Original Article

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Correlation analysis of cancer incidence after pravastatin treatment

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Background: Few studies have investigated the cancer-preventive effects of statins, which are known to protect against cardio-cerebrovascular diseases. In this study, we analyzed the degree to which pravastatin, a low-potency statin, could prevent cancer.
Methods: This retrospective cohort study used data from the Korean National Health Insurance Service database. Patients diagnosed with diabetes after the age of 50 years were divided into a pravastatin group and a control group that did not receive any statin prescriptions.
Results: This study included 557 patients in the pravastatin group and 2,221 patients in the control (no statin) group. During the 5-year follow-up, the incidence of cancer was 16.7% (93 of 557 patients) in the pravastatin group and 19.9% (442 of 2,221 patients) in the control group. The incidence of cancer was 22% higher in the control group than in the pravastatin group (hazard ratio, 1.22; 95% confidence interval, 0.97–1.52; P=0.09). Death from various causes occurred at a 45% higher frequency in the control group than in the pravastatin group (hazard ratio, 1.45; 95% confidence interval, 0.99–2.12; P=0.06). However, neither of those relationships reached statistical significance.
Conclusions: Although pravastatin use did not show a significant causal relationship with cancer incidence, fewer cases of cancer occurred in pravastatin users than in controls. However, further large-scale studies are required to confirm these findings.

Keywords: Pravastatin; Diabetes mellitus; Neoplasms; Death

INTRODUCTION

Statins, which are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, are the most commonly used drugs in clinical practice for the primary and secondary prevention of cardiovascular disease. Statin use has been increasing in accordance with the active recommendations of treatment guidelines [1–3]. The West of Scotland Coronary Prevention Study (WOSCOPS) confirmed the primary preventive effect of pravastatin on cardiovascular disease in patients with hypercholesterolemia who had no history of myocardial infarction [4]. In Japan, the effectiveness and safety of pravastatin in preventing cardiovascular diseases in Asians have also been demonstrated by the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study [5]. These studies have established the preventive effects of statins against cardiocerebrovascular diseases.

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In addition to their preventive effects against cardiocerebrovascular diseases, statins can reduce cancer incidence owing to their anti-inflammatory properties [6,7]. Statins are not yet prescribed clinically to lower the risk of cancer; however, recent reports have shown the suppression of cancer occurrence in patients prescribed statins [8]. However, these results are inconsistent. For example, some studies showed that statins reduced the incidence of prostate and breast cancers [9,10], whereas another study reported that low-dose statins were ineffective in suppressing prostate cancer recurrence [11]. Therefore, the relationship between statins and cancer remains a matter of debate and requires further research. In this study, we examined the correlation between the administration of pravastatin, a low-potency statin, and the incidence of cancer [12,13].

METHODS

Ethics statements

This study was approved by the Institutional Review Board of The Catholic University of Korea (No. KC21ZISI0545). The requirement for informed consent was waived due to the retrospective nature of the study.

Research data source

This retrospective cohort study used data from the National Health Insurance Service (NHIS; Wonju, Korea) [14]. These included sociodemographic data from 2002 to 2015 and detailed information on medical behavior and prescriptions, such as each subject's visits to medical institutions, diagnostic history, treatment history, prescription history, and pharmacy usage.

Study population and design

This study targeted patients who were diagnosed with diabetes after the age of 50 years and were administered antidiabetic drugs. The diagnostic criteria for diabetes were defined as the presence of two or more International Classification of Diseases, 10th Revision (ICD-10) codes E10 to E14 and two or more prescriptions for diabetes medications. Patients who received pravastatin were included in this study, while those who received any other statin at least once during the study period were excluded. In addition, patients who switched from pravastatin to another type of statin, or vice versa, were excluded. However, cases in which pravastatin was prescribed multiple times were included. The control group included patients who had never received any statin prescription.

In the pravastatin group, the date of the first pravastatin prescription was designated as the index date. Patients diagnosed with cancer before the index date were excluded from this study. The pravastatin group was followed up based on the index date. The control group was matched to the pravastatin group by year of hospital visits, and January 1 was set as their index date. The control group was selected using propensity score matching (PSM) and matched to the pravastatin group for age, sex, hypertension, and dyslipