly, 3) To evaluate the impact of medication exposure prior to kidney cancer diagnosis, estimates were adjusted for cumulative exposure of medications from age 65 to kidney cancer diagnosis.
RESULTS

COHORT CHARACTERISTICS

Over the 16-year study period, I identified 9518 patients aged 65 or older with incident kidney cancer. Of these, 9214 patients met the inclusion criteria (Figure 5.1). Their characteristics are described in Table 5.1. During follow-up, 5022 patients died, including 2106 who died from kidney cancer. Medication use following kidney cancer diagnosis is shown in Table 5.2.

KIDNEY CANCER-SPECIFIC SURVIVAL

After applying the multivariable fractional polynomial algorithm, all medications were included in the final model evaluating cancer-specific survival. Cumulative use of ACEIs, beta-blockers, and ASA had a linear relationship with the log-hazard of the outcome, while non-identity transformations were required for the best functional form for the remaining medications (Figure 5.2 and Table 5.3). Due to the linear relationship of these medications, each 6 month increase of use of ACEIs was associated with a 3% (HR 0.97, 95% CI 0.96 to 0.99) significantly reduced risk of cancer-specific mortality, while each 6 month increase in use of beta-blockers (HR 0.99, 95% CI 0.98 to 1.00) or ASA (HR 0.99, 95% CI 0.97 to 1.01) were not significantly associated with risk of cancer-specific mortality. Compared to no use, the first 6 months of exposure to ARBs and statins were associated with a slight increased risk of cancer-specific mortality (Table 5.4). Conversely, the same durations of exposure to NSAIDs and SSRIs were associated with significantly improved cancer-specific survival. Compared to no use, exposure of 36 – 42 months of ACEIs (HR 0.84, 95% CI 0.72 to 0.98), NSAIDs (HR 0.52, 95% CI 0.33 to 0.82), and SSRIs (HR 0.38, 95% CI 0.24 to 0.62) were associated with markedly reduced risk of
cancer-specific mortality, while ARBs, statins, and PPIs were associated with a modest reduced risk of cancer-specific mortality.

In the current-use analyses, current use of ASA and NSAIDs were associated with significantly worse cancer-specific survival, while current use of ARBs, CCBs, and statins were associated with improved cancer-specific survival (Table 5.4).

In evaluating the association between use at the time of diagnosis and cancer-specific survival, only ARBs and CCBs were associated with significantly improved survival (Table 5.4).

ALL-CAUSE MORTALITY

After applying the multivariable fractional polynomial algorithm, ACEIs, ASA, and CCBs were excluded from the final model evaluating overall survival. For no medication did cumulative duration of use follow a linear relationship with the log-hazard of overall survival and transformations were required for all medications (Figure 5.3 and Table 5.3). Compared to no use, only exposure to NSAIDs for the first 6 months conferred a significant survival advantage (Table 5.5). The benefits of NSAIDs exposure increased over time, with a 30% (HR 0.70, 95% CI 0.58 to 0.83) improvement in overall survival after 36 – 42 months of use. Compared to no use, exposure of 36 – 42 months of ARBs, statins, or PPIs were associated with a modest improvement in overall survival, while beta-blockers were associated with a modestly reduced overall survival.

In the current-use analyses, ARBs, beta-blockers, NSAIDs, and statins were associated with significantly improved overall survival (Table 5.5).
Finally, use of beta-blockers, NSAIDs, and SSRIs at the time of diagnosis were associated with significantly worse overall survival (Table 5.5).

SENSITIVITY ANALYSES

The associations between cumulative use of medications and survival outcomes were consistent in all sensitivity analyses, particularly the protective association of ACEIs, NSAIDs, and SSRIs on cancer-specific survival and NSAIDs on overall survival (Tables 5.6, 5.7, and 5.8).
DISCUSSION

This population-based cohort study evaluating nine putative anti-neoplastic medications in 9124 patients with incident kidney cancer found that the associations between medication exposure and survival outcomes were dependent on the method of exposure classification. These findings have important implications for kidney cancer therapy and research in pharmacoepidemiology.

Comprehensive data on medication prescriptions are difficult to obtain outside of administrative data where the population is eligible for drug coverage. As such, the majority of studies evaluating chemoprevention in cancer have classified exposure in a dichotomous manner (use vs. non-use over a given period in time)(50, 89-91, 94, 95, 97-101, 103), including studies in kidney cancer(83, 84, 123, 153, 156, 171-177, 181). This method of classifying exposure is prone to several biases, which limit the interpretation of the results from such studies. First, there is the potential for misclassification bias if patients classified as users subsequently discontinue therapy or vice-versa. This is particularly relevant when considering putative anti-neoplastic medications in the prospective setting. For example, a recent study evaluated the use statins in patients with kidney cancer and defined medication exposure as use at the time of surgery(83). This study found that statin use was associated with significantly improved disease-free survival and overall survival, and the authors suggested that statins be evaluated prospectively in kidney cancer. However, it is unknown how many patients continued statins after surgery; if many discontinued, the survival benefit observed in this study in the ‘user’ group may reflect other explanations. Second, though not applicable in my method of classifying use vs. non-use at diagnosis, there is the potential for immortal-time bias if patients who begin medication after a certain amount of survival time are considered as users(70). Indeed, a recent systematic review
and meta-analysis evaluating beta-blockers and cancer survival found that when including all studies, beta-blocker use was associated with significantly improved overall and cancer-specific survival (134). However, when excluding studies at high or unclear risk of immortal-time bias, the association between beta-blocker use was extinguished for overall survival, and approached the null for cancer-specific survival. Finally, there is the potential for selection bias with the simple comparison of users vs. non-users as these groups may differ with regard to their prognosis at baseline.

Cumulative use and current-use analyses, on the other hand, mitigate these biases as they account for intermittent use. Indeed, it has been previously shown that analyses taking into account intermittent use do not correspond with results that compare use vs. non-use during a specific period of time (84, 182). Furthermore, selection bias is offset as the same patient can contribute survival time to different exposure levels in the cumulative use analysis and to both the exposed and unexposed group in the current-use analysis, depending on the dates and durations of prescriptions. Finally, the results from these analyses are more applicable to the clinical setting as only post-diagnostic use was evaluated, lending support for initiating a putative anti-neoplastic agent in patients with incident kidney cancer, rather than relying on prior exposure history.

The results from the current and cumulative use analyses did not consistently suggest an association in the same direction. For example, NSAIDs were associated with a significantly increased risk of cancer-specific mortality in the current-use analysis while the cumulative use analyses suggested that increasing use of NSAIDs conferred a survival advantage. This situation can arise if patients die while taking an NSAID, regardless of duration of exposure, while those with longer exposure have longer survival (Figure 5.4). Conversely, statins demonstrated a
markedly protective association on cancer-specific survival in the current-use analysis, but a
limited association in the cumulative use analysis. This situation can arise from a methodological
perspective if patients with varying durations of statin exposure tended to die after the end of
their prescription (Figure 5.4). From a biological perspective, this may occur if the putative anti-
neoplastic effects may be limited to the duration that the medication is present in the circulation.
This is consistent with the observed effects upon the discontinuation of tyrosine kinase
inhibitors, such as sunitinib (half-life 40 – 60 hours) or pazopanib (half-life 31 hours), which
results in accelerated tumour growth and tumour flare in kidney cancer patients(183).

While the current-use analysis is more robust than a simple comparison of users vs. non-
users, I propose that cumulative use analyses are the most appropriate as they allow for an
evaluation of a dose-response relationship, supporting causality for chemoprevention(88).
Results from this study suggest that ACEIs and SSRIs are potential candidates to improve
cancer-specific survival, while NSAIDs may improve both cancer-specific and overall survival.
These results were consistent in several sensitivity analyses. Laboratory studies have
demonstrated efficacy of ACEIs and NSAIDs in kidney cancer(184-186), while further research
is needed for SSRIs, as has been done in other urological malignancies(187, 188).

Given that health care is publicly administered in Ontario, this study has several
strengths. First, selection bias is minimized compared to institutional cohorts. Second, the
availability of comprehensive prescription data allows for more robust analyses evaluating
medication exposure. Third, the majority of studies in cancer chemoprevention have evaluated a
single medication or medication class. In contrast, I evaluated multiple medications
simultaneously, allowing me to determine the independent association of each medication with
survival outcomes. Furthermore, I performed several sensitivity analyses to ensure the robustness

124
of the results. Finally, the results of this study are generalizable to patients aged 65 or older with an incident diagnosis of kidney cancer. While randomized controlled trials provide the highest level of evidence, patients included in randomized controlled trials tend to be younger and healthier and may not be representative of all patients with kidney cancer.

This study also has several limitations. First, various factors govern whether or not patients will be exposed to putative anti-neoplastic medications (such as physician preference) or experience all-cause or cancer-specific mortality (such as tumour characteristics) that were not available in this study. However, these are unlikely to represent true confounders because they are not associated with both exposure and outcome. As such, controlling for these factors will not improve the estimation of the exposure-outcome relationship; rather, it would reduce statistical precision. Furthermore, many studies have shown that tumour stage was not significantly different in users vs. non-users of some of the putative anti-neoplastic studies evaluated(83, 84, 156, 177). Second, since the dates of prescriptions and the days supplied field were used as a surrogate for medication exposure, the actual exposure may not correspond to the estimated exposure if patients are non-compliant with their medication prescriptions. However, patients that consistently renew their prescriptions are likely compliant; indeed, both the continuous cumulative use and binary time varying analyses account for the lapses between prescriptions. Third, I could not account for medication exposure prior to age 65 because these data are incomplete. However, it has previously been shown that exposure to putative anti-neoplastic medications prior to cancer diagnosis was not associated with survival outcomes(131, 132). Fourth, secondary data with imperfect sensitivity and specificity were used for the study. However, several of the databases have been validated(139). Fifth, as mentioned previously, many NSAIDs are available without prescription and it is possible that some exposure was not
captured due to this. However, considering that patients would not have to pay the full cost for medication had they obtained it by prescription, it is unlikely that over the counter exposure would bias the results to a strong degree. Furthermore, although NSAIDs can be available over the counter, it has been demonstrated that using administrative data for exposure such drugs is a reasonable estimate of actual exposure(135). Finally, it may be possible that the patients with more prescriptions are the healthy-users that are more likely to be compliant with follow-up and subsequent treatment for kidney cancer, resulting in increased survival. However, I attempted to address this potential healthy-user bias by using a method of analysis in which the same user can be compared to themselves with varying durations of exposure, as well as several sensitivity analyses which demonstrated consistent results. Despite these limitations, this is the first study to simultaneously evaluate multiple putative anti-neoplastic medications in patients with kidney cancer and suggests that ACEIs, NSAIDs, and SSRIs may have a role in kidney cancer therapy.
CONCLUSION

This study evaluating the association of putative anti-neoplastic medications on survival outcomes in patients with kidney cancer found that the results were dependent on the method of classifying medication exposure. I propose that cumulative use analyses are the most robust and future studies in chemoprevention should utilize this method. The results from cumulative use analyses in this study suggest that angiotensin converting enzyme inhibitors, selective serotonin reuptake inhibitors, and non-steroidal anti-inflammatory drugs may have a role in improving survival outcomes in patients with kidney cancer.
FIGURES FOR CHAPTER 5
Figure 5.1: Cohort derivation

Patients with incident kidney cancer aged ≥65
n = 9518

394 excluded
• Histology inconsistent with a primary renal malignancy (n = 348)
• Missing data for SES (n = 45)
• Missing follow-up data (n = 1)

Patients included in the survival analysis
n = 9124

Abbreviations: SES: socioeconomic status
Figure 5.2: Relationship between cumulative exposure to medications after kidney cancer diagnosis and cancer-specific survival.
Figure 5.3: Relationship between cumulative exposure to medications after kidney cancer diagnosis and overall survival.
Figure 5.4: Comparing continuous cumulative use and binary time varying analyses.

A)

B)

Red star indicates death, blue star indicates censored, yellow bar indicated time on medication, and black bar indicated time off medication.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Survival time</th>
<th>Death</th>
<th>Example A Cumulative use</th>
<th>Example B Cumulative use</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1</td>
<td>No</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>Yes</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>5</td>
<td>No</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>D</td>
<td>8</td>
<td>Yes</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>E</td>
<td>10</td>
<td>Yes</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>
In example A, all deaths occurred while on medication. In this context, the binary time varying analysis denoting current exposure would show a detrimental effect of medication use on survival. However, among all patients, those that survived longer had increasing cumulative use of medication and therefore the cumulative use analysis would demonstrate a protective effect. In the same figure, if blue stars are interchanged with red stars then the binary time varying analysis would show a protective effect of medication and results from the cumulative use analysis would be unchanged.

In example B, all deaths occurred while off medication. In this context, the binary time varying analysis denoting current exposure would show a protective effect of medication use on survival. However, among all patients with statin use, cumulative use was equivalent despite varying survival times and therefore the cumulative use analysis would show no effect of medication use on survival. In the same figure, if blue stars are interchanged with red stars then the binary time varying analysis would show a detrimental effect of medication and results from the cumulative use analysis would be unchanged.
TABLES FOR CHAPTER 5

Table 5.1: Cohort characteristics of 9124 patients aged 65 or older with incident kidney cancer.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at kidney cancer diagnosis</td>
<td></td>
</tr>
<tr>
<td>65 - 66</td>
<td>1076 (11.8)</td>
</tr>
<tr>
<td>67 – 68</td>
<td>1051 (11.5)</td>
</tr>
<tr>
<td>69 – 70</td>
<td>990 (10.8)</td>
</tr>
<tr>
<td>71 – 72</td>
<td>1016 (11.1)</td>
</tr>
<tr>
<td>73 – 74</td>
<td>935 (10.2)</td>
</tr>
<tr>
<td>75 – 76</td>
<td>862 (9.4)</td>
</tr>
<tr>
<td>77 – 78</td>
<td>809 (8.9)</td>
</tr>
<tr>
<td>79 – 80</td>
<td>645 (7.1)</td>
</tr>
<tr>
<td>81 – 82</td>
<td>508 (5.6)</td>
</tr>
<tr>
<td>83 – 84</td>
<td>441 (4.8)</td>
</tr>
<tr>
<td>85+</td>
<td>791 (8.7)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3768 (41.3)</td>
</tr>
<tr>
<td>Male</td>
<td>5356 (58.7)</td>
</tr>
<tr>
<td>*Comorbidity score</td>
<td></td>
</tr>
<tr>
<td>0 – 4</td>
<td>231 (2.5)</td>
</tr>
<tr>
<td>5 – 9</td>
<td>1644 (18.0)</td>
</tr>
<tr>
<td>10 – 14</td>
<td>4188 (45.9)</td>
</tr>
<tr>
<td>15 – 19</td>
<td>2704 (29.6)</td>
</tr>
<tr>
<td>20+</td>
<td>357 (3.9)</td>
</tr>
<tr>
<td>Rural residence</td>
<td>1331 (14.6)</td>
</tr>
<tr>
<td>†Socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>Income quintile 1 (lowest)</td>
<td>1801 (19.7)</td>
</tr>
<tr>
<td>Income quintile 2</td>
<td>1918 (21.0)</td>
</tr>
<tr>
<td>Income quintile 3</td>
<td>1805 (19.8)</td>
</tr>
<tr>
<td>Income quintile 4</td>
<td>1820 (20.0)</td>
</tr>
<tr>
<td>Income quintile 5 (highest)</td>
<td>1780 (19.5)</td>
</tr>
<tr>
<td>Year of kidney cancer diagnosis</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>434 (4.8)</td>
</tr>
<tr>
<td>1998</td>
<td>440 (4.8)</td>
</tr>
<tr>
<td>1999</td>
<td>437 (4.8)</td>
</tr>
<tr>
<td>2000</td>
<td>497 (5.4)</td>
</tr>
<tr>
<td>2001</td>
<td>464 (5.1)</td>
</tr>
<tr>
<td>2002</td>
<td>451 (4.9)</td>
</tr>
<tr>
<td>2003</td>
<td>465 (5.1)</td>
</tr>
<tr>
<td>Year</td>
<td>Value</td>
</tr>
<tr>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td>2004</td>
<td>490 (5.4)</td>
</tr>
<tr>
<td>2005</td>
<td>571 (6.3)</td>
</tr>
<tr>
<td>2006</td>
<td>592 (6.5)</td>
</tr>
<tr>
<td>2007</td>
<td>627 (6.9)</td>
</tr>
<tr>
<td>2008</td>
<td>667 (7.3)</td>
</tr>
<tr>
<td>2009</td>
<td>599 (6.6)</td>
</tr>
<tr>
<td>2010</td>
<td>581 (6.4)</td>
</tr>
<tr>
<td>2011</td>
<td>562 (6.2)</td>
</tr>
<tr>
<td>2012</td>
<td>584 (6.4)</td>
</tr>
<tr>
<td>2013</td>
<td>663 (7.3)</td>
</tr>
</tbody>
</table>

**Primary treatment**

- Surgery, cryotherapy, or radiofrequency ablation: 6241 (68.4)
- No primary treatment, immunotherapy, or targeted therapy: 2883 (31.6)

**Kidney cancer-specific death**: 2106 (27.2)

**Overall mortality**: 5022 (55.0)

*Comorbidity scores were calculated by using Johns Hopkins Adjusted Clinical Groups Case-Mix System assigning a specific weight to each adjusted diagnostic group (low, weighted adjusted diagnostic group score 5 or lower; intermediate, 6-9; high, 10 or higher).

†Income quintiles from median income in neighborhoods from 1 (low) to 5 (high).
Table 5.2: Medication exposure following kidney cancer diagnosis.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patients with any exposure (n (%))</th>
<th>Cumulative exposure in months of patients with any exposure (median (IQR))</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>4621 (50.6)</td>
<td>23.0 (6.6 – 57.4)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>2150 (23.6)</td>
<td>29.6 (8.9 – 60.5)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>1368 (15.0)</td>
<td>9.9 (3.3 – 35.8)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>4295 (47.1)</td>
<td>26.0 (6.9 – 61.1)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>4615 (50.6)</td>
<td>28.9 (9.1 – 65.1)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>3312 (36.3)</td>
<td>2.1 (1.0 – 7.8)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>1996 (21.9)</td>
<td>12.5 (3.0 – 37.4)</td>
</tr>
<tr>
<td>Statins</td>
<td>5025 (55.1)</td>
<td>36.1 (13.3 – 72.3)</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>4651 (51.0)</td>
<td>14.0 (3.1 – 43.5)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; ACE, angiotensin converting enzyme; NSAIDs, non-steroidal anti-inflammatory drug
Table 5.3: Transformations applied through the use of the multi-variable fractional polynomial algorithm.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cancer-specific mortality (transformation (power(s)))</th>
<th>All-cause mortality (transformation (power(s)))</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Linear</td>
<td>Excluded</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>FP1 (0)</td>
<td>FP1 (0)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>Linear</td>
<td>Excluded</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Linear</td>
<td>FP1 (0)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>FP1 (0.5)</td>
<td>Excluded</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>FP2 (0, 1)</td>
<td>FP2 (-2, -0.5)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>FP2 (0, 0.5)</td>
<td>FP1 (-2)</td>
</tr>
<tr>
<td>Statins</td>
<td>FP1 (0)</td>
<td>FP1 (0)</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>FP2 (-0.5, 0)</td>
<td>FP2 (-0.5, 0)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE: angiotensin converting enzyme; FP: fractional polynomial; NSAIDs: non-steroidal anti-inflammatory drugs
Table 5.4: The association between medication exposure and kidney cancer-specific survival by method of analysis.

<table>
<thead>
<tr>
<th></th>
<th>Use vs. non-use at diagnosis (HR (95% CI))</th>
<th>Active use (HR (95% CI))</th>
<th>0 – 6 months</th>
<th>6 – 12 months</th>
<th>12 – 18 months</th>
<th>18 – 24 months</th>
<th>24 – 30 months</th>
<th>30 – 36 months</th>
<th>36 – 42 months</th>
<th>42 – 48 months</th>
<th>48 – 54 months</th>
<th>54 – 60 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td>0.98 (0.88 to 1.08)</td>
<td></td>
<td>1.02 (0.89 to 1.16)</td>
<td>0.99 (0.94 to 1.00)</td>
<td>0.96 (0.88 to 0.99)</td>
<td>0.94 (0.84 to 0.99)</td>
<td>0.91 (0.80 to 0.99)</td>
<td>0.89 (0.76 to 0.98)</td>
<td>0.86 (0.72 to 0.98)</td>
<td>0.84 (0.72 to 0.97)</td>
<td>0.80 (0.65 to 0.97)</td>
<td>0.77 (0.62 to 0.97)</td>
</tr>
<tr>
<td><strong>Angiotensin II receptor blockers</strong></td>
<td>0.82 (0.68 to 0.99)</td>
<td></td>
<td>0.67 (0.53 to 0.86)</td>
<td>1.01 (1.01 to 1.02)</td>
<td>0.99 (0.99 to 1.00)</td>
<td>0.98 (0.97 to 0.99)</td>
<td>0.97 (0.96 to 0.98)</td>
<td>0.97 (0.95 to 0.98)</td>
<td>0.96 (0.95 to 0.98)</td>
<td>0.96 (0.94 to 0.98)</td>
<td>0.96 (0.94 to 0.98)</td>
<td>0.96 (0.94 to 0.98)</td>
</tr>
<tr>
<td><strong>Acetylsalicylic acid</strong></td>
<td>0.93 (0.79 to 1.10)</td>
<td></td>
<td>1.50 (1.19 to 1.90)</td>
<td>0.99 (0.97 to 1.02)</td>
<td>0.98 (0.87 to 1.06)</td>
<td>0.97 (0.82 to 1.12)</td>
<td>0.96 (0.77 to 1.19)</td>
<td>0.93 (0.73 to 1.23)</td>
<td>0.92 (0.69 to 1.27)</td>
<td>0.91 (0.65 to 1.31)</td>
<td>0.88 (0.58 to 1.35)</td>
<td>0.88 (0.58 to 1.35)</td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
<td>0.93 (0.84 to 1.03)</td>
<td></td>
<td>1.02 (0.90 to 1.16)</td>
<td>1.00 (0.95 to 1.02)</td>
<td>0.98 (0.92 to 1.04)</td>
<td>0.97 (0.86 to 1.08)</td>
<td>0.95 (0.84 to 1.10)</td>
<td>0.94 (0.81 to 1.11)</td>
<td>0.93 (0.78 to 1.13)</td>
<td>0.92 (0.76 to 1.13)</td>
<td>0.92 (0.73 to 1.14)</td>
<td>0.92 (0.73 to 1.14)</td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>0.86 (0.77 to 0.96)</td>
<td></td>
<td>0.87 (0.77 to 0.99)</td>
<td>0.96 (0.92 to 1.01)</td>
<td>0.93 (0.86 to 1.00)</td>
<td>0.91 (0.79 to 1.01)</td>
<td>0.89 (0.75 to 1.01)</td>
<td>0.87 (0.73 to 1.01)</td>
<td>0.86 (0.71 to 1.01)</td>
<td>0.84 (0.68 to 1.01)</td>
<td>0.83 (0.68 to 1.01)</td>
<td>0.83 (0.68 to 1.01)</td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>1.16 (1.00 to 1.36)</td>
<td></td>
<td>1.83 (1.48 to 2.25)</td>
<td>0.94 (0.90 to 0.97)</td>
<td>0.86 (0.77 to 0.95)</td>
<td>0.78 (0.66 to 0.90)</td>
<td>0.71 (0.47 to 0.81)</td>
<td>0.58 (0.39 to 0.84)</td>
<td>0.52 (0.33 to 0.79)</td>
<td>0.47 (0.28 to 0.74)</td>
<td>0.42 (0.20 to 0.74)</td>
<td>0.38 (0.20 to 0.74)</td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td>1.14 (0.95 to 1.36)</td>
<td></td>
<td>0.96 (0.81 to 1.14)</td>
<td>0.73 (0.63 to 0.85)</td>
<td>0.62 (0.49 to 0.79)</td>
<td>0.56 (0.40 to 0.71)</td>
<td>0.49 (0.34 to 0.67)</td>
<td>0.45 (0.26 to 0.65)</td>
<td>0.41 (0.24 to 0.62)</td>
<td>0.36 (0.21 to 0.58)</td>
<td>0.33 (0.19 to 0.58)</td>
<td>0.31 (0.17 to 0.57)</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td>0.89 (0.80 to 1.00)</td>
<td></td>
<td>0.62 (0.54 to 0.72)</td>
<td>1.01 (1.01 to 1.01)</td>
<td>0.99 (0.99 to 1.00)</td>
<td>0.99 (0.98 to 0.99)</td>
<td>0.98 (0.97 to 0.99)</td>
<td>0.98 (0.97 to 0.99)</td>
<td>0.98 (0.96 to 0.98)</td>
<td>0.97 (0.96 to 0.98)</td>
<td>0.97 (0.96 to 0.98)</td>
<td>0.97 (0.96 to 0.98)</td>
</tr>
<tr>
<td><strong>Proton-pump inhibitors</strong></td>
<td>1.01 (0.89 to 1.16)</td>
<td></td>
<td>1.10 (0.98 to 1.23)</td>
<td>1.01 (0.96 to 1.02)</td>
<td>0.97 (0.95 to 0.98)</td>
<td>0.93 (0.92 to 0.97)</td>
<td>0.92 (0.87 to 0.96)</td>
<td>0.91 (0.86 to 0.95)</td>
<td>0.90 (0.85 to 0.95)</td>
<td>0.89 (0.84 to 0.94)</td>
<td>0.89 (0.84 to 0.94)</td>
<td>0.89 (0.84 to 0.94)</td>
</tr>
</tbody>
</table>

For cumulative use analyses, the hazard ratio was obtained by comparing the midpoint of each increment to no use (0 months)

Adjusted for age, sex, comorbidity score, disease stage, socioeconomic status, rurality, and year of diagnosis
Table 5.5: The association between medication exposure and overall survival by method of analysis.

