The risk of prostate cancer for men on aspirin, statin or antidiabetic medications

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Abstract Background: A decreased risk of prostate cancer (PCa) has been suggested in men taking aspirin, statins and metformin, although the evidence has been conflicting. We estimated the association between prescribed medications, prostate specific antigen (PSA) levels and the risk of either any PCa or high-grade PCa.

Methods: This population-based cohort study included 185,667 men having a first recorded PSA test and 18,574 men having a first prostate biopsy in Stockholm County, Sweden for the period 2007–2012. Detailed clinical information including PSA levels, biopsy results, comorbidities and educational level were obtained from population-based registers. High-grade prostate cancer was defined as a Gleason score of seven or higher. Differences in PSA levels by medication status were estimated using linear regression on log PSA values. PCa risk was estimated using multivariate logistic regression.

Results: Compared with men who were not on medication, the PSA level at the first PSA test was lower among men using 75 mg/dose aspirin (−3.9% change in PSA concentration; 95% confidence interval (CI): −5.8 to −2.1), statin (−4.6%; 95% CI: −6.2 to −2.9), metformin (−14%; 95% CI: −17 to −12) and insulin (−16%; 95% CI: −18 to −14). Men using any statins had an increased risk of both high-grade PCa (odds ratio (OR) 1.25; 95% CI: 1.10–1.42) and PCa of any grade (OR 1.16; 95% CI 1.04–1.29). There were no significant associations between aspirin or any antidiabetic medication and the risk of PCa.

Conclusion: We found no protective effect of aspirin, statins or antidiabetics in terms of risk for any PCa or high-grade PCa. Use of any statins was associated with an elevated risk of being diagnosed with high-grade prostate cancer.

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1. Introduction

Prostate cancer is a leading cause of cancer death for men in the Western world [1]. Its burden on society is substantial and the direct costs of prostate cancer care in Sweden are expected to double until 2020 [2]. PSA testing and ultrasound guided biopsies remain the cornerstone of prostate cancer diagnostics. Referral to prostate biopsy may depend on age, family history of prostate cancer, ethnicity, total and free PSA levels, previous biopsy results or other biomarker levels. Considerable effort has been expended to improve the prediction of biopsy outcomes and different risk calculators have been developed to aid decision-making [3,4]. Better risk prediction tools are needed due to increasing diagnosis-related costs, biopsy-related morbidity, including a rising incidence of infectious complications due to antibiotic-resistant bacteria [5], and increased costs and morbidity due to over-diagnosis and over-treatment [6].

A number of observational studies have addressed how statins, aspirin and metformin treatment affects the risk of prostate cancer. It has been suggested that prostate cancer risk is reduced by 10% in regular aspirin users [7]. This was supported by a meta-analysis in 2014 including 39 observational studies suggesting a risk reduction for prostate cancer (odds ratio (OR) 0.92), advanced prostate cancer (OR = 0.81) and prostate cancer mortality (OR = 0.86) [8]. This has also been found in randomised trials of aspirin versus placebo [9].

Statins have been suggested to be associated with a decreased incidence of several cancers including prostate cancer, possibly with a larger effect of the hydrophobic compared with the hydrophilic statins [10–13]. Results are, however, conflicting and recent studies of men in the Prostate Cancer Prevention Trial (PCPT) and Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study showed no protective effect of statins with seven and four year follow-up, respectively [14,15].

Moreover, antidiabetic drugs, particularly metformin, have been suggested to increase disease-specific survival after prostate cancer diagnosis, but evidence has been conflicting for the association between metformin treatment and prostate cancer risk [16–18].

The published observational studies have commonly lacked data on socioeconomic status, comorbidity or PSA levels. We incorporated such data from a large population-based cohort of men to assess whether aspirin, statins and antidiabetic medications were predictors of cancer risk following a prostate biopsy.

2. Methods

2.1. Study population

The study population for this retrospective cohort study were men in Stockholm County undergoing a PSA test between 2003 and 2012. For an analysis of the effect of different medications on PSA levels, we restricted the cohort to men undergoing a first PSA test between 2007 and 2012, providing at least four years from the start of the cohort and 2 years from the start of the Swedish Prescribed Drug Register in 2005. For an analysis of the effect of medications on the risk of prostate cancer following a biopsy specimen, we restricted the cohort to those men having a first prostate biopsy in Stockholm County between 2007 and 2012, providing at least four years since the start of the cohort. A flowchart illustrating the study cohort is given in Fig. 1 and further described in Tables 1A and B.

