**HYDROPHILIC STATINS DEMONSTRATE A CONSISTENT BENEFICIAL EFFECT ON PROSTATE CANCER OUTCOMES**

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**Abstract**

***Introduction***

The chemo-preventative effect of various medications in prostate cancer has been previously assessed. The specific role of statins in PCa has also been studied, but statins have always been analyzed as one single group and not stratified by its various subgroups (hydrophobic and hydrophilic statins). Based on a previous in-vitro study demonstrating a beneficial role of a hydrophobic statin, we aimed to clinically assess the specific role of both subgroups on PCa diagnosis.

***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. We analyzed the effect of commonly used medications (hydrophobic and hydrophilic statins, metformin, insulin, sulfonylurea, thiazolidinediones, proton pump inhibitors [PPIs], five-alpha-reductase inhibitors, alpha blockers, dipyridamole, chloroquine, and glaucoma eye drops) on the cumulative rate of PCa diagnosis, PCa-specific death, and risk of undergoing another prostate biopsy.

***Results***

A total of 21,512 men were analyzed with a mean follow-up time of 8.06 years (5.44). The most commonly used medications included statins (50.3%), PPIs (51.1%) and alpha-blockers (39.5%). A total of 24.1% were diagnosed with PCa, and 3.7% died from it. Any use of hydrophilic statins was associated with a 20% (95% CI 10-28%), 18% (95% CI 6.1-27.3%), and 32.4% (95% CI 12.9-47.5%) lower risk of undergoing an additional prostate biopsy, being diagnosed with PCa and dying from it, respectively. More specifically, for every six-months of hydrophilic statin use a 3.2% (95% CI 0.8-5.6%), 2.7% (95% CI 0.5-4.9%), and 4.3% (95% CI 1-8%) reduced risk was noted for undergoing an additional biopsy, being diagnosed with PCa, and dying from it, respectively.

***Conclusion***

Hydrophilic statins are associated with a significantly reduced risk of having another prostate biopsy, being diagnosed with PCa, and dying from it. The suggested chemo-preventative effect of this statin subgroup on PCa outcomes needs to be further explored.

**Introduction**

Prostate cancer (PCa) is the most common visceral 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). About 1 out of 9 men will be diagnosed with PCa during his lifetime, with 60% developing in men older than 65, with an average age of 66[1](#_ENREF_1).

Various medications have been assessed regarding their role in lowering PCa diagnosis rates and improving PCa-specific outcomes. These include prostate-specific drugs such as five-alpha-reductase-inhibitors[2](#_ENREF_2) and alpha blockers[3](#_ENREF_3), and other commonly used medications, such as metformin[4](#_ENREF_4), proton pump inhibitors (PPIs)[5](#_ENREF_5), and statins[6](#_ENREF_6). The role of statins in PCa and other malignancies has been extensively studied, but statins have mostly been analyzed as one single group and not stratified by its various subgroups.

Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) inhibitors, are mainly used to improve lipid profiles and reduce cardiovascular morbidity and mortality[7](#_ENREF_7). HMGCR is the rate-limiting enzyme of the mevalonate pathway, which is an integral pathway for cell growth and survival[8](#_ENREF_8). 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[9](#_ENREF_9). Although both groups are similar in their effect of reducing cholesterol; they harbor different pleiotropic effects. Recent in-vitro experiments showed that HMGCR inhibition 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. Additionally, SREBP2 inhibition with dipyridamole, an anti-platelet medication, potentiated fluvastatin-induced apoptosis in PCa cells[10](#_ENREF_10). There is also unpublished evidence showing that chloroquine, used for treating rheumatoid arthritis and malaria, might have a similar beneficial effect.

These findings led us to investigate the effect of hydrophilic and hydrophobic statins, dipyridamole, chloroquine, and other commonly used medications on PCa diagnosis. We hypothesized that hydrophobic statins would lower the diagnosis rate of PCa more than hydrophilic statins and other commonly used medications.

**Methods**

This study was approved by the University of Toronto’s ethics board committee. The study was designed and conducted according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines[11](#_ENREF_11), and Reporting of Studies Conducted Using Observational Routinely-Collected Health Data Statement[12](#_ENREF_12). We performed a retrospective population-based cohort study using data from the Institute for Clinical and Evaluative Sciences (ICES). In Ontario, all essential medical care is reimbursed by one single, government-operated health insurance system, the Ontario Health Insurance Plan (OHIP), enabling us to capture the entire adult population.