<table>
<thead>
<tr>
<th></th>
<th>Use vs. non-use at diagnosis (HR (95% CI))</th>
<th>Active use (HR (95% CI))</th>
<th>Cumulative use (HR (95% CI))</th>
<th>0 – 6 months</th>
<th>6 – 12 months</th>
<th>12 – 18 months</th>
<th>18 – 24 months</th>
<th>24 – 30 months</th>
<th>30 – 36 months</th>
<th>36 – 42 months</th>
<th>42 – 48 months</th>
<th>48 – 54 months</th>
<th>54 – 60 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>0.91 (0.82 to 1.01)</td>
<td>0.42 (0.37 to 0.48)</td>
<td>1.01 (1.00 to 1.01)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>0.99 (0.99 to 1.00)</td>
<td>0.99 (0.99 to 1.00)</td>
<td>0.99 (0.98 to 0.99)</td>
<td>0.99 (0.98 to 0.99)</td>
<td>0.99 (0.98 to 0.99)</td>
<td>0.98 (0.98 to 0.99)</td>
<td>0.98 (0.98 to 0.99)</td>
<td>0.98 (0.98 to 0.99)</td>
<td>0.98 (0.98 to 0.99)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>1.10 (1.03 to 1.18)</td>
<td>0.75 (0.70 to 0.81)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.01 (1.01 to 1.01)</td>
<td>1.01 (1.01 to 1.01)</td>
<td>1.01 (1.01 to 1.02)</td>
<td>1.01 (1.01 to 1.02)</td>
<td>1.01 (1.01 to 1.02)</td>
<td>1.01 (1.01 to 1.02)</td>
<td>1.02 (1.01 to 1.02)</td>
<td>1.02 (1.01 to 1.02)</td>
<td>1.02 (1.01 to 1.02)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1.20 (1.08 to 1.33)</td>
<td>0.72 (0.63 to 0.84)</td>
<td>0.90 (0.86 to 0.95)</td>
<td>0.84 (0.77 to 0.92)</td>
<td>0.80 (0.71 to 0.89)</td>
<td>0.77 (0.67 to 0.88)</td>
<td>0.74 (0.64 to 0.86)</td>
<td>0.72 (0.61 to 0.85)</td>
<td>0.70 (0.56 to 0.82)</td>
<td>0.68 (0.54 to 0.81)</td>
<td>0.66 (0.52 to 0.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>1.27 (1.14 to 1.43)</td>
<td>0.98 (0.89 to 1.08)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>1.00 (1.00 to 1.00)</td>
</tr>
<tr>
<td>Statins</td>
<td>0.97 (0.91 to 1.04)</td>
<td>0.41 (0.38 to 0.44)</td>
<td>1.01 (1.00 to 1.01)</td>
<td>1.00 (1.00 to 1.00)</td>
<td>0.99 (0.99 to 0.99)</td>
<td>0.99 (0.99 to 0.99)</td>
<td>0.99 (0.98 to 0.99)</td>
<td>0.99 (0.98 to 0.99)</td>
<td>0.98 (0.98 to 0.99)</td>
<td>0.98 (0.98 to 0.99)</td>
<td>0.98 (0.98 to 0.99)</td>
<td>0.98 (0.98 to 0.99)</td>
<td>0.98 (0.98 to 0.99)</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>1.05 (0.96 to 1.14)</td>
<td>1.06 (0.99 to 1.13)</td>
<td>1.00 (1.00 to 1.01)</td>
<td>0.98 (0.96 to 0.99)</td>
<td>0.97 (0.95 to 0.99)</td>
<td>0.97 (0.94 to 0.98)</td>
<td>0.96 (0.93 to 0.98)</td>
<td>0.96 (0.93 to 0.98)</td>
<td>0.95 (0.93 to 0.98)</td>
<td>0.95 (0.93 to 0.98)</td>
<td>0.95 (0.93 to 0.98)</td>
<td>0.95 (0.93 to 0.98)</td>
<td>0.95 (0.92 to 0.98)</td>
</tr>
</tbody>
</table>

For cumulative use analyses, the hazard ratio was obtained by comparing the midpoint of each increment to no use (0 months).

Adjusted for age, sex, comorbidity score, disease stage, socioeconomic status, rurality, and year of diagnosis.
Table 5.6: The association between cumulative medication exposure and survival, adjusted for screening tests.

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>Cumulative use (HR (95% CI))</th>
<th>CANCER-SPECIFIC SURVIVAL</th>
<th>OVERALL SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 – 6 months</td>
<td>6 – 12 months</td>
<td>12 – 18 months</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>0.98 (0.97 to 1.00)</td>
<td>0.96 (0.92 to 0.99)</td>
<td>0.93 (0.87 to 0.98)</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>1.01 (1.01 to 1.02)</td>
<td>0.99 (0.99 to 1.00)</td>
<td>0.98 (0.98 to 0.99)</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>0.99 (0.97 to 1.01)</td>
<td>0.97 (0.91 to 1.04)</td>
<td>0.95 (0.85 to 1.07)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>0.99 (0.98 to 1.00)</td>
<td>0.98 (0.94 to 1.01)</td>
<td>0.96 (0.91 to 1.02)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>0.96 (0.91 to 1.00)</td>
<td>0.93 (0.86 to 1.00)</td>
<td>0.90 (0.82 to 1.00)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0.94 (0.90 to 0.97)</td>
<td>0.85 (0.77 to 0.95)</td>
<td>0.77 (0.65 to 0.92)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>0.77 (0.66 to 0.89)</td>
<td>0.67 (0.52 to 0.85)</td>
<td>0.60 (0.44 to 0.82)</td>
</tr>
<tr>
<td>Statins</td>
<td>1.01 (1.00 to 1.01)</td>
<td>0.99 (1.00 to 1.01)</td>
<td>0.98 (0.99 to 0.99)</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>1.01 (1.00 to 1.02)</td>
<td>0.96 (0.94 to 0.99)</td>
<td>0.95 (0.92 to 0.98)</td>
</tr>
</tbody>
</table>

For cumulative use analyses, the hazard ratio was obtained by comparing the midpoint of each increment to no use (0 months).

Further adjusted for age, sex, comorbidity score, disease stage, socioeconomic status, rurality, and year of diagnosis.
## Table 5.7: The association between cumulative medication exposure and survival, adjusted for presence of comorbidities.

<table>
<thead>
<tr>
<th></th>
<th>Cumulative use (HR 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 – 6 months</td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Reuptake inhibitors</td>
<td>0.99</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>1.01</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>0.99</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>1.00</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>0.96</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0.94</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>0.73</td>
</tr>
<tr>
<td>Statins</td>
<td>1.01</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>1.01</td>
</tr>
</tbody>
</table>

### CANCER-SPECIFIC SURVIVAL

### OVERALL SURVIVAL

For cumulative use analyses, the hazard ratio was obtained by comparing the midpoint of each increment to no use (0 months).

Further adjusted for age, sex, comorbidity score, disease stage, socioeconomic status, rurality, and year of diagnosis.
Table 5.8: The association between cumulative medication exposure and survival, adjusted for medication use from age 65 to kidney cancer diagnosis.

