**THE UNIQUE ASSOCIATION BETWEEN HYDROPHILIC STATINS AND PROSTATE CANCER OUTCOMES**

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**Abstract**

***Introduction***

The preventative effect of various medications in prostate cancer (PCa) outcomes is of great interest. Specifically, the potential impact of statins in PCa incidence has been previously studied, but solely as a ‘drug family’ overlooking distinctive pharmacological properties. Based on previous in-vitro data showing a beneficial role of a hydrophobic statin in decreasing PCa-cell death, we aimed to clinically assess the specific role of both hydrophobic and hydrophilic statins in the context of other medications which potentially modulate PCa outcomes.

***Materials & methods***

In this retrospective, population-based cohort study, data from the Institute for Clinical and Evaluative Sciences was used to identify all men aged 66 and above with a history of a single negative prostate biopsy in Ontario between 1994 and 2016. Using Cox regression multivariable models with time-dependent covariates, we analyzed the effect of hydrophobic and hydrophilic statins on PCa diagnosis, PCa-specific death, and hazard of undergoing another prostate biopsy. We included other medications potentially affecting PCa (proton pump inhibitors, 5-alpha-reductase inhibitors, alpha-blockers, dipyridamole, and chloroquine). We also adjusted for age, rurality, comorbidity, diabetes, and study inclusion year.

***Results***

A total of 21,512 men were analyzed with a mean follow-up time of 8.06 years (SD 5.44 years). Statins were taken by 11,401 patients (50.3%). A total of 5,184 men (24.1%) were diagnosed with PCa, and 805 patients (3.7%) died from it. Overall, 7,556 patients (35.1%) underwent at least one additional biopsy. A total of 10,818 patients (50.3%) took at least one statin. Any use of hydrophilic statins was associated with an 18% (95% CI 6.1-27.3%), 32.4% (95% CI 12.9-47.5%), and 20% (95% CI 10-28%) decreased likelihood of being diagnosed with PCa, dying from PCa, and undergoing a prostate biopsy. Hydrophobic statins did not demonstrate any similar statistically significant protective effect.

***Conclusion***

In contrast to our initial hypothesis, the suggested protective effect of hydrophilic rather than hydrophobic statins on PCa outcomes appears promising and needs further exploration.

**Introduction**

Prostate cancer (PCa) is the most common non-cutaneous cancer diagnosed in North-American men[1](#_ENREF_1). The American Cancer Society estimates that in 2019, approximately 174,650 new cases will be diagnosed, and 31,620 cancer-specific deaths will occur[1](#_ENREF_1). Approximately 60% of PCa develop in men older than 65, with an average age of 66[1](#_ENREF_1).

Multiple medications have been assessed regarding their role in primary and secondary PCa prevention. These include prostate-directed drugs such as 5-alpha-reductase-inhibitors[2](#_ENREF_2) and alpha blockers[3](#_ENREF_3), and other medications, proton pump inhibitors (PPIs)[4](#_ENREF_4) and statins[5](#_ENREF_5). The role of statins in PCa and other malignancies has been extensively studied, albeit mostly as a ‘drug family’ without consideration of existing subgroups with distinct pharmacological properties.

Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCoAR) inhibitors, are mainly used to improve lipid profiles and reduce cardiovascular morbidity and mortality[6](#_ENREF_6). However, statins may also have a role in cancer prevention as reduction in cholesterol availability may limit the cellular proliferation required for cancer growth and metastasis[5](#_ENREF_5). HMGCoAR is the rate-limiting enzyme of the mevalonate pathway, which is integral for cell growth and survival[7](#_ENREF_7). The mevalonate pathway enzymes are transcriptionally regulated by sterol regulatory element-binding protein-2 (SREBP2). Statins can be divided into hydrophilic (pravastatin and rosuvastatin) and hydrophobic (simvastatin, lovastatin, fluvastatin, atorvastatin, and cerivastatin) statins[8](#_ENREF_8). Although both groups have similar cholesterol reduction effect, they hold different pleiotropic effects, caused by the variance in their lipophilicity. This affects their pharmacokinetic attributes, culminating in metabolic changes.