**Data sources**

Data was acquired from several specific datasets housed at ICES[13](#_ENREF_13) and detailed in supplemental Table 1. Patient-specific information from these databases is linkable using unique, encoded identifiers.

**Study design, setting, and participants**

We identified all men aged 66 and older with a history of a single negative transrectal ultrasound-guided prostate biopsy (TRUS-Bx) in the state of Ontario, Canada (estimated population of ~14 million) between 1st of January 1994 and 30th of September 2016. Relevant patients were identified using OHIP billing codes for TRUS-Bx, with no evidence of PCa diagnosis, nor receipt of PCa-specific treatment. 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. Moreover, this was the optimal method to minimize the risk of including men with an underlying misdiagnosed PCa on study entry. We utilized a look-back window from January 1991 until the date of cohort entry (minimum of 3 years) to ascertain that included TRUS-Bxs were truly the first negative biopsies and that men 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 commonly used medications on PCa-related outcomes. These included statins (hydrophilic and hydrophobic ), most common diabetic medications (metformin, insulin, sulfonylureas, thiazolidinediones), PPIs (pantoprazole, and all other PPIs), five-alpha-reductase inhibitors, alpha blockers, dipyridamole and chloroquine (to validate the previously shown in-vitro association with fluvastatin), and glaucoma eye drops as a tracer drug, serving as a negative control, to demonstrate no association with any of the outcomes. A complete list of all medications included in the analysis is shown in Appendix 1.

Although we could have captured all men aged 65 and above, we used the age of 66 as the minimum age for study inclusion. This was done 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. Therefore, we assumed that all men included in the analysis were not on any of the analyzed medications before the study period. 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). Men with missing data were excluded.

**Study outcomes**

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

**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. Additional collected variables included patient age categorized as (66-69, 70-74, 75-79, 80-84, and 85 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. A higher number represented a more rural area)[14](#_ENREF_14), Index year (year of study entry), 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)[15](#_ENREF_15). Comorbidities were captured with a 3-year look-back period. Prostate-specific antigen (PSA) levels were available only from 2007. Additionally, we also collected data on PCa treatments and PCa-specific death rates.

**Statistical analyses**

Continuous variables were described using means and standard deviations (SD), categorical variables were characterized using proportions. To estimate the effects of medication exposure on all outcomes of interest, several types of analyses were performed, assessing predictors of undergoing an additional prostate biopsy, being diagnosed with PCa, and PCa-specific death. 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 on all outcomes of interest. All 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. All covariates used for adjustment were selected a priori and were treated as time-independent variables using the values at study onset. For PCa-specific mortality, the analysis was restricted to PCa patients, with PCa diagnosis as the baseline, and PCa-specific treatments were incorporated as well. The proportionality and log-linearity assumptions underlying the models were assessed using residual-based diagnostics, and no violations were identified. Statistical significance was set at a two-sided P value of 0.05. 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 models, but specifically included only patients enrolled in the study from 2007, as PSA was only available from that year. 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**

A total of 21,512 men met our inclusion criteria. Figure 1 demonstrates the flow chart of the final cohort. Table 1 demonstrates basic demographic data, showing that 74.3% of men were aged 74 or younger. While the mean rurality index was similar across all patients, the mean ADG score increased with age, and the percentage of men with medically-treated diabetes decreased. The mean follow-up time was 8.06 years (5.44).

A total of 7,556 patients (35.1%) had at least one additional biopsy, as shown in supplemental figure 1. Figure 2 demonstrates the rates of medication usage, showing a high rate of statin use, with 10,818 patients (50.3%) taking at least one statin during the study period, with hydrophobic statins being the most common (6,607 patients, [61.1% of statin users]). Other commonly used medications included PPIs (10,999 patients [51.1%]) and alpha-blockers (8,505 patients [39.5%]). Supplemental figure 2 shows the rates of PCa diagnosis, PC-specific death, and all-cause mortality, while supplemental figure 3 demonstrates 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 for some other reason (1,811 patients, [34.9%]), with the rest treated with primary ADT (1,442 patients, [27.8%]), radiotherapy (1,155 patients. [22.3%]), or radical prostatectomy (779 patients, [15%]).