<table>
<thead>
<tr>
<th>Medication</th>
<th>0 – 6 months</th>
<th>6 – 12 months</th>
<th>12 – 18 months</th>
<th>18 – 24 months</th>
<th>24 – 30 months</th>
<th>30 – 36 months</th>
<th>36 – 42 months</th>
<th>42 – 48 months</th>
<th>48 – 54 months</th>
<th>54 – 60 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td>0.99</td>
<td>0.96</td>
<td>0.94</td>
<td>0.91</td>
<td>0.89</td>
<td>0.86</td>
<td>0.84</td>
<td>0.82</td>
<td>0.80</td>
<td>0.78</td>
</tr>
<tr>
<td>(0.97 to 1.00)</td>
<td>(0.93 to 1.00)</td>
<td>(0.88 to 0.99)</td>
<td>(0.84 to 0.99)</td>
<td>(0.80 to 0.99)</td>
<td>(0.76 to 0.99)</td>
<td>(0.72 to 0.99)</td>
<td>(0.68 to 0.98)</td>
<td>(0.65 to 0.98)</td>
<td>(0.62 to 0.98)</td>
<td></td>
</tr>
<tr>
<td><strong>Angiotensin II receptor blockers</strong></td>
<td>1.01</td>
<td>0.99</td>
<td>0.98</td>
<td>0.97</td>
<td>0.97</td>
<td>0.97</td>
<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>(1.01 to 1.02)</td>
<td>(0.99 to 0.99)</td>
<td>(0.97 to 0.99)</td>
<td>(0.96 to 0.98)</td>
<td>(0.96 to 0.98)</td>
<td>(0.95 to 0.98)</td>
<td>(0.95 to 0.98)</td>
<td>(0.94 to 0.98)</td>
<td>(0.94 to 0.97)</td>
<td>(0.94 to 0.97)</td>
<td></td>
</tr>
<tr>
<td><strong>Acetylsalicylic acid</strong></td>
<td>0.99</td>
<td>0.98</td>
<td>0.96</td>
<td>0.95</td>
<td>0.94</td>
<td>0.92</td>
<td>0.91</td>
<td>0.90</td>
<td>0.88</td>
<td>0.87</td>
</tr>
<tr>
<td>(0.97 to 1.02)</td>
<td>(0.91 to 1.05)</td>
<td>(0.86 to 1.08)</td>
<td>(0.81 to 1.11)</td>
<td>(0.76 to 1.15)</td>
<td>(0.72 to 1.18)</td>
<td>(0.68 to 1.22)</td>
<td>(0.64 to 1.26)</td>
<td>(0.60 to 1.30)</td>
<td>(0.56 to 1.34)</td>
<td></td>
</tr>
<tr>
<td><strong>Beta blockers</strong></td>
<td>1.00</td>
<td>0.99</td>
<td>0.98</td>
<td>0.97</td>
<td>0.97</td>
<td>0.96</td>
<td>0.96</td>
<td>0.95</td>
<td>0.94</td>
<td>0.94</td>
</tr>
<tr>
<td>(0.98 to 1.01)</td>
<td>(0.95 to 1.03)</td>
<td>(0.93 to 1.04)</td>
<td>(0.90 to 1.06)</td>
<td>(0.87 to 1.08)</td>
<td>(0.84 to 1.10)</td>
<td>(0.82 to 1.12)</td>
<td>(0.79 to 1.14)</td>
<td>(0.77 to 1.16)</td>
<td>(0.74 to 1.18)</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td>0.96</td>
<td>0.93</td>
<td>0.91</td>
<td>0.89</td>
<td>0.88</td>
<td>0.87</td>
<td>0.86</td>
<td>0.85</td>
<td>0.84</td>
<td>0.83</td>
</tr>
<tr>
<td>(0.91 to 1.01)</td>
<td>(0.85 to 1.01)</td>
<td>(0.81 to 1.01)</td>
<td>(0.78 to 1.01)</td>
<td>(0.76 to 1.02)</td>
<td>(0.74 to 1.02)</td>
<td>(0.72 to 1.02)</td>
<td>(0.70 to 1.02)</td>
<td>(0.69 to 1.02)</td>
<td>(0.67 to 1.02)</td>
<td></td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>0.94</td>
<td>0.86</td>
<td>0.79</td>
<td>0.71</td>
<td>0.65</td>
<td>0.58</td>
<td>0.53</td>
<td>0.48</td>
<td>0.43</td>
<td>0.39</td>
</tr>
<tr>
<td>(0.90 to 0.97)</td>
<td>(0.78 to 0.96)</td>
<td>(0.66 to 0.93)</td>
<td>(0.56 to 0.91)</td>
<td>(0.47 to 0.88)</td>
<td>(0.40 to 0.85)</td>
<td>(0.34 to 0.83)</td>
<td>(0.28 to 0.80)</td>
<td>(0.24 to 0.78)</td>
<td>(0.20 to 0.75)</td>
<td></td>
</tr>
<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td>0.73</td>
<td>0.61</td>
<td>0.54</td>
<td>0.48</td>
<td>0.44</td>
<td>0.41</td>
<td>0.38</td>
<td>0.35</td>
<td>0.33</td>
<td>0.31</td>
</tr>
<tr>
<td>(0.63 to 0.84)</td>
<td>(0.48 to 0.78)</td>
<td>(0.40 to 0.73)</td>
<td>(0.34 to 0.69)</td>
<td>(0.29 to 0.66)</td>
<td>(0.26 to 0.63)</td>
<td>(0.23 to 0.61)</td>
<td>(0.21 to 0.59)</td>
<td>(0.19 to 0.57)</td>
<td>(0.17 to 0.55)</td>
<td></td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td>1.01</td>
<td>0.99</td>
<td>0.98</td>
<td>0.97</td>
<td>0.97</td>
<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
<td>0.94</td>
<td>0.95</td>
</tr>
<tr>
<td>(1.01 to 1.02)</td>
<td>(0.99 to 0.99)</td>
<td>(0.98 to 0.99)</td>
<td>(0.97 to 0.98)</td>
<td>(0.96 to 0.98)</td>
<td>(0.96 to 0.97)</td>
<td>(0.95 to 0.97)</td>
<td>(0.95 to 0.97)</td>
<td>(0.94 to 0.97)</td>
<td>(0.94 to 0.97)</td>
<td></td>
</tr>
<tr>
<td><strong>Proton-pump inhibitors</strong></td>
<td>1.01</td>
<td>0.97</td>
<td>0.96</td>
<td>0.95</td>
<td>0.94</td>
<td>0.93</td>
<td>0.93</td>
<td>0.92</td>
<td>0.92</td>
<td>0.92</td>
</tr>
<tr>
<td>(1.00 to 1.02)</td>
<td>(0.96 to 0.99)</td>
<td>(0.93 to 0.98)</td>
<td>(0.92 to 0.98)</td>
<td>(0.90 to 0.98)</td>
<td>(0.89 to 0.98)</td>
<td>(0.88 to 0.98)</td>
<td>(0.88 to 0.97)</td>
<td>(0.87 to 0.97)</td>
<td>(0.86 to 0.97)</td>
<td></td>
</tr>
</tbody>
</table>

**CANCER-SPECIFIC SURVIVAL**

For cumulative use analyses, the hazard ratio was obtained by comparing the midpoint of each increment to no use (0 months).

Further adjusted for age, sex, comorbidity score, disease stage, socioeconomic status, rurality, and year of diagnosis.
CHAPTER 6: DISCUSSION AND CONCLUSIONS

THESIS SUMMARY

This thesis evaluates whether exposure to statins, in addition to several other commonly prescribed medications with putative anti-neoplastic effects, is associated with risk and survival outcomes in kidney cancer, a disease that is common, increasing in incidence, and often lethal. This thesis also examines how this association varies with different methods of classifying exposure.

In Chapter 3, I performed a population-based nested case-control study and found that increasing cumulative exposure to statins was not associated with reduced risk of kidney cancer. Specifically, statins had little influence on the statistical model and were excluded from the final model when applying the multivariable fractional polynomial algorithm. This finding was contrary to the hypothesis based on the biological rationale that support anti-neoplastic effects of statins on kidney cancer. However, the results were consistent with a meta-analysis evaluating the association of statins and kidney cancer risk(105), though the studies included in this meta-analysis have several limitations, as described in Chapter 1.

One potential explanation for my observation is residual confounding. In the case-control study, I attempted to simulate the counterfactual model by matching individuals on potential confounders. However, I was unable to match patients on smoking history or obesity, as their data are not available in administrative databases. I used geographic area and comorbidity score as a surrogate for these established risk factors for kidney cancer; however, it is unknown to what degree these factors account for smoking history and obesity. Considering that smokers and obese individuals are more likely to have cardiovascular disease and hence be prescribed a statin,
residual confounding in this situation would have overestimated the association between statin exposure and kidney cancer risk. Therefore, it may be possible that the true association between exposure to statins and incident kidney cancer is more protective than the null association observed in our study.

This concept of residual confounding is also applicable to many of the other medications evaluated in which I found significantly reduced risk of incident kidney cancer with increasing cumulative use of acetylsalicylic acid, non-steroidal anti-inflammatory drugs, and selective serotonin-reuptake inhibitors, and significantly increased risk associated with any anti-hypertensive medication. Indeed, the distribution of smoking and obesity may be higher in users of some these medications compared to non-users, resulting in overestimation of the true effect. Therefore, if statins are protective in terms of kidney cancer risk, even after accounting for the possibility of residual confounding, they may not be as important modifiers of kidney cancer risk compared to other medications in my study for which significant associations were found.