Recent in-vitro experiments by our group demonstrated that HMGCoAR inhibition, caused by statins, was insufficient to induce apoptosis in most PCa cell lines. However, sensitivity to fluvastatin, a hydrophobic statin, was inversely associated with SREBP2 activation following statin treatment, leading to increased PCa cell death. Additionally, SREBP2 inhibition with dipyridamole, an anti-platelet medication, potentiated fluvastatin-induced apoptosis in PCa cells[9](#_ENREF_9).

These findings led us to investigate the effect of hydrophilic and hydrophobic statins, and dipyridamole, in the context of other medications potentially affecting PCa diagnosis, including, alpha-blockers[3](#_ENREF_3), five-alpha-reductase inhibitors[10](#_ENREF_10), chloroquine[11](#_ENREF_11), and PPI[12](#_ENREF_12). Based on in-vitro evidence, we hypothesized that hydrophobic statins would lower PCa diagnosis rate more than hydrophilic statins in men at an elevated risk of developing PCa, and in the setting of other putative PCa influential medications.

**Methods**

This study was approved by the University of Toronto’s ethics board committee. The study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines[13](#_ENREF_13), and Reporting of Studies Conducted Using Observational Routinely-Collected Health Data Statement[14](#_ENREF_14). We performed a retrospective population-based cohort study using administrative data housed at the Institute for Clinical and Evaluative Sciences (ICES). In Ontario, all essential medical care is reimbursed by a single, government-operated health insurance system, the Ontario Health Insurance Plan (OHIP), enabling us to capture the entire adult population. Moreover, in Ontario, everyone 65 years and older is eligible for prescription drug coverage through the Ontario Drug Benefit (ODB) program, enabling accurate capture of all prescriptions provided to this specific population.

**Data sources**

Data were acquired from several specific datasets housed at ICES[15](#_ENREF_15) and detailed in supplemental Table 1. The retrieved data contained demographic, baseline comorbidity, medication prescription, cancer diagnosis, and vital status details. Patient-specific information from these databases is linkable using unique, encoded identifiers.

**Study design, setting, and participants**

We used the age of 66 as the minimum age for study inclusion to enable a one-year look-back period, confirming that no drug prescription of any of the analyzed medications was provided between the age of 65 and 66. We identified all men aged 66 and older with a history of a single negative transrectal ultrasound-guided prostate biopsy (TRUS-Bx) in the province of Ontario, Canada (estimated population of ~14 million) between January 1st, 1994 and September 30th, 2016. Relevant patients were identified using OHIP billing codes for TRUS-Bx, with no evidence of PCa diagnosis, nor receipt of PCa-specific treatment within the following three months after the biopsy, using the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP), as detailed in Supplemental Table 2. Men with a history of a previous negative biopsy were chosen as part of a pre-screening tool to include a ‘healthier’ population, seen fit to undergo a biopsy. We utilized a look-back window from January 1991 until the date of cohort entry (minimum of 3 years) to ascertain that included men had a TRUS-Bx that were truly the first negative biopsy and that they had no previous PCa diagnosis. The index date was defined as 90 days after the date of the first negative prostate biopsy to ensure no PCa diagnosis.

We analyzed the effect of hydrophobic and hydrophilic statins on PCa-related outcomes. We analyzed additional medications that may also potentially affect PCa outcomes. These included PPIs, five-alpha-reductase inhibitors, alpha-blockers, dipyridamole and chloroquine. Glaucoma eye drops were included as a tracer drug, serving as a negative control, to show no association with any of the outcomes. A complete list of all medications included in the analysis is shown in Appendix 1.

Patients were followed from the date of negative TRUS-Bx until death, last health services contact in Ontario, becoming OHIP ineligible, or end of the study period (September 30th, 2016).

**Study outcomes**

Our primary outcome was the incidence of PCa diagnosis. Secondary outcomes included incidence of PCa-specific mortality and an additional prostate biopsy.