Table 2 demonstrates the Cox-proportional hazard multivariable model assessing for predictors of having an additional prostate biopsy. Hydrophilic statins were associated with a lower risk of undergoing an additional prostate biopsy, whether modelled as ever vs. never usage (HR 0.8, 95% CI 0.72-0.9), six months cumulative use (HR 0.968, 95% CI 0.944-0.992), and ever vs. never use incorporating PSA data from 2007 only (HR 0.71, 95% CI 0.529-0.968). When assessing PCa diagnosis, supplemental table 2 shows that when both statin group were combined, they were associated with a reduced risk of being diagnosed with PCa, when medications use was modeled per six months of cumulative use (HR 0.989, 95% CI 0.978-0.999). When adjusting for each statin group separately, Table 3 demonstrated that hydrophilic statins were associated with a decreased risk of being diagnosed with PCa, when medications use was modeled as ever. vs. never (HR 0.82, 95% CI 0.727-0.939) or six months cumulative use (HR 0.973, 95% CI 0.951-0.995). Supplemental table 3 examined the predictors of being diagnosed with PCa, with medications 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 for being diagnosed with PCa. We also analyzed statin interactions with medications that were shown to have a beneficial influence on PCa in-vivo and in-vitro. These included metformin and dipyridamole, but no statistically significant interaction effect was shown (Supplemental Table 4).

For PC-specific death, supplemental table 5 demonstrated that statins combined were associated with a decreased risk of dying from PCa when medications were modeled as ever vs. never (HR 0.76, 95% CI 0.64-0.90). When adjusting for each statin group, both hydrophilic and hydrophobic statins were associated with a lower risk of PCa death (Table 4), but the hydrophilic statin conferred a more significant effect, when modeled as ever vs. never (HR 0.676, 95% CI 0.525-0.871), and as six-months cumulative use (HR 0.957, 95% CI 0.92-0.99).

As for the other covariates in the models, age was associated a lower risk of undergoing a biopsy, and increased risk of being diagnosed and dying from PCa. ADG score was associated with a lower risk of undergoing a biopsy. Medically treated diabetes was associated with a lower risk of undergoing a biopsy and an increased risk of dying from PCa. The rurality index was associated with an increased risk of being diagnosed and dying from PCa. A rising index year was associated with a lower risk of having an additional biopsy, being diagnosed and dying from PCa. Lastly, PSA was associated with an increased risk of undergoing a prostate biopsy and being diagnosed with PCa.

Our negative control model, assessing predictors of being diagnosed with presbyopia demonstrated no statistically significant effect of any of the statins (supplemental Table 6). Furthermore, glaucoma eye drops, serving as a tracer drug, did not demonstrate any statistically significant association with any of the study outcomes.

**Discussion**

Our study demonstrated 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. Almost a quarter of them were eventually diagnosed with PCa with a 3.7% mortality rate. More than half of the men were taking a statin medication (most using a hydrophobic statin). Unexpectedly, our study demonstrated that hydrophilic rather than hydrophobic statin use, was generally associated with a 20%, 18% and 32.4% lower risk of undergoing an additional prostate biopsy, being diagnosed with PCa and dying from it, respectively. More specifically, every six-months of taking a hydrophilic statin, conferred a 3.2%, 2.7% and 4.3% reduced risk for undergoing an additional biopsy, being diagnosed with PCa, and dying from it, respectively.

Experimental in-vitro studies have shown that statins manifest antitumor effects against cancer cells by inhibiting cell proliferation, inducing apoptosis and impeding angiogenesis and metastasis[8](#_ENREF_8). HMGCR, the enzyme inhibited by statins, catalyzes the conversion of HMG-CoA into mevalonate. Mevalonic acid is a precursor of cholesterol and the isoprenoid intermediates farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). These isoprenoids are critical in the process of prenylation, where FPP or GGPP are post-translationally added to a protein facilitating cell-membrane anchoring[16](#_ENREF_16). Prenylation also occurs in oncoproteins involved in numerous malignancies, facilitating their cell-membrane anchorage[17](#_ENREF_17). The statin-induced inhibition of these processes reduces tumor cell proliferation, destabilizes membrane integrity and impedes cell signalling[18](#_ENREF_18).

