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Null Results in Brief

Cancer Epidemiology, Biomarkers & Prevention

Statin Use and Prostate Cancer Incidence in Manitoba, Canada: A Population-Based Nested Case–Control Study

Christiaan H. Righolt, Robert Bisewski, and Salaheddin M. Mahmud

Abstract

Background: A link between statin use and prostate cancer risk has been proposed. Epidemiologic evidence is, however, inconclusive, and data for specific statin types as well as for period, duration, and dose of use are lacking.

Methods: We conducted a population-based nested case–control study using administrative data in Manitoba, Canada. Prostate cancer cases were matched to cancer-free controls, and their statin use (including period, duration, and dose of use) was assessed (with adjustment for prostate cancer screening) for statins as a class and for each specific statin.

Results: We matched 9,384 prostate cancer cases to 46,749 cancer-free controls. Ever use of any statin was not associated with prostate cancer risk, odds ratio (OR) 0.96 (95% confidence interval, 0.90–1.03). Except for pravastatin, 0.82 (0.71–0.96), individual statins were not associated with prostate cancer risk. There was no dose or duration response for pravastatin (or any other statin).

Conclusions: We found limited evidence of an association between statin use and prostate cancer risk. The association between pravastatin and prostate cancer risk may be due to chance.

Impact: We show that statin use is not associated with prostate cancer risk after adjustment for screening for a large population with data going back to the mid-1990s.

Introduction

Little is known about modifiable risk factors for prostate cancer, which is the most frequently diagnosed cancer in men and a leading cause of cancer-related deaths. A link between statin use and prostate cancer risk has been proposed, but the epidemiologic evidence is inconclusive (although some evidence suggests a small, inverse association between statin use and advanced prostate cancer; ref. 1). Study results could differ, because most studies did not adjust for confounding by prostate cancer screening (2). Because statin users are more likely to be screened (possibly due to more frequent physician visits, which can increase early detection and confound results for both total and advanced prostate cancer), screening should be adjusted for (3, 4). Most studies did not examine variability due to differences in lipophilicity and potency of specific statins (1, 5). Only a few studies examined the associations for period, duration, or dose of use. We examined the association between statin use and prostate cancer incidence in the Canadian province of Manitoba.

Methods

We linked the Manitoba Cancer Registry (MCR) to the provincial prescription drugs database (DPIN) and other Manitoba Health (MH) databases (covering virtually all residents) to conduct a nested case–control study using the same methods we employed in previous studies (6, 7).

Briefly, we identified all men 40 years or older who were registered with MH during 2000 to 2014 with $\geq$5 years of insurance coverage (to ensure exposure data has sufficient length). Using a unique personal identifier, we linked to the MCR to identify all prostate cancer diagnoses [*International Classification of Diseases for Oncology*, Third Edition (ICD-O-3) code C61.9], and used incidence density sampling to match each case (on birth date, duration of coverage, and region of residence) to up to five cancer-free controls. Using the DPIN, we measured all statin use before the index date (the case's diagnosis date). We used conditional logistic regression (to account for matching) to calculate odds ratios (OR) of the association between prostate cancer risk and statin use (both as a class and for each individual statin) while adjusting for confounders, including a previously described screening score (ref. 7; data on routine bloodwork, including PSA testing, were not available). We also assessed the association by period (years before the index date), duration, and dose of statin use.

Results

We matched 9,384 prostate cancer cases to 46,749 cancer-free controls (Table 1). Ever use of any statin was similar between cases (24.5%) and controls (25.2%). As expected, cases were screened more often (78%) than controls (35%). Otherwise, the two groups were comparable in terms of medication use, history of chronic diseases, and patterns of healthcare utilization.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Table 1. Number (%) of prostate cancer cases and their controls according to certain socioeconomic and clinical characteristics