**Study variables**

PCa was considered the reason for death if noted as the immediate cause of death on the patient’s death certificate. PCa diagnosis was defined as having either a record of PCa or having received PCa-specific treatment (radical prostatectomy, primary radiotherapy to the prostate or androgen deprivation therapy [ADT]). Active surveillance (AS) per se was not captured. Therefore, if none of the mentioned treatments were noted, we assumed the patient was either on AS, watchful waiting or was not treated. Additional collected variables included patient age (categories: 66-69, 70-74, 75-79, 80-84, 85 years and above), rurality index (continuous variable incorporating the community population and population density, travel time to a nearest basic referral center and nearest advanced referral center, with a higher number representing a more rural area)[16](#_ENREF_16), Index year (year of study inclusion), medically treated diabetes (binary variable), and comorbidity status quantified with the Collapsed Ambulatory Diagnostic Groups (ADG) score (a continuous comorbidity variable derived from the Johns Hopkins Adjusted Clinical Groups System, harboring better discrimination than the Charlson score)[17](#_ENREF_17). Comorbidities were captured with a 3-year look-back period, and Prostate-specific antigen (PSA) levels were available only from 2007.

**Statistical analyses**

Continuous variables were described using means and standard deviations (SD); categorical variables were characterized using proportions. To estimate the effects of any exposure and cumulative exposure per unit of time for all medications on all outcomes of interest, two types of analyses were performed. First, multivariable Cox proportional hazard regression models with time-dependent exposure were used for each cause-specific hazard. The exposure to each medication was modeled as a time-dependent status indicator (ever vs. never exposure at any time point during the follow-up). Second, we estimated the effect of the cumulative time of taking each medication in six-months intervals. All models included the above mentioned putative PCa influential medications. Additionally, models were adjusted for the person’s age group, rurality index (0-100), index year (1994-2016) and the ADG comorbidity score, with the last three being modeled as continuous variables with log-linear effects. These covariates were selected a priori and were treated as time-independent variables using the values at study onset. For PCa-specific mortality, PCa-specific treatments were incorporated in the model as well (radical prostatectomy, primary radiotherapy, and ADT). The proportional and log-linearity assumptions underlying the models were assessed using residual-based diagnostics, and no violations were identified. All statistical tests were two-tailed, and after using Bonferroni correction due to multiple comparisons, a p-value of < (0.05/14 = 0.0035) was considered significant. All statistical analyses were performed using R software version 3.3.1.

**Sensitivity analyses**

We performed several preplanned sensitivity analyses. We analyzed the effect of both hydrophilic and hydrophobic statins combined, statin dosage above and below the median dose, and incorporated statin interactions with metformin and dipyridamole in the model assessing PCa diagnosis. To adjust for PSA levels as well, we used the same analyses but specifically included only patients enrolled in the study from 2007, as PSA was only available from that year. If more than one PSA test was available, the median PSA for each patient was used with a limited time frame of one year form the first negative biopsy date. Lastly, for dataset validation, a negative control analysis was performed. For this, we assessed the effects of all medications on being diagnosed with presbyopia.

**Results**

**Medication use and prostate cancer outcomes:**

A total of 21,512 men met our inclusion criteria, with mean follow-up time (SD) of 8.06 years (5.44 years). Figure 1 shows the flow chart of the final cohort, and Table 1 depicts basic demographic data.

Figure 2 highlights the rates of medication usage, showing a high rate of statin use, with 10,818 patients (50.3%) starting a statin medication during the study period, with hydrophobic statins being the most common (6,607 patients, [61.1% of statin users]). The other commonly used medications included PPIs (10,999 patients [51.1%]) and alpha-blockers (8,505 patients [39.5%]).

Supplemental figure 1 shows the rates of PCa diagnosis, PC-specific death, and all-cause mortality, while supplemental figure 2 highlights the various treatment modalities for PCa-diagnosed patients. A total of 5,187 patients (24.1%) were diagnosed with PCa, and 805 patients (3.7%) died from it. Most PCa patients were on either active surveillance/watchful waiting or not actively treated (1,811 patients, [34.9%]), with the rest treated with primary ADT, radiotherapy, or radical prostatectomy. Lastly, a total of 7,556 patients (35.1%) had at least one additional biopsy, as detailed in supplemental figure 3.