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 demonstrated an association between statins and PSA level reduction[19](#_ENREF_19) (lowering the risk of being referred for a prostate biopsy), lower PC diagnosis rate[20](#_ENREF_20), longer time to progression during ADT in hormone-sensitive PCa[21](#_ENREF_21), and lower PCa-specific mortality[22-25](#_ENREF_22). In contrast, other large retrospective studies have shown no beneficial effect of statins as a group on PCa diagnosis[26](#_ENREF_26) and biochemical recurrence rate[27](#_ENREF_27), [28](#_ENREF_28). One possible reason for these mixed contradictory findings is that statins were analyzed as one group. There are in-vitro studies demonstrating that hydrophobic statins may be more effective at suppressing micrometastatic outgrowth due to increased uptake into cancer cells[29](#_ENREF_29). However, the only prospective randomized controlled trial comparing a hydrophobic statin (atorvastatin) to placebo before radical prostatectomy did not demonstrate a lower PCa proliferation rate with atorvastatin[30](#_ENREF_30).

The differences in the pleiotropic effects between hydrophilic and hydrophobic statins are most likely caused by the inequality in their lipophilicity, caused by the presence or absence of polar moieties on their main hydrophobic structure[31](#_ENREF_31). This, in turn, affects their solubility and localization, resulting in significant metabolic changes[32](#_ENREF_32). 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[33](#_ENREF_33), using the organic anion transporters (OAT)[9](#_ENREF_9). 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[34](#_ENREF_34). Several OATs are not exclusive to the liver and can be found in the brain, colon, heart, kidney, lung, ovary, pancreas and prostate[35](#_ENREF_35). Additionally, many cancer tissues, including PCa, have abnormal expression of liver-specific OATs[36](#_ENREF_36), enabling direct uptake of hydrophilic statins into the prostate[37](#_ENREF_37). The aberrant OATs overexpression has been shown to facilitate survival of metastatic prostate lesions during ADT by enabling uptake of critical cell nutrients[36](#_ENREF_36), [38](#_ENREF_38). However, this overexpression also boosts the sensitivity of castrate-resistant tumors towards 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 supersedes that of the other statin group has been previously explored in breast[39](#_ENREF_39), cervical[40](#_ENREF_40), ovarian[41](#_ENREF_41), and hepatic[42](#_ENREF_42) malignancies only. In breast cancer, hydrophobic statins were not shown to lower the cancer rate[39](#_ENREF_39), while In cervical cancer, they had a beneficial effect on progression-free- and overall survival[40](#_ENREF_40). In hepatic and ovarian cancer, both hydrophilic and hydrophobic statins were demonstrated to lower the rate of cancer diagnosis[42](#_ENREF_42) and improve overall survival[41](#_ENREF_41), respectively. In a very recently published population-based study, hydrophilic statins were associated with an improved overall- and PCa-specific survival in men with metastatic/advanced PCa on ADT[43](#_ENREF_43). This study helps validate our findings, showing the favorable role of hydrophilic statins as a subgroup in PCa.

Our study is unique due to its large cohort of men, consisting of elaborate clinical data with a relatively long follow-up time. 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), and treatment concepts 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. Fourth, we did not account for all the prescribed medications and could not account for over the counter medications at all. Fifth, diabetes was defined as medication-treated diabetes only, and diet-treated diabetic patients were not considered diabetic. 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 appear to significantly lower the risk of an additional prostate biopsy, PCa diagnosis, and PCa-specific death. Hydrophilic statins appear to be the driving force behind the risk reductions witnessed when statins are combined. Randomized controlled studies assessing the specific effect of hydrophilic and hydrophobic statins on PCa-specific outcomes, should be considered to ascertain and validate their chemo-preventative effect.

**Abbreviations:**

ADT = Androgen deprivation therapy

ADG = Ambulatory Diagnostic Groups

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

FFP = Farnesyl pyrophosphate

GGPP = Geranylgeranyl pyrophosphate

HMGCR = 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

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

Data collection and analyses: HG, FKM, OS, RS, AB, SH, CJDW, LP, GSK, NF

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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