2.2. Clinical data

PSA values, biopsy records and prostate cancer records were retrieved from the STHLM0 database [19]. Briefly, this database consists of all men in the Stockholm County who had at least one PSA analysed since 2003 together with their biopsy records and prostate cancer history as recorded by the National Prostate Cancer Register (NPCR). The NPCR has greater than 93% coverage of prostate cancer cases in Sweden. Pathology reports on all prostate biopsy results were retrieved from pathology laboratories in Stockholm and included malignancy coding in the SNOMED format. The individual data were matched against the National Cancer Registry and the NPCR to obtain cancer status and clinical information [20]. Although cancer findings on biopsy (cancer/no cancer) were complete, the Gleason score was missing in 6% of cases. Comorbidity was assessed using the Charlson Comorbidity Index (CCI) [21] 1 month prior to PSA test or prostate biopsy using the National Patient Register. This nationwide register includes the main diagnosis and up to seven secondary diagnoses from all inpatient hospitalisations since 1987 [22]. All men with antidiabetic medication in the Prescribed Drug Register were coded as having diabetes.

All participants were linked with information from Statistics Sweden on the highest level of education. Educational level was categorised into three levels: 0–9 years of education, high school, and university or higher.

2.3. Medication assessment

Information on prescribed drug use was obtained from the Swedish Prescribed Drug Register [23], which is mandated in Swedish law and includes all drug prescriptions in Sweden since 2005. Drugs were classified according to Anatomical Therapeutic Chemical (ATC) classifications [24]. Drug use was defined as any dispensed prescription of the drug within two years before biopsy. While high-dose aspirin (commonly 500 mg) can be bought over the counter in Sweden usually for
treatment of pain, aspirin prescriptions predominantly consist of low-dose (75 mg daily) treatment for prevention of cardiovascular disease.

2.4. Statistical methods

Potential confounders in the analyses included: age at prostate biopsy; age at PSA test; educational level; CCI; PSA value before biopsy; PSA quotient (Free PSA/Total PSA); and co-existing medication with statins, aspirin and antidiabetics.

The distribution of total PSA was right skewed and hence PSA levels by age-groups were presented as geometric means. The geometric mean was calculated as $\sqrt[n]{x_1 \cdot x_2 \cdot \ldots \cdot x_n}$. To illustrate differences in PSA levels, a linear regression was fitted on the log-transformed PSA levels with adjustment for age at the PSA test, comorbidity and medications. The anti-logs were calculated to express the percentage differences in PSA levels between groups.

Uni- and multi-variate logistic regressions were fitted on the risk of having prostate cancer and high-grade prostate cancer. Analysing high-grade prostate cancer, lower grade cancers were classified as controls together with benign findings. The regression model was adjusted for age, log-transformed PSA level, PSA quotient, comorbidity, educational level and medication use. For analyses of medication sub-groups, users of other sub-groups were excluded (e.g. when analysing the association between hydrophilic statins and risk of prostate cancer, men using other statins were excluded from the analysis).

The statistical analyses were performed using Stata 12 (Stata Corp, College Station, TX).

3. Results

For the period 2007–2012, 185,657 men without a prior prostate cancer or prostate biopsy had their first PSA test taken in Stockholm County. The prevalence of low-dose aspirin, statins and antidiabetic use was 12%, 12% and 4%, respectively, with a high degree of overlap between medications (see Table 1A). Men taking one or more of these medications tended to be older (mean age 65 versus 56; $p < 0.001$) and had significantly more comorbidities ($p < 0.001$).

For the same period, 18,574 men had their first prostate biopsy in Stockholm County. Of these, 10,144 (54%) had a benign biopsy finding, and 3076 (17%) and 4280 (23%) had prostate cancer diagnosed with Gleason score $\leq 6$ and $\geq 7$, respectively (Table 1B).

The geometric mean PSA increased from 1.05 ng/ml (95% confidence interval (CI): 1.04–1.06) for men aged 50–59 years through to 3.79 ng/ml (95% CI: 3.60–3.99) for men aged 80–89 years (Table 2). Metformin users had a 14% (95% CI: 12–17) lower PSA level than non-users after adjusting for age, comorbidity and other medications. Insulin users had a 16% lower PSA (95% CI: 14–18) than non-users. When excluding metformin users from the analysis, the decrease among insulin-users was similar (15%; 95% CI: 11–18). Men using
Aspirin had 3.4% (95% CI: 1.7–5.2; p < 0.001) lower PSA and men using statins had 4.6% lower PSA (95% CI: 2.9–6.2; p < 0.001) than non-users. PSA levels among subgroups of statin users were moderately lower than among men without medication (Table 2).

We performed a sub-group analysis on 4788 men coming for their first PSA test and subsequently being diagnosed with prostate cancer, comparing men using medications with non-users. In this analysis aspirin users had 9% lower PSA (95% CI: 0–18; p = 0.063) than...
non-users and men using statins had 8% lower PSA (95% CI: 2–17; p = 0.11) than non-users. Again the effect size between antidiabetic medication use and PSA was stronger than the effect for the other medications, where PSA was 19% (95% CI: 4–36; p = 0.011) lower among users than non-users.

