CLINICAL RESEARCH STUDY

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Statins and Cancer Risk

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ABSTRACT

OBJECTIVE: Despite numerous randomized clinical trials and observational epidemiologic studies, evidence on the potential effectiveness of statins for prevention of cancer remains controversial. The objective of this study was to investigate the relation between lipophilic statin use and cancer occurrence.

METHODS: We conducted a retrospective observational study based on a medical administrative database in the province of Quebec, Canada (1998-2004). Patients aged 45 years or more and discharged from the hospital alive after admission for acute myocardial infarction were included. High- and low-dose statin use were defined as a filled prescription, within 3 days after index discharge, at or above (below) the statin-specific target dose, for any of the 4 lipophilic statin medications: atorvastatin, simvastatin, lovastatin, or fluvastatin. Statin non-use was defined as non-use of any statins while simultaneously using major non-statin cardiac medications. A total of 30,076 patients, including high-dose statin users (n = 6015), low-dose statin users (n = 5323), and non-users (n = 18,738), were followed for up to 7 years. Multivariable Cox regression analyses were performed to estimate associations between statin dose category and the incidence of admission to hospital with a diagnosis of any type of cancer.

RESULTS: The crude incidence rates of hospital admission with the diagnosis of any type of cancer were 13.9, 17.2, and 26.0 per 1000 person-years in statin high-dose users, low-dose users, and non-users, respectively. The estimated adjusted hazard ratios were 0.75 (95% confidence interval [CI], 0.60-0.95) for statin use at high dose and 0.89 (95% CI, 0.75-1.07) for statin use at low dose. No significant time-dependence of the effect of statins at either dose was detected.

CONCLUSION: The use of lipophilic statins at sufficiently high dose might be associated with a clinically important reduction in the incidence of cancer.

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KEYWORDS: Cohort studies; Drug effects; Hydroxymethylglutaryl-CoA reductase inhibitors; Neoplasms

Statins have been shown to be effective for secondary prevention of coronary heart disease. In addition, several unintended beneficial effects have been proposed,[1] including antitumorigenic effects, although original reports had actually suggested the potential opposite, procarcinogenic effects of statins.[2] Despite massive amounts of data, the issue remains inconclusive.[3-7] Apart from the fact that the duration of follow-up and the extent of adherence to the regimen across the previous studies have been varied, the reasons for the lack of coherence of the results might be that the effects could depend on the statin type, dose, or cancer at issue. In particular, cerivastatin and atorvastatin have been found to enhance angiogenesis tumor growth and vascularization at high doses, whereas the opposite effects were observed at

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low doses.[8-12] With respect to statin type, it has been hypothesized that only lipophilic statins can potentially be capable of inhibiting tumor development; in contrast, hydrophilic statins could be expected to actually promote tumor development.[13]

In this light, recently there have emerged repeated calls for new randomized clinical trials to resolve the controversy.[14-17] Pending the outcome of those trials, we set out to investigate potential antitumorigenic effects of statins in a cohort of patients post-acute myocardial infarction (AMI) in the province of Quebec, Canada.

CLINICAL SIGNIFICANCE

- High-dose use of lipophilic statins was associated with a clinically significant reduction in the incidence of hospital admissions with a diagnosis of cancer.
- The pattern of association suggests potential anti-promotion effects of lipophilic statins on cancer growth.
- The extent to which long-term exposure to lipophilic and lipophobic statins affects the incidence of cancer remains to be investigated in future studies.

MATERIALS AND METHODS

Data Sources

The Quebec hospital discharge summary database, which includes information on all AMI hospitalizations, was linked to provincial physicians and drug claims database. In Quebec, patients aged less than 65 years are typically insured through employment, whereas those who are not, as well as all patients aged 65 years or more, receive prescription coverage at minimal cost through a government program. Available prescription information includes type, dosage, quantity, and days of supply. Vital status information was obtained from the same databases linked to pension, car insurance, and death registry for completeness of the information. The patients' unique, encrypted health care insurance number was used for the linkage.

Source Population

Patients were included if they had their first recorded AMI-related hospital admission and were discharged between April 1, 1998, and March 31, 2004. All patients had AMI (International Classification of Diseases-9-CM code 410)[18] recorded as the most responsible diagnosis (ie, the principal diagnosis contributing to the greatest extent to hospital stay) in the hospital discharge database.

Patients were excluded if they met any of the following criteria: The AMI was coded as an in-hospital complication; the AMI-related hospital admission was a transfer from another hospital; the total length of hospital stay was less than 2 days; the patient was discharged to a long-term care institution or a rehabilitation center or moved out of the province; or the health care number was invalid. More details of the rationale for these criteria can be found elsewhere.[19]

Study Population and Definition of Study Groups

First, for all instances of statin use, daily dosages for each patient were computed on the basis of the information on dosage category, frequency, and duration for each prescription. Statin high-dose use was defined as a filled prescription, at or within 3 days after hospital discharge, at or above the statin-specific target dose (according to original randomized clinical trials), for any of the 4 statin medications: atorvastatin, simvastatin, lovastatin, or fluvastatin. Statin low-dose use was defined as a filled prescription, at or within 3 days after hospital discharge, below the statin-specific target dose for any of the 4 statins. (The narrow post-discharge time window for statin use/dose definition was chosen in an attempt to achieve a higher degree of comparability among the patients and to minimize the possibility of the "survival bias.")[20] These 4 statin medications were chosen because of their lipophilic properties,[21,22] regarded as essential for potential antitumorigenic effect.[23,24] Thus, subjects whose first statin prescription was for pravastatin or rosuvastatin were excluded because of these statins' hydrophilic properties and because their use was too infrequent. Further, subjects whose first statin prescription was for cerivastatin were excluded because this statin is no longer used in practice. Next, subjects who were not prescribed a statin at or within 3 days after hospital discharge were identified. Among the statin non-users, those who were not prescribed a major non-statin cardiac medication (ie, a beta-blocker, a calcium-channel blocker, an angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocker, a diuretic, a nitrate, digoxin, acetylsalicylic acid, or clopidogrel) at or within 3 days after hospital discharge were excluded.

Each patient was followed from hospital discharge until the occurrence of the study outcome, end of follow-up (March 31, 2005), loss to follow-up, or discontinuation of the initially adopted statin use/non-use or dose (high or low) regimen, whichever came first. In the latter case, statin high-dose users were considered to have discontinued statin use if they reached at least 60 consecutive days on which they did not fill a prescription for a high-dose statin (as defined above), whereas statin low-dose users were considered to have discontinued statin use if they reached at least 60 consecutive days on which they did not fill a prescription for a low-dose statin (as defined above). Analogously, statin non-users were considered to have discontinued a major non-statin cardiac medication use if they reached at least 60 consecutive days on which they did not fill a prescription for a non-statin cardiac medication (as defined above). The restriction of the category of statin non-use to a subdomain of use of other major cardiac medications and the incorporation of similar criteria of discontinuation of regimens were done in an effort to achieve comparability between the 3