Another possibility is that the association between statin use and kidney cancer risk observed in other studies may have been due to concomitant use of another medication that modulates cancer risk. For example, ASA is also used in the treatment of cardiovascular disease(189) and it is likely that statin users are more likely to be on ASA compared to non-statin users. A study evaluating statin use on risk of incident kidney cancer without controlling for concomitant ASA use may therefore show a spurious protective association of statins. Indeed, studies that found a significant protective association of statins on kidney cancer risk did not explicitly control for ASA use(48, 65). Given my findings, studies in chemoprevention for cancer should control for other putative anti-neoplastic medications to understand the independent association of a particular medication class on outcomes.
In Chapter 4, I reviewed the current literature on studies evaluating statin use and kidney cancer survival outcomes. My findings indicate that this is an ongoing topic of interest among clinicians and researchers, with several publications in the more recent years. In pooling the results from these studies, I found that statin use was associated with markedly improved cancer-specific survival and improved overall survival. However, there was no significant association between statin use on recurrence-free survival or progression-free survival.

While the protective effect of statins on cancer-specific survival and overall survival in the pooled analysis generate interest in possibly including these medications as part of the treatment armamentarium for kidney cancer, and previous meta-analyses with similar findings in other malignancies have suggested that statins be studied in the prospective setting (166, 167), I would caution against this simple interpretation. Indeed, the conclusions of a meta-analysis depend on the quality of the included studies (190). As described above, all but one study included in the meta-analysis did not account for intermittent use; rather, individuals were grouped into the statin user category based on any use during a given period of time. The issues associated with this method of classifying medication exposure have been described above. Furthermore, none of the studies included in the meta-analysis evaluated cumulative use, a method of analysis that supports the biological rationale behind chemoprevention. As prospective studies are resource intensive and can take many years to complete, it is necessary to undertake such studies judiciously. Despite our findings in the meta-analysis demonstrating a significant protective effect of statins on cancer-specific and overall survival, I feel that these findings alone are insufficient evidence to support a prospective study in this topic due to methodological issues.
In Chapter 5, I attempted to account for these methodological issues to further explore the potential role of statins in improving survival outcomes in kidney cancer. I performed a population-based cohort study and found that increasing cumulative use of statins was associated with minimal improvement in cancer-specific and overall survival. This finding is contrary to what I found in Chapter 4.

Similar to my case-control study, it is important to evaluate the potential for residual confounding. In addition to the established prognostic factors in kidney cancer described in Chapter 1, other studies have found that smoking and obesity may be associated with kidney cancer survival (191, 192). These studies have their own set of limitations, on which I do not elaborate here, however, it remains unclear whether these are independent prognostic factors. If they do represent true confounders, then there is the possibility of residual confounding, as described above, if comorbidity scores do not adequately capture these factors. Nonetheless, the role of statins in kidney cancer treatment may not be as influential as some of the other medications for which I found a significant association.

Similar to studies evaluating statins and kidney cancer risk, the majority of studies in the literature evaluating statins and kidney cancer survival have not controlled for other putative anti-neoplastic medications. For similar reasons described above, failure to control for other putative medications that may influence survival may result in the possible spurious relationship between statins and kidney cancer survival outcomes that has been observed in other studies.

While statins were not markedly protective for kidney cancer survival when evaluating cumulative use, statin use was associated with considerable improved cancer-specific and overall survival in the current use analyses. Therefore, another possible explanation for the minimal
protective association in the cumulative use analyses is that statins are only effective for the duration that they are present in the circulation. Since statins have a short half-life, if this were true of the anti-neoplastic effects of statins then indeed the cumulative use analysis may show little to no benefit while a strong benefit would be observed in the time varying analysis. These results are hypothesis generating and further research is required.

Finally, this thesis compared risk estimates from different methods of classifying medication exposure. I found that, in general, the risk estimates were sensitive to the method of classifying medication exposure. In some cases, a medication found to have a null association in one method of analysis was found to have a significant association when using another method. One example of this was selective serotonin reuptake inhibitors with kidney cancer risk which had a null association when dichotomizing exposure to $\geq 3$ years vs $< 3$ years, but were associated with significantly reduced risk in the cumulative use analysis with fractional polynomials. Conversely, and perhaps more concerning, some medications were found to be significantly protective in one method of analysis but significantly harmful in another method. An example of this was non-steroidal anti-inflammatory drugs which significantly improved overall survival in the cumulative use analysis with fractional polynomials, but significantly reduced overall survival in the current use analysis. These findings highlight the importance of critically evaluating the methods of classifying exposure in pharmacoepidemiology studies. I propose that when feasible, cumulative use analyses with fractional polynomials be used for the reasons that are detailed in Chapter 2.
IMPLICATIONS AND RECOMMENDATIONS

CLINICAL IMPLICATIONS

My studies found no significant association between statin use and kidney cancer risk, and a minimal protective association with survival outcomes when using a cumulative use analysis with fractional polynomials. Therefore, with the evidence to date, I do not recommend that statins be used to reduce the risk of or improve survival in kidney cancer. However, I did find a strong association for several other medications with kidney cancer risk and survival, and these findings have important clinical implications.

In patients at high risk of developing kidney cancer, such as those with a genetic predisposition, preference should be given to prescribing acetylsalicylic acid, selective serotonin reuptake inhibitors, or proton-pump inhibitors for medical conditions that these medications are deemed appropriate, compared to other medication classes with equal efficacy for the condition being treated. For example, the Canadian Network for Mood and Anxiety Treatments 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder recommend several potential first-line options in addition to selective serotonin reuptake inhibitors such as bupropion, which is an noradrenaline and dopamine reuptake inhibitors, and mirtazapine, which is an alpha-2-adrenergic and serotonin antagonist(193). Based on the results from our study, I would recommend that patients with a high risk of developing kidney cancer with concomitant depression should be preferentially treated with selective serotonin reuptake inhibitors.

Conversely, I found that increasing cumulative exposure to all anti-hypertensive drugs evaluated was associated with increased risk of incident kidney cancer. This is a concerning finding and will need to be validated in other studies. However, based on my results, it may be
worth considering rigorous lifestyle changes such as reducing smoking and obesity in hypertensive patients at high risk of kidney cancer, before initiating pharmacotherapy.

This thesis also found that increasing cumulative exposure to angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, and selective serotonin reuptake inhibitors were associated with markedly improved cancer-specific survival; increasing exposure to non-steroidal anti-inflammatory drugs was associated with markedly improved overall survival. Similar to what is described above for kidney cancer risk, patients diagnosed with kidney cancer should be preferentially treated with these medications for other concomitant medical conditions. Increasing cumulative use of no medication was associated with worse survival and therefore patients on these medications can continue them without concern for their impact on survival.
METHODOLOGICAL IMPLICATIONS

This thesis also has several methodological implications. First, this thesis demonstrates that population-based administrative databases can be used to study questions that may be underpowered from institutional cohorts. Furthermore, administrative data in which the population is eligible for prescription drug coverage allows for more robust methods of analyses that are generally not feasible in institutional cohorts. For example, in Chapter 4 only one of the 12 studies was able to account for intermittent use (84). Although this study was an institutional cohort, the authors described that they reviewed medical records, which contained detailed information on statin initiation and cessation. While this is possible, it is unlikely that lapses between prescriptions were captured if these lapses occurred in between clinic visits. Therefore, studies utilizing validated administrative data in a universal health care system may be more valid than institutional cohorts that cannot account for intermittent and cumulative use to the same extent.

Second, I have described in detail the advantages and disadvantages of dichotomizing a continuous variable. I have also reviewed the limitations of assuming a linear relationship between a continuous exposure and an outcome. I therefore propose that fractional polynomials may be the most robust method to model a continuous variable in relationship to an outcome as it allows for considerable flexibility and this method should be used preferentially when feasible.

Third, I have demonstrated how measures of association between an exposure and an outcome can vary based on the method of classifying exposure. It is therefore essential for researchers and clinicians to be aware of this situation when translating research into clinical practice. Based on our results from Chapter 4, some may consider prospectively studying statins to improve survival outcomes in kidney cancer. However, I would caution against initiating a
resource-intensive prospective study based on results from any individual study or pooled studies that do not account for intermittent or cumulative use.