For men with moderate life expectancy, the decision to perform a prostate biopsy is based primarily on the risk that man has prostate cancer and, in particular, the risk of high-grade prostate cancer. In the multivariate analysis, an increased risk of prostate cancer and high-grade prostate cancer were associated with increasing age, increasing PSA level and decreasing free/total PSA (Table 3). Statin use was associated with a significantly increased risk of finding any prostate cancer (OR 1.16; 95% CI: 1.04–1.29) and high-grade prostate cancer (OR 1.25; 95% CI: 1.10–1.42). This association persisted when restricting the analysis to either hydrophilic statins or hydrophobic statins and also when excluding education and comorbidity from the regression model. A borderline significant association was also seen between the risk of prostate cancer and aspirin use (OR 1.12; 95% CI: 0.99–1.25; p = 0.06); this association was not significant for high-grade cancer (OR 1.03; 95% CI: 0.89–1.17; p = 0.72).

The excess risk of high-grade prostate cancer at first biopsy among statin users compared with non-users by level of PSA is illustrated in Fig. 2. We note that the risk of high-grade prostate cancer is increased among men on statin medication.

4. Discussion

In this large, population-based cohort study, use of aspirin or statins were associated with lower PSA levels, and PSA was also substantially lower among men taking insulin or metformin compared with non-users. Use of these medications was not associated with a lower incidence of prostate cancer.

In line with previous knowledge, we report a slightly lower PSA among men on aspirin and statins, possibly affecting the results of previous observational studies without access to PSA data. More interestingly, we found that men on an anti-diabetic medication had a significantly lower PSA compared with non-users. This might quite substantially affect findings in observational studies by both selection bias and confounding, and should be taken into account when designing future studies. The importance of PSA is indicated by the diminishing association between medication and cancer when adding covariates to the univariate analysis (Table 3).

The evidence on the association between any given of the studied medications and prostate cancer is inconsistent. The association between statins and prostate cancer have been addressed in the setting of 23,320 men PSA-tested in organised screening (1584 cancer cases) by Murtola et al. indicating a modest dose-dependent decreased risk of statins on the risk of all and low-grade prostate cancer [13]. However, the effect size of other cholesterol-lowering drugs were the same
Table 3
Uni- and multivariate logistic regression analysis on risk of any prostate cancer (n = 8430) and high-grade prostate cancer (n = 4242) in men undergoing first prostate biopsy (n = 18,574).

<table>
<thead>
<tr>
<th></th>
<th>Any prostate cancer</th>
<th>High-grade prostate cancer (Gleason sum ≥ 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate analysis</td>
<td>Multivariate analysis</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>Confidence interval (CI) (95%)</td>
</tr>
<tr>
<td>Age</td>
<td>1.028</td>
<td>1.024–1.031</td>
</tr>
<tr>
<td>Ln (Total PSA)</td>
<td>2.381</td>
<td>2.252–2.480</td>
</tr>
<tr>
<td>PSA quotient</td>
<td>0.0023</td>
<td>.0015–.0035</td>
</tr>
<tr>
<td>Charlson Index</td>
<td>1.154</td>
<td>1.106–1.205</td>
</tr>
<tr>
<td>Educational level</td>
<td>0.915</td>
<td>0.880–0.951</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>1.206</td>
<td>1.123–1.294</td>
</tr>
<tr>
<td>Any statin use</td>
<td>1.159</td>
<td>1.085–1.238</td>
</tr>
<tr>
<td>Hydrophilic statin(^1) use</td>
<td>1.186</td>
<td>1.051–1.338</td>
</tr>
<tr>
<td>Hydrophobic(^2) statin use</td>
<td>1.150</td>
<td>1.070–1.238</td>
</tr>
<tr>
<td>Any antidiabetic use</td>
<td>1.095</td>
<td>0.986–1.214</td>
</tr>
<tr>
<td>Insulin use(^2)</td>
<td>1.110</td>
<td>0.935–1.317</td>
</tr>
<tr>
<td>Metformin use(^2)</td>
<td>1.063</td>
<td>0.909–1.243</td>
</tr>
</tbody>
</table>

Note: Multivariate analysis adjusted for age, natural log-transformed prostate specific antigen (PSA) concentration, PSA quotient, Charlson Comorbidity Index, educational level, use of aspirin, use of statin and use of antidiabetic medication. OR - Odds ratio.

\(^1\) Other statin types excluded from analysis.