	Case (*N* = 9,384)	Control (*N* = 46,749)
Age group		
40–55	793 (8.5%)	3,976 (8.5%)
56–60	1,045 (11.1%)	5,215 (11.2%)
61–65	1,606 (17.1%)	8,015 (17.1%)
66–70	1,858 (19.8%)	9,270 (19.8%)
71–75	1,630 (17.4%)	8,105 (17.3%)
76–80	1,179 (12.6%)	5,862 (12.5%)
81+	1,273 (13.6%)	6,306 (13.5%)
Rural residence	3,735 (39.8%)	18,508 (39.6%)
Income quintile		
Q1 (lowest)	1,459 (15.5%)	8,147 (17.4%)
Q2	1,860 (19.8%)	9,433 (20.2%)
Q3	1,889 (20.1%)	9,776 (20.9%)
Q4	1,989 (21.2%)	9,605 (20.5%)
Q5 (highest)	2,009 (21.4%)	8,664 (18.5%)
Unknown	178 (1.9%)	1,124 (2.4%)
Ever use of statins		
Any statin	2,299 (24.5%)	11,794 (25.2%)
Atorvastatin	1,460 (15.6%)	7,455 (15.9%)
Cerivastatin	132 (1.4%)	692 (1.5%)
Fluvastatin	73 (0.8%)	323 (0.7%)
Lovastatin	92 (1.0%)	520 (1.1%)
Pravastatin	237 (2.5%)	1,340 (2.9%)
Rosuvastatin	442 (4.7%)	2,181 (4.7%)
Simvastatin	567 (6.0%)	2,892 (6.2%)
Ever use of other prescription drugs		
Non-statin lipid-lowering drug	452 (4.8%)	2,500 (5.3%)
Metformin	693 (7.4%)	4,237 (9.1%)
Other oral hypoglycemic drug	561 (6.0%)	3,562 (7.6%)
Insulin	155 (1.7%)	975 (2.1%)
Aspirin	1,306 (13.9%)	7,070 (15.1%)
Non-aspirin NSAID	3,880 (41.3%)	18,646 (39.9%)
Any chronic disease	4,610 (49.1%)	23,387 (50.0%)
Chronic cardiovascular disease (excluding hypertension)	2,793 (29.8%)	14,511 (31.0%)
Peripheral cardiovascular disease	674 (7.2%)	3,298 (7.1%)
Diabetes	1,560 (16.6%)	8,904 (19.0%)
Chronic renal failure	258 (2.7%)	1,110 (2.4%)
Chronic respiratory disease (excluding asthma)	1,220 (13.0%)	6,433 (13.8%)
Chronic liver disease	53 (0.6%)	304 (0.7%)
Number of physician visits in the 5-year period before the index date		
0–19	1,700 (18.1%)	11,929 (25.5%)
20–39	2,937 (31.3%)	13,584 (29.1%)
40–59	2,140 (22.8%)	9,525 (20.4%)
60+	2,607 (27.8%)	11,711 (25.1%)
Number of hospitalizations in the 5-year period before the index date		
0	4,266 (45.5%)	23,323 (49.9%)
1	2,193 (23.4%)	9,731 (20.8%)
2	1,206 (12.9%)	5,544 (11.9%)
3	700 (7.5%)	3,067 (6.6%)
4+	1,019 (10.9%)	5,084 (10.9%)
Screening indicator[a]	7,271 (77.5%)	16,452 (35.2%)

[a]Hyperplasia, inflammation, or disorder of the prostate in the year before the index date or a urologist visit 1–11 years before the index date.

Ever use of any statin was not associated with prostate cancer risk: OR = 0.96 (95% confidence interval, 0.90–1.03; Table 2). Except for pravastatin, 0.82 (0.71–0.96), ever use of individual statins was not associated with prostate cancer risk. There was also no period-, duration-, or dose-response for use of statins (Table 2) except for use of pravastatin [0.60 (0.40–0.89) among those who used it 11–20 years before the index date]. We found similar results when we limited our analysis to clinically significant prostate cancer [Supplementary Table S1; 1,636 cases; lymph nodes positive for metastatic prostate cancer or clinical stage American Joint Committee on Cancer (AJCC) 3–4; prostate cancer–specific grading is not included in the MCR].

Discussion

We found no evidence of an association between statin use and prostate cancer risk. Although a 2012 meta-analysis reported a relative risk of 0.93 (0.87–0.99; ref. 8), more recent reviews highlighted significant heterogeneity between published studies, many of which relied on questionnaires for exposure data and lacked adjustment for screening (1, 2). We used routinely collected point-of-sale prescription information to avoid recall bias and attempted to adjust for screening.