**Statins and Prostate cancer diagnosis:**

When assessing PCa diagnosis, supplemental table 3 shows that when both statin groups were combined, they were associated with a reduced hazard of being diagnosed with PCa, when medication use was modeled as ever vs. never (HR 0.933, 95% CI 0.858-1.010, p=0.1) and per six months of cumulative use (0.989, 95% CI 0.978-0.999, p=0.046), but these did not reach the required statistical significance level. However, when we modeled each statin group separately, hydrophilic statins were associated with a decreased hazard of being diagnosed with PCa (Table 2), when medications use was modeled as ever. vs. never (HR 0.820, 95% CI 0.727-0.939, p=0.003) and when modeled per six months of cumulative use (HR 0.973, 95% CI 0.951-0.995, p=0.017). Hydrophobic statins did not have any similar protective effect in any of the analyses. Supplemental Table 4 examined the predictors of being diagnosed with PCa, with medications only modeled as ever. vs. never use and incorporated the median dose of each statin group. For hydrophilic statins, a dose higher than the median dose conferred a protective effect (HR 0.791, 95% CI 0.651-0.963, p=0.019), but this did not meet the required statistical significance level. We also analyzed statin interactions with medications that were shown to have a beneficial influence on PCa in in-vivo and in-vitro settings. These included metformin and dipyridamole, but no statistically significant interaction effect was shown (Supplemental Table 5). In the subset analysis incorporating PSA data from 2007, no significant statistical association was noted between both statin groups and PCa diagnosis.

**Statins and prostate cancer-specific death:**

For PC-specific death, supplemental table 6 shows that statins combined were associated with a decreased hazard of dying from PCa when medications were modeled as ever vs. never (HR 0.760, 95% CI 0.640-0.900, p=0.0018). When modeling each statin group separately (Table 3), only hydrophilic statins were associated with a statistically significant lower likelihood of dying from PCa, when modeled as ever vs. never usage (HR 0.676, 95% CI 0.525-0.871, p=0.0024). However, when modeled as per six months of cumulative use (HR 0.957, 95% CI 0.920-0.990, p=0.018), it did not reach the required statistical significance level. A model incorporating PSA values was not done for this outcome of interest as the number of PCa-specific deaths from 2007 was too low.

**Statins and undergoing an additional prostate biopsy:**

In the model assessing predictors of having an additional prostate biopsy, only hydrophilic statins were associated with a lower likelihood of undergoing an additional biopsy, when modeled as ever vs. never usage (HR 0.800, 95% CI 0.720-0.900, p=0.0002), and when modeled as cumulative six months of use (HR 0.968, 95% CI 0.944-0.992, p=0.0002). Hydrophobic statins did not show any similar association (Table 4). In the subset analysis incorporating PSA data from 2007, hydrophilic statins were also shown to be associated with a decreased likelihood of undergoing an additional biopsy (HR 0.710, 95% CI 0.529-0.968, p=0.029), but this did not reach the required statistical significance level.

**Additional covariates and medications:**

As for the other covariates in the models, age was associated with a higher hazard of dying from PCa and a decreased likelihood of undergoing an additional biopsy. Increasing ADG score and medically treated diabetes were associated with a decreased likelihood of undergoing a biopsy. Increasing rurality was associated with an increased hazard of being diagnosed with PCa. A more recent index year was associated with a decreased hazard of being diagnosed with and dying from PCa and having an additional biopsy. As expected, higher PSA was associated with an increased hazard of being diagnosed with PCa. Lastly, none of the other medications analyzed in the models had shown any protective association with any of the outcomes examined (Supplemental tables 7-9). A focused assessment of each of these medications, especially for those conferring a worse association with PCa outcomes is beyond the scope of the present manuscript and will be considered elsewhere.

**Negative Control model:**

Our negative control model, assessing predictors of being diagnosed with presbyopia depicted no statistically significant effect of the medications (Supplemental Table 10). Furthermore, glaucoma eye drops, serving as a tracer drug, did not demonstrate any statistically significant association with any of the study outcomes (Supplemental Tables 7-9).