Finally, studies evaluating the association between medication exposure on outcomes should control for other medications that can also influence the outcome. Failure to do so may result in a spurious relationship between the medication being evaluated and the outcome, due to concomitant use of another medication for which the association should be attributed to.
HEALTH POLICY IMPLICATIONS

Although this thesis has no immediate implications on health policy, there may be some implications that arise from work based on this thesis. If additional population-based studies and eventually prospective clinical trials confirm my findings, then the drug prescribing policies for specific commonly-prescribed medications may change to include kidney cancer related indications. Furthermore, the cost of treatment in kidney cancer is substantial; compared to a matched patient without cancer, the annual cost to treat a patient with kidney cancer is more than $US11,000 per year. If that patient goes on to receive targeted therapy for metastatic disease, the cost burden increases by three to four fold (151). Therefore, if these commonly-prescribed medications, which are drastically inexpensive in comparison, are used to prevent kidney cancer and replace targeted therapy by demonstrating similar efficacy, the cost-savings to the public health-care system will be substantial.
THESIS LIMITATIONS

There are several limitations to this thesis that warrant mention. First, although I attempted to use a comprehensive search strategy in the systematic review and meta-analysis, it is possible that some articles were missed, particularly those whose primary objective was not to evaluate statins on kidney cancer outcomes but may have reported a risk estimate for statins as part of the multivariable analysis. Furthermore, although from a statistical perspective there was no strong evidence for publication bias in my study, the scientific literature in general may favour the publication of “positive” studies (194). Therefore, if unpublished “negative” data exist, then accounting for these may bring the pooled associations closer to the null. These limitations apply to all meta-analyses.

Second, the population-based studies were restricted to older patients given the age at which individuals become eligible for prescription drug coverage in Ontario. However, given that the majority of all incident kidney cancer cases are diagnosed in patients aged 65 or older (1), most of the population of interest was included in my studies. Nonetheless, it is unknown whether these findings can be generalized to younger patients. Conversely, my population-based studies included individuals of all ethnicities, comorbidities, socioeconomic strata, etc. and therefore the results have strong generalizability to all older patients.

Third, I used administrative data that were not designed for research and some variables that are related to statin exposure, kidney cancer risk, or kidney cancer survival, were not available in the data used. Although I attempted to use surrogates for variables that may be considered confounders, it is unknown to what degree these surrogates are related to the measures of interest and the potential for residual confounding remains.
Fourth, I did not study individual drugs within classes of medications as this may have resulted in an over-parameterized model. However, the biological rationale for chemoprevention should apply for all medications within a particular class. Nonetheless, it is possible that there is heterogeneity among individual medications within a particular class on the direction and magnitude of association with the outcome.

Fifth, cumulative use analyses assign equal weight to remote exposure and more recent exposures; whether this is appropriate is a matter of debate. Although weighted cumulative use analyses have been proposed to account for time varying variables (195), it is unclear how to define a clinically relevant window which is needed to assign weight values for remote exposures, and how this rate of change in weight varies over time. Furthermore, fractional polynomials have not yet been studied in this context.

Finally, my population-based studies were observational in design and therefore cannot prove causality. I attempted to simulate the counterfactual model but the possibility of inherent differences between the exposed and unexposed group that may be related to the outcome still remains. Randomized controlled trials evaluating medication use on kidney cancer risk or survival outcomes will be able to address this limitation.
FUTURE STUDIES

This thesis provides further insight on the potential for chemoprevention in kidney cancer. However, several questions remain unanswered.

First, I used geographic area and comorbidity score as a surrogate to capture information related to smoking and obesity as their data were not available. Although this information can often be obtained by chart review, this is not easily feasible in population-based studies with a large number of patents from various hospitals. Indeed, being unable to directly account for these factors is often noted as a limitation in research using administrative data (131, 196). However, the degree to which geographic area and measures of comorbidity relate to smoking and obesity is unknown. Furthermore, some measures of comorbidity may be more suitable than others at controlling for smoking and obesity. On the other hand, if geographic area and measures of comorbidity do not adequately control for smoking and obesity, interpretation of research from administrative data may be subject to residual confounding bias. Therefore, further investigation is needed to understand whether existing administrative data can be used to minimize bias due to missing data on smoking and obesity.

Second, I was able to study cancer-specific survival and overall survival as administrative data exists to capture these events, namely date and cause of death. However, I was unable to study recurrence-free survival as this event is not explicitly captured. Conceptually, it is possible to attempt to capture this outcome in administrative data; for example, a patient who undergoes surgery shortly after being diagnosed with localized kidney cancer can be followed over time for receipt of targeted therapy, which would be used as a surrogate to describe treatment for recurrence. However, using this method of describing recurrence may also capture individuals who undergo a cytoreductive nephrectomy for pre-existing metastatic disease, in which case
these individuals would be false positives for disease recurrence. Conversely, there may be individuals with localized disease who develop recurrence but choose palliation as opposed to treatment with targeted therapy; these individuals would be false negatives. Furthermore, not all recurrences are treated with targeted therapy as isolated localized recurrences can be treated with surgery(197). However, it is difficult to disentangle whether using potential billing codes for surgery would be procedures for recurrence, or other indications. Therefore, algorithms that are sensitive and specific to capture cancer recurrence are needed to study this outcome with administrative data.

Third, in addition to studying putative anti-neoplastic medications in younger patients, my results provide impetus to study many of the medications that modify kidney cancer risk and survival through randomized controlled trials in elderly patients. Indeed, randomized controlled trials are currently underway evaluating some of these medications as a stand-alone, or in combination therapy in the adjuvant or neo-adjuvant setting for various malignancies(169, 170). Some potential relevant trials in kidney cancer include:

- Putative anti-neoplastic medication vs. placebo to reduce risk of kidney cancer in patients found to have a predisposing genetic disorder.
- Targeted therapy in combination with a putative anti-neoplastic medication vs. targeted therapy alone in the setting of advanced kidney cancer.

Finally, malignant small renal masses are increasingly being managed with active surveillance as opposed to an intervention due to competing risks of death. Further investigation is needed to evaluate the role of putative anti-neoplastic medications on reducing the risk of kidney cancer progression on active surveillance.
CONCLUSIONS

In this thesis, I found that increasing cumulative use of statins was not significantly associated with kidney cancer risk, and associated with minimal improvement in survival outcomes. Therefore, the evidence to date does not provide strong evidence for the use of statins to prevent or improve survival in kidney cancer. However, I did find that there were several other medications that could markedly influence kidney cancer risk and survival and these medications should be evaluated prospectively. Finally, results from studies in pharmacoepidemiology may be sensitive to the method of classifying medication exposure. In this context, cumulative use analyses using fractional polynomials may be the most robust method and should be used when feasible.
### APPENDIX: Detailed search strategy

#### MEDLINE:

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<td>1</td>
<td>Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or ((HMG adj2 CoA adj2 reductase adj2 inhibitor*) or (hmg adj2 coenzyme adj2 reductase adj2 inhibitor*) or (&quot;hmg-coa&quot; adj2 reductase adj2 inhibitor*) or (hydroxymethylglutaryl adj2 coa adj2 reductase adj2 inhibitor*) or (&quot;hydroxymethylglutaryl-coa&quot; adj2 reductase adj2 inhibitor*) or statin or statins or vastatin).mp.</td>
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<td>[<strong><strong>EMBASE since 2006</strong></strong>]</td>
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<td>[<strong><strong>EMBASE since 2013</strong></strong>]</td>
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<td>atorvastatin plus ramipril/ or (&quot;atocor R&quot; or &quot;atorvastatin-ramipril&quot; or &quot;atorvastatin/ramipril&quot; or (ramipril adj3 atorvastatin) or &quot;ramipril-atorvastatin&quot; or &quot;ramipril/atorvastatin&quot;).mp. [<strong><strong>EMBASE since 2010</strong></strong>]</td>
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no prareduct or prascoend or prastan or prava or pravachol or pravacol or pravaselect or pravasin or pravasine or pravator or pravyl or sanaprav or selectine or selipran or "sq 31000" or sq31000 or standine or vasopran or vasten or xipral).mp. or (81093-37-0 or 81131-70-6).rn. [****EMBASE since 1986****]

24 (avandastat or "rosiglitazone-simvastatin" or "rosiglitazone/simvastatin" or (simvastatin adj2 rosiglitazone) or "simvastatin-rosiglitazone" or "simvastatin/rosiglitazone").mp. [****EMBASE since 2007****]

25 rosuvastatin or (crestor or rosuvastatin or "s 4522" or s4522 or "zd 4522" or zd4522).mp. or (147098-18-8 or 147098-20-2).rn. [****EMBASE since 2002****]