The statistically significant association between pravastatin use and prostate cancer risk is not supported by other studies (5).

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Table 2. Adjusted[a] OR (95% confidence interval) of the association between statin use and prostate cancer according to statin type

	Any statin	Atorvastatin[b]	Cerivastatin[b]	Fluvastatin[b]	Lovastatin[b]	Pravastatin[b]	Rosuvastatin[b]	Simvastatin[b]
Ever use	0.96 (0.90–1.03)	1.00 (0.93–1.08)	1.01 (0.82–1.24)	1.18 (0.89–1.56)	0.95 (0.74–1.21)	0.82 (0.71–0.96)	0.99 (0.88–1.12)	1.00 (0.90–1.11)
Period of use (years prior to the index date)[c]								
Never use	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
2–5	1.00 (0.93–1.08)	1.00 (0.92–1.09)	1.34 (0.97–1.85)	1.31 (0.90–1.92)	0.93 (0.66–1.31)	0.97 (0.79–1.18)	1.02 (0.89–1.17)	1.00 (0.87–1.14)
6–10	0.95 (0.86–1.05)	0.93 (0.82–1.05)	0.94 (0.68–1.31)	0.72 (0.43–1.18)	1.17 (0.78–1.76)	0.90 (0.70–1.15)	0.94 (0.74–1.19)	1.04 (0.87–1.23)
11–20	1.03 (0.87–1.21)	1.21 (0.98–1.49)	0.97 (0.63–1.49)	1.44 (0.73–2.83)	0.63 (0.33–1.20)	0.60 (0.40–0.89)	0.71 (0.08–6.07)	1.10 (0.83–1.45)
Duration of use (years)								
Never use	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
<1	0.97 (0.88–1.07)	1.01 (0.90–1.12)	0.98 (0.77–1.25)	1.65 (1.14–2.37)	0.75 (0.48–1.18)	0.83 (0.65–1.04)	1.01 (0.85–1.20)	1.03 (0.88–1.22)
1	0.96 (0.84–1.09)	1.14 (0.98–1.32)	1.07 (0.73–1.57)	0.88 (0.44–1.77)	1.06 (0.63–1.77)	0.82 (0.56–1.19)	0.87 (0.66–1.14)	0.88 (0.68–1.14)
2–4	0.97 (0.88–1.07)	0.92 (0.81–1.04)	N/A	0.74 (0.35–1.54)	1.00 (0.64–1.57)	0.81 (0.60–1.09)	1.14 (0.92–1.40)	0.93 (0.76–1.13)
5+	0.94 (0.84–1.06)	1.00 (0.86–1.16)	N/A	0.72 (0.30–1.70)	1.11 (0.66–1.86)	0.84 (0.59–1.19)	0.68 (0.43–1.08)	1.14 (0.91–1.42)
Relative time of use (% of follow-up)								
Never use	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
1–9	0.94 (0.85–1.04)	1.03 (0.92–1.15)	1.08 (0.85–1.38)	1.62 (1.08–2.42)	0.72 (0.45–1.16)	0.82 (0.63–1.06)	0.90 (0.75–1.07)	1.02 (0.86–1.22)
10–24	0.97 (0.88–1.08)	1.02 (0.90–1.15)	1.12 (0.70–1.78)	0.90 (0.48–1.69)	1.23 (0.80–1.89)	0.79 (0.58–1.07)	1.05 (0.85–1.28)	0.92 (0.75–1.12)
25–49	0.93 (0.84–1.03)	0.91 (0.80–1.04)	N/A	0.53 (0.24–1.14)	0.93 (0.59–1.46)	0.82 (0.60–1.10)	0.92 (0.66–1.27)	0.96 (0.79–1.16)
50+	0.96 (0.82–1.13)	0.96 (0.74–1.26)	N/A	1.84 (0.52–6.48)	1.17 (0.57–2.41)	0.95 (0.57–1.58)	N/A	1.34 (0.97–1.87)
Average annual dose (DDD)								
Never use	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
1–182	0.96 (0.90–1.03)	1.00 (0.92–1.08)	1.00 (0.82–1.23)	1.17 (0.88–1.55)	0.96 (0.75–1.23)	0.87 (0.74–1.02)	1.00 (0.88–1.13)	0.98 (0.88–1.10)
183–365	0.98 (0.83–1.14)	1.04 (0.83–1.31)	N/A	N/A	0.73 (0.20–2.67)	0.52 (0.31–0.86)	0.63 (0.30–1.33)	1.11 (0.82–1.51)
366–546	0.92 (0.63–1.34)	0.53 (0.28–1.01)	N/A	N/A	N/A	1.08 (0.27–4.32)	1.20 (0.22–6.69)	1.80 (0.92–3.51)
547+	1.10 (0.61–1.98)	4.14 (1.37–12.54)	N/A	N/A	1.89 (0.12–30.43)	0.91 (0.07–11.64)	N/A	1.27 (0.48–3.35)
Total dosage (DDD)								
Never use	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
1–119	1.02 (0.90–1.16)	1.06 (0.92–1.21)	0.64 (0.39–1.05)	1.40 (0.91–2.15)	0.79 (0.47–1.34)	0.90 (0.65–1.24)	1.19 (0.94–1.50)	1.11 (0.91–1.36)
120–479	0.96 (0.86–1.07)	1.05 (0.93–1.19)	1.13 (0.86–1.50)	1.25 (0.78–2.01)	1.02 (0.67–1.54)	0.74 (0.54–1.03)	0.83 (0.66–1.03)	0.93 (0.76–1.13)
480–1,199	0.94 (0.85–1.05)	0.91 (0.80–1.03)	1.15 (0.79–1.68)	1.10 (0.53–2.27)	1.03 (0.65–1.64)	0.81 (0.60–1.10)	1.02 (0.82–1.27)	0.90 (0.73–1.12)
1,200+	0.94 (0.85–1.05)	0.98 (0.86–1.12)	N/A	0.59 (0.24–1.46)	0.90 (0.53–1.55)	0.85 (0.65–1.10)	0.97 (0.76–1.23)	1.05 (0.87–1.26)