**Discussion**

Our study showed that over a mean follow-up time of eight years more than a third of men aged 66 and above with a negative prostate biopsy had at least one additional biopsy. A total of 24.1% of them were eventually diagnosed with PCa with a 3.7% mortality rate, similar to a previous analysis of men older than 40 with a history of a negative prostate biopsy, showing a PCa diagnosis rate of 23.7%[18](#_ENREF_18). More than half of the men in our study had started a statin medication (most using a hydrophobic statin). Unexpectedly, our study showed that hydrophilic rather than hydrophobic statin use was associated with an 18%, 32.4%, and 20% decreased hazard of being diagnosed with PCa, dying from PCa, and undergoing an additional prostate biopsy, respectively. Furthermore, every six-months of taking a hydrophilic statin, conferred a 2.7% (95% CI 0.9-4.5, p=0.017), 4.3% (95% CI, 1.0-8.0, p=0.018), and 3.2% (95% CI 0.8-5.6, p=0.0002) decreased the hazard of being diagnosed with PCa, dying from PCa, and undergoing an additional biopsy, respectively.

Experimental in-vitro studies have shown that statins manifest antitumor effects by inhibiting cell proliferation, inducing apoptosis and impeding angiogenesis and metastasis[7](#_ENREF_7). HMGCoAR, the enzyme inhibited by statins, catalyzes the conversion of HMG-CoA into mevalonate, a precursor of cholesterol and the isoprenoid intermediates. These isoprenoids are critical in the process of prenylation, facilitating anchoring of proteins to cell-membranes[19](#_ENREF_19), including oncoproteins involved in numerous malignancies[20](#_ENREF_20). The statin-induced inhibition of these processes reduces tumor cell proliferation, destabilizes membrane integrity, and impedes cell signalling[21](#_ENREF_21).

Despite these in-vitro findings, there have been several clinical studies showing contradictory findings regarding the beneficial role of statins as a group in PCa. Large retrospective studies have shown an association between statins and PSA level reduction[22](#_ENREF_22) (lessening the likelihood of being referred for a prostate biopsy), decreased PC diagnosis rate[23](#_ENREF_23), longer time to progression during ADT in hormone-sensitive PCa[24](#_ENREF_24), and decreased PCa-specific mortality[25-28](#_ENREF_25). In contrast, other large retrospective studies have shown no beneficial effect of statins as a group on PCa diagnosis[29](#_ENREF_29) and on the biochemical recurrence rate[30](#_ENREF_30), [31](#_ENREF_31). One possible reason for these contradictory findings is that statins were analyzed as a pooled drug family. There are in-vitro studies showing that hydrophobic statins may be more effective at suppressing micrometastatic outgrowth due to increased uptake into cancer cells[32](#_ENREF_32). However, the only prospective randomized controlled trial comparing a hydrophobic statin (atorvastatin) to placebo before radical prostatectomy did not demonstrate a decreased PCa proliferation rate with atorvastatin[33](#_ENREF_33).

The differences in the pleiotropic effects between hydrophilic and hydrophobic statins are most likely caused by the different lipophilicity, caused by the presence or absence of polar moieties on their main hydrophobic structure[34](#_ENREF_34). This affects their solubility and localization, resulting in significant metabolic changes[35](#_ENREF_35). While hydrophobic statins passively diffuse into cells and are widely distributed throughout various tissues, hydrophilic statins are hepato-specific, and employ carrier-mediated mechanisms for hepatic cell uptake[36](#_ENREF_36), using the organic anion transporters (OAT)[8](#_ENREF_8). OATs normally transport endogenous substrates such as steroids, hormones, and neurotransmitters, but can also transport numerous drugs, including hydrophilic statins, antivirals, antibiotics, and anticancer drugs[37](#_ENREF_37). Several OATs are not exclusive to the liver and can be found in various other organs, including the prostate[38](#_ENREF_38). Additionally, many cancer tissues, including PCa, have abnormal expression of liver-specific OATs[39](#_ENREF_39), enabling direct uptake of hydrophilic statins into the prostate[40](#_ENREF_40). The aberrant overexpression of OATs has been shown to facilitate survival of metastatic prostate lesions during ADT by enabling uptake of critical cell nutrients[39](#_ENREF_39), [41](#_ENREF_41). However, this overexpression also boosts the sensitivity of castrate-resistant tumors towards anticancer medications such as docetaxel, due to its increased uptake. Direct PCa cell uptake of hydrophilic statins could facilitate their beneficial effect by enabling direct interaction with PCa cells.

