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Original article

Effect of statins as a secondary chemopreventive agent among individuals with non–muscle-invasive bladder cancer: A population-based analysis

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Abstract

Background: Non–muscle-invasive bladder cancer (NMIBC) is especially prevalent among the elderly. Many patients with NMIBC also have significant concomitant comorbidities, including cardiovascular diseases and hypercholesterolemia. Statins are the most commonly used cholesterol-depleting agents, and they may possess anticancer properties. The objective of this population-based study was to evaluate the effect of statins on the survival of individuals diagnosed with NMIBC.

Methods: This is a retrospective population-based cohort study that used administrative databases to identify individuals 66 years of age and older who were diagnosed with NMIBC between 1992 and 2012. Subjects with documented use of statins before they were 66 years of age were excluded from the analysis. Cumulative daily use of statins was calculated before and after the diagnosis of NMIBC. Their effect on cancer-specific survival and overall survival was estimated using a multivariable competing risk and Cox proportional hazards model, respectively.

Results: The final cohort was composed of 13,811 individuals ≥66 years diagnosed with NMIBC. Of these, 4,748 individuals (34%) were exposed to statins during follow-up. The median statin exposure after NMIBC diagnosis was 21.4 months (interquartile range: 7.8–45.4). After a median follow-up of 7.1 years (interquartile range: 4.0–11.3) from NMIBC diagnosis, 8,900 (64%) individuals had died. The cumulative use of statins after NMIBC diagnosis did not significantly affect cancer-specific survival ($P = 0.10$). However, its cumulative use after NMIBC diagnosis was associated with a better overall survival ([0.93; 95% CI: 0.91–0.96], per year of use).

Conclusions: This large population-based study has provided evidence that cumulative statin use was not associated with an improved cancer-specific survival among individuals with NMIBC. However, our findings did demonstrate that statin users had a better overall survival than nonusers.

Keywords: Statins; Outcome; Urinary bladder neoplasms

1. Introduction

Urothelial bladder cancer (UBC) is one of the most common solid organ cancers in the Western world. Nearly 75,000 new cases are diagnosed every year in the United States alone [1]. Approximately 75% of these cases are non–muscle-invasive bladder cancer (NMIBC) [2]. UBC is especially prevalent among the elderly population, many of whom are also afflicted with significant concomitant comorbidities, including cardiovascular diseases and hypercholesterolemia.

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase),

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which is the key enzyme in the cholesterol synthesis pathway. These agents are approved and established in the treatment of cardiovascular diseases and hypercholesterolemia [3]. Since the early 1990s, the role of these cholesterol-depleting agents in cancer chemoprevention has been the focus of many investigative studies. The exact mechanism of action through which statins exert their anticancer activity or activities remains unclear, and many theories have been postulated [4]. Several preclinical studies have suggested that their potential anticancer effect may be the result of cell cycle arrest, apoptosis induction, suppression of angiogenesis, and tumor growth inhibition [5–8].

The role of statins as a chemopreventive agent among the UBC population has previously been supported by a preclinical study demonstrating cytotoxic effects on UBC cell lines [9]. However, clinical studies have, to this date, failed to confirm these findings. A meta-analysis of 13 studies evaluating the role of statins as primary chemoprevention for UBC was published in 2013 and concluded that long-term use did not significantly affect the risk of UBC [10]. The role of statins as a secondary chemopreventive agent has only been assessed by a handful of studies [11–14], and only one of these studies specifically assessed the effect of statins on survival outcomes among the NMIBC population [11]. Although this study failed to demonstrate an association between statins and UBC outcomes, sample size and diminished statistical power likely limited its interpretation.

To address the ongoing uncertainty, we designed a population-based study to evaluate the effect of statins on survival outcomes in individuals diagnosed with NMIBC. We hypothesized that statins would improve both cancer-specific survival and overall survival.

2. Materials and methods

2.1. Study population

This was an institutional review board-approved, population-based, retrospective study. Individuals ≥66 years of age with newly diagnosed UBC between January 1, 1992 and December 31, 2012, in Ontario, Canada, were identified using administrative databases. Individuals with other concommitant neoplasms were excluded from the current analysis. Given that staging and pathologic data were unavailable or incompletely captured in the available administrative databases, we restricted our cohort to individuals with probable NMIBC by excluding the following: (1) individuals who had undergone a cystectomy or radiotherapy, or systemic chemotherapy treatments within 180 days of the diagnosis of UBC as they were deemed to likely have muscle-invasive bladder cancer (MIBC) or advanced UBC (Appendix A); (2) individuals who died or were lost to follow-up within 6 months of diagnosis as these patients likely had advanced disease unfit for additional therapy
(i.e., managed with endoscopic resection) and would not have benefited from any potential effect of statin use owing to the short follow-up period. Subjects with documented use of statins before the age of 66 were also excluded from the main analysis, as drug usage data were only available for patients over the age of 66 (Fig.).

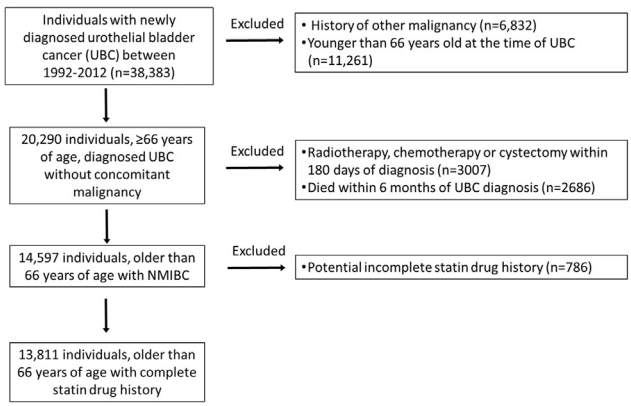

Fig. Study's flow diagram.

2.2. Data sources

In Ontario, all medical procedures are reimbursed by a single-payer program (Ontario Health Insurance Plan) that covers more than 95% of Ontarians [15,16]. To identify the baseline characteristics and the management of individuals diagnosed with NMIBC, several administrative databases were linked together (Ontario Cancer Registry, the Registered Persons Database, the Ontario Drug Benefit [ODB] claim database, and the Ontario Diabetes Database). Each of these databases has previously been validated [16–18].

More specifically, the ODB is a database that contains information on all medications dispensed in Ontario to individuals older than 65 years [18]. It has previously been shown to be reliable and accurate, capturing prescribed medications at a rate in excess of 99% [18]. As previously discussed, to accurately document statin exposure before NMIBC diagnosis, we restricted the cohort to individuals ≥66 years of age at the time of UBC diagnosis to allow for a minimum look-back window of 1 year. This was done to minimize the inclusion of individuals with an incomplete history of statin usage (i.e., no prior usage before the age 66 would enable us to identify an accurate start date of statin intake).

2.3. Outcomes

The primary outcome of interest was cancer-specific survival and the secondary outcome was overall survival.