Abbreviations: DDD, defined daily dose (the assumed average maintenance dose per day for a drug used for its main indication in adults; the DDD is 20 mg for atorvastatin, 0.2 mg for cerivastatin, 60 mg for fluvastatin, 45 mg for lovastatin, 30 mg for pravastatin, 10 mg for rosuvastatin, and 30 mg for simvastatin); N/A, not applicable.

[a]Adjusted for the matching variables (age, regional health authority of residence, and length of drug use coverage), income quintile, number of physician visits in the 5-year period before the index date, screening indicator, chronic cardiovascular disease (excluding hypertension), diabetes, and ever use of non-statin lipid-lowering drugs, metformin, other oral hypoglycemic drugs, insulin, aspirin, and non-aspirin NSAIDs.

[b]Also adjusted for use of the other individual statins.

[c]Also adjusted for use of that statin in the other periods.

Because we performed multiple comparisons for different statins and lacked *a priori* biological rationale to single out pravastatin, we cannot rule out a chance finding, especially given the absence of a dose or duration response.

A major strength of this study is the availability of high-quality, population-based health administrative databases in Manitoba. The completeness and accuracy of the MCR and MH databases are well established. Outcome misclassification is unlikely, as reporting of cases is mandated by provincial law. Although we lacked prescription information prior to 1995 (the start of DPIN), statins were infrequently prescribed before then. We lacked information on lipid levels, so we could not account for the severity of dyslipidemia (an indication for statin use), and used an indicator to adjust for screening, which may have caused residual confounding.

In conclusion, we found no evidence of an association between statin use and prostate cancer risk. In the absence of a dose or duration response, the association between pravastatin and prostate cancer risk may be due to chance.

Disclosure of Potential Conflicts of Interest

S.M. Mahmud reports receiving commercial research grants from Merck, Sanofi, and Roche and is a consultant/advisory board member for Sanofi. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. The opinions presented in the article do not necessarily reflect those of the funders.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.H. Righolt, S.M. Mahmud
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.H. Righolt, R. Bisewski, S.M. Mahmud
Writing, review, and/or revision of the manuscript: C.H. Righolt, R. Bisewski, S.M. Mahmud
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.H. Righolt, R. Bisewski, S.M. Mahmud
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