Whether a beneficial effect of a specific statin group supersedes that of the other group has been previously explored in breast[42](#_ENREF_42), cervical[43](#_ENREF_43), ovarian[44](#_ENREF_44), and hepatic[45](#_ENREF_45) malignancies only. In breast cancer, hydrophobic statins were not shown to lower the cancer incidence rate[42](#_ENREF_42), while In cervical cancer, they had a beneficial effect on progression-free- and overall survival[43](#_ENREF_43). In hepatic and ovarian cancer, both hydrophilic and hydrophobic statins were shown to decrease the rate of cancer incidence[45](#_ENREF_45) and improve overall survival[44](#_ENREF_44), respectively. In a very recently published population-based study, hydrophilic statins were associated with an improved overall- and PCa-specific survival in a cohort of men with metastatic/advanced PCa on ADT[46](#_ENREF_46). This latter study supports our findings, showing the favorable role of hydrophilic over hydrophobic statins in PCa.

Our study is unique due to its large cohort of men, consisting of elaborate ‘real-world’ clinical data with relatively long follow-up time. To our knowledge, this is the only study specifically assessing the role of hydrophilic and hydrophobic statins on PCa diagnosis and PC-specific death, while also assessing the effect on undergoing an additional prostate biopsy. However, our study has several limitations. First, this was a retrospective population-based analysis with its associated selection bias and accompanying health administrative database inaccuracies. Second, the data is limited to men older than 66, and it contains information on patients who were diagnosed more than twenty years ago, when different prostate biopsy strategies (sextant as opposed to the contemporary systematic 12-core biopsy protocol), were utilized. Third, we lacked complete PSA data (limited from 2007), details of clinical-stage, prostate imaging, pertinent family history, ethnicity, and biopsy pathology results. With regards to PSA, our associations still held in this sub-cohort, but did not fully reach Bonferroni corrected statistical significance. Fourth, diabetes was defined as medication-treated diabetes only, and for this analysis, diabetic patients treated with diet only were not considered diabetic. Fifth, the fact that index year was significant in all models could also be explained by the fact that less time had passed for any of the events of interest to occur for the more recently included patients. The newly added men were censored before any outcomes of interest had occurred. Importantly, in such an analysis, there is always the risk of an immortal person-time bias that needs to be considered. Lastly, although our data is derived from a large province in Canada, it might not be generalizable to other similar populations.

**Conclusions**

In contrast to suggested in-vitro findings, hydrophilic statins uniquely appear to be associated with a decreased likelihood of being diagnosed with and dying from PCa and undergo an additional prostate biopsy. Hydrophilic statins appear to be the driving force behind the hazard reductions reported when statins are pooled as a drug family. Ideally, randomized controlled studies assessing the effect of statins on PCa-specific outcomes would help validate our findings. Barring such trials, statin prescribing doctors may want to consider utilizing hydrophilic statins among male patients.

**Abbreviations:**

ADT = Androgen deprivation therapy

ADG = Ambulatory Diagnostic Groups

AS = Active surveillance

CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database

HMGCoAR = 3-hydroxy-3-methylglutaryl coenzyme A reductase

ICES = Institute for Clinical and Evaluative Sciences

OAT = Organic anion transporters

OCR = Ontario cancer registry

ODB = Ontario drug benefit

OHIP = Ontario health insurance plan

OLIS = Ontario laboratory information system

ORG = Ontario office of the Registrar

RPDB = Registered persons database

PCa = Prostate cancer

PPI = Proton pump inhibitors

PSA = Prostate specific antigen

SREBP2 = Sterol regulatory element-binding protein-2

TRUS BX = Transrectal ultrasound guided prostate biopsy

**Author Contributions:**

Design and conception: HG, NF, SA, GSK, RS

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Writing of manuscript: HG, FKM

Editing and reviewing of manuscript: FKM, AB, SA, RS, CJDW, ZK, TC, AEA, RKS, OS, LP, GB, GSK, NF

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