\(^2\) Other antidiabetic medications excluded from analysis.
as for statins (though insignificant), which might indicate an effect of lipid levels rather than medication. A recent Danish population-based study used 42,480 register-identified men with prostate cancer and population controls to show a lower risk of both all (OR 0.94) and high-stage (OR 0.90) prostate cancer among users [12]. However, as the study lacked data on both PSA and tumour grade, there is a risk of substantial residual confounding, which is also discussed by the authors. Using the control-arm of the PCPT trial, Platz and colleagues found no association between medication during the trial and the risk of prostate cancer at end-biopsy (HR 1.03)[15]. This trial was performed in a screening setting and included few advanced cancers (n = 156).

A majority of observational studies indicate small to non-significant beneficial effects of aspirin on prostate cancer risk [25]. This is in line with the 10% risk reduction reported by Dhillon in a study of 1296 cancer cases [26] and Veitonmäki using 24,657 case-control pairs [27]. The latter study, however, lacked data on tumour grade and PSA levels.

Recently, it has been suggested that metformin may decrease the risk of prostate cancer. The evidence for this is more sparse; in 2007, Murtola and colleagues reported a decreased prostate cancer risk among users (OR 0.87), but without taking PSA levels into account [28]. Margel recently reported no relation between metformin on the risk of prostate cancer, but a lower prostate cancer-specific mortality among diabetic men with prostate cancer on metformin (OR 0.76) [16,17]. A meta-analysis done by Zhang et al. found no beneficial effect of metformin on prostate cancer incidence [18]. Similarly, a recent small study on men in the Aarau arm of ERSPC did not show any difference in PSA levels or prostate cancer incidence among men with or without metformin medication [30]. As aspirin, statin or metformin are well-tolerated and inexpensive medications, they are potential drug targets for a chemoprevention trial for prostate cancer, as has been repeatedly suggested [10,17,27]. However current evidence does not convincingly support a moderate or strong reduction in prostate cancer risk from these drugs.

It has been suggested that the associations between statin use and prostate cancer are mediated by an effect of blood lipid levels on cancer risk. In a case-control setting, Morote et al. recently demonstrated that serum cholesterol was an independent predictor of both prostate cancer and high-grade cancer (Gleason 8–10), but statin use was not [29]. In line with their study, we show a 25% increased risk of finding high-grade cancer among statin users. We cannot rule out residual confounding as an explanation of this finding since we lack data on lipid levels.

Strengths of this study include its size and population-based nature together with independent medication ascertainment and access to original biopsy specimen data as well as PSA, clinical and socioeconomic data.

There are several limitations of the study. First, we lack information on the indications for PSA testing among men in Stockholm, giving a risk of selection bias. However, more than two thirds of men aged over 50 years have undergone PSA testing in the region [19]. Second, as suggested by Murtola [13], there is a risk

Fig. 2. The risk of high-grade prostate cancer findings on prostate biopsy by prostate-specific antigen (PSA) level and stratified by statin medication as predicted by multivariate logistic regression. A logistic regression model was fitted and adjusted for age, log-transformed PSA level, PSA quotient, Charlson Comorbidity Index, educational level, aspirin use and antidiabetic use. Predicted probability of finding Prostate Cancer is shown on the original (un-logarithmised) scale. 18,574 biopsied men of which 8,430 had Prostate Cancer diagnosed (4242 were Gleason sum ≥6) were included.
that men on medications seek PSA testing more frequently or are recommended testing by their treating physician, introducing a detection bias that masks potential protective effects of the medication and possibly results in lower PSA levels among these men. However, this also implies that the protective effect of medication on high-grade disease would be over-estimated if men on medication have their cancers detected earlier due to more frequent PSA testing. These biases may be counter-balanced by the observation that men who seek PSA testing tend to be more health-conscious overall. Third, older patients tend to have higher grade disease and are using both cardiovascular and antidiabetic drugs to a higher extent. We sought to address this issue by including both comorbidity and age in our multivariate model.

Fourth, there is a risk of exposure misclassification for aspirin as we lack data on medication bought over-the-counter. However, although the dose usually is higher (250–500 mg) this is mostly for short term use to treat pain or fever.

Fifth, this study focuses on the association between drug use and the risk of finding prostate cancer on biopsy. We do not provide any data on the risk of disease progression or mortality, which must be kept in mind when comparing with previous studies. Sixth and finally, as for other observational studies, residual confounding may have been introduced by unmeasured risk factors for prostate cancer (e.g. minor comorbidities, physical activity, diet and body mass index).

In conclusion, we found that aspirin, statins and metformin were not associated with any protective effect on prostate cancer or high-grade prostate cancer, thus giving no support for the use of these drugs in chemopreventive trials. Furthermore, we found an association between antidiabetic medication and PSA levels.

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References