26 simvastatin or (avastin or cheostat or clinfar or colastatina or colestronic or covastin or denan or epistatin or esvat or ethicor or eucoor or ifistatin or kavelor or klonastin or koselestan or or "1 644128" or l644128 or lipecer or lipex or lipinorm or lipoince or lipovas or lodoval or medipo or mersivas or "mk 733" or "mk733 or nor-vastina" or normofat or orovas or rechol or simbado or simcard or simchol or simovil or simtint or simvace or simvaxeh or simvalord or simvast or simvata or simvin or simvor or simvotin or simvcao or simvast or simvina or simvinol or starzoc or synvinolin or torio or valemia or vasilip or vasotenal or vizam or vidastat or zimmnex or zocor or zocord or zovast).mp. or 79902-63-9.rn. [****EMBASE since 1986****]

27 (juvisync or (simvastatin adj2 sitagliptin) or "simvastatin-sitagliptin" or "simvastatin/sitagliptin" or "simvastatin-simvastatin" or "sitagliptin-simvastatin" or "sitagliptin/simvastatin").mp. [****EMBASE since 2012****]

28 tenivastatin.mp. or (121009-77-6 or 151006-18-7).rn. [****EMBASE since 2011****]

29 triglycerides/ or (triacylglycerol* or (tri adj2 acylglycerol*) or trigllyceride* or (triacyl adj2 glyceride*) or tryglylyceride).mp. [****EMBASE since 1974****]

30 ("ac 1202" or ac1202 or axona or ketasyn).mp. [****EMBASE since 2013****]

31 ((glycerol adj2 phenylbutyrate) or (glycerol adj2 phenylbutyrate) or "hpn 100" or hpn100 or ravicti).mp. or 611168-24-2.rn. [****EMBASE since 2012****]

32 ((glycerol adj3 trioleate) or (Lorenzo adj2 oil)).mp. [****EMBASE since 1999****]

33 triacetin/ or (triacetin or enzactin or fungacetin or fungoid or glycerol adj2 triacetate or (glycerol adj2 triacetate) or glycpc or triacetet or triaceton or triacetylglycerol or vanay).mp. or 102-76-1.rn. [****EMBASE since 1974****]

34 (tributyrin or (glycerol adj2 tributyrate) or (glycerol adj2 tributyrate)).mp. or 60-01-5.rn. [****EMBASE since 2000****]

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36 (trilinolein or (glycerol adj2 trilinoleate) or (linoleic adj2 acid adj2 triglyceride) or (trilinoleic adj2 glycerol)).mp. or 537-40-6.rn. [****EMBASE since 1976****]

37 (trioctanoin or (glycerol adj2 tricaprylate) or (glycerol adj2 tricostanate) or (glycerol adj2 tricaprylate) or (glycerol adj2 trioctanate) or (glycerol adj2 tricaprin) or (tricaprin or tricaprylin or tricapryline or trioctanoine)).mp. or 538-23-8.rn. [****EMBASE since 1974****]

38 triolein/ or (triolein or (glycerol adj2 trioleate) or glyceroltriolein or (glycerol adj2 trioleate) or olein or radiotriolein or trioleate or trioleoylglycerol or trioleylglycerol)).mp. or 122-32-7.rn. [****EMBASE since 1974****]

39 (tripalmitin or (glycerol adj2 tripalmitate) or (glycerol adj2 tripalmitate) or palmitin or tripalmitoylglycerol).mp. or 555-44-2.rn. [****EMBASE since 1974****]

40 (tristearin or (glycerol adj2 tristearate) or glyceroltristearate or (glycerol adj2 tristearate) or stearin).mp. or 555-43-1.rn. [****EMBASE since 1999****]

41 or/1-40

42 kidney neoplasms/ or carcinoma, renal cell/ or wilms tumor/ or nephroma, mesoblastic/

43 ((renal or kidney* or nephro*) adj5 (carcinoma* or cancer* or tumor* or tumour* or neoplas*)).mp.

44 or/42-43

45 41 and 44

46 neoplasms/no or neoplasms, second primary/ or neoplastic processes/ or neoplasm invasiveness/ or neoplasm metastasis/ or neoplasm micrometastasis/ or neoplasm seeding/ or neoplasm recurrence, local/ or neoplasm regression, spontaneous/ or neoplasm, residual/

47 41 and 46

48 45 or 47

158
hydroxymethylglutaryl coenzyme a reductase inhibitor/ or ((HMG adj2 CoA adj2 reductase adj2 inhibitor*) or (hmg adj2 coenzyme a reductase adj2 inhibitor*) or ("hmg-coa" adj2 reductase adj2 inhibitor*) or (hydroxymethylglutaryl coa adj2 reductase adj2 inhibitor*) or ("hydroxymethylglutaryl-coa" adj2 reductase adj2 inhibitor*) or statin or statins or vastatin).mp.

hypocholesterolemic agent/ or "3 (12 carboxy 12 methyltridecyl) 3 hydroxyglutaric acid"/ or 3,5 dihydroxy 9,9 diphenyl 6,8 nonadienoic acid methyl ester/ or "6 [2 (4 fluoro 3,3,5 trimethyl 2 biphenylyl)vinyl] 4 hydroxy 2 oxothrethrapyrany/" or "6 [4,4 bis(4 fluorophenyl) 3 (1 methyl 1h tetrazol 5 yl) 1,3 butadienyl] 3,4,5,6 tetrahydro 2h pyran 2 2 (methyl(1 methyl 1h 1,2,4 triazol 5 yl)amino) 5 pyrimidinyl] 3,5 dihydroxy 6 heptenoic acid"/

acetylsalicylic acid plus pravastatin/ or ((acetylsalicylic acid adj2 pravastatin) or (pravastatin adj2 acetylsalicylic acid) or (pravastatin adj2 acetylsalicylic acid) or pravigard).mp. [****EMBASE since 2011****]

amlodipine plus atorvastatin/ or ((amlodipine adj2 atorvastatin) or (atorvastatin adj2 amlodipine) or caduet).mp. [****EMABSE since 2006****]

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atorvastatin plus ezetimibe/ or ((atorvastatin adj3 ezetimibe) or "atorvastatin-ezetimibe" or "atorvastatin/ezetimibe" or liptruzet).mp. [****EMBASE since 2013****]

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crilvastatin/ or (crilvastatin or "pmd 387" or pmd387).mp. [****EMBASE since 2011****]

dalvastatin/ or (dalvastatin or "rg 12561" or rg-12561).mp. or (132100-55-1 or 135910-20-2).rn. [****EMBASE since 1999****]

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ezetimibe plus simvastatin/ or ((ezetimibe adj2 simvastatin) or "ezetimibe/simvastatin" or "ezetimibe simvastatin" or "ezetimibe/simvastatin" or inegy or "simvastatin-ezetimibe" or "simvastatin/ezetimibe" or vytorin or zetsim or zintrepid).mp. [****EMBASE since 2006****]

fenofibrate plus pravastatin/ or ((fenofibrate adj2 pravastatin) or pravafenix).mp. [****EMBASE since 2011****]

fluindostatin/ or (fluindostatin or canef or cranoc or fluvastatin or "fractal lp" or lescol or leucol or locol or l"sri 62320" or sri62320 or vastin or "xu 62320" or xu62320).mp. or 93957-54-1.rn. [****EMBASE since 1987****]

glenvastatin/ or (glenvastatin or "hr 780" or hr780).mp. [****EMBASE since 2011****]

lovastatin plus nicotinic acid/ or (advicor or (lovastatin adj2 niacin) or "lovastatin-niacin").mp. [****EMBASE since 2007****]

mevinolin/ or (mevinolin or altocor or ltoprev or artein or belvas or biorin or cholestra or cyisin or ellano or elstatin or l 654969" or lipdip or lipivas or lofacol or lomar or lostatin or lovacel or lovalip or lovalord or lovastan or lovastatin or lowasterol or lovastin or lovatadin or lowachol or lozutin or medostatin or mevacor or meverstin or mevinacor or "mk 0803" or "mk 803" or mk0803 or mk803 or monacolin or "msd 803" or neolipid or nergadan or ovasta or rotadin or rovacor or tavocor).mp. or 75330-75-5.rn. [****EMBASE since 1980****]

mevinolinic acid/ or mevinolinate.mp. or 75225-51-3.rn. [****EMBASE since 1980****]

monacolin J/ or monacolin.mp. or 76343-78-7.rn. [****EMBASE since 1985****]
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REFERENCES


75. Hsieh PY, Liu CJ, Teng CJ. Immortal time bias and reverse causality in retrospective analysis: Comment on "effect of cumulative bortezomib dose on survival in multiple myeloma patients receiving bortezomib-melphalan-prednisone in the phase III VISTA study". American journal of hematology. 2015;90(8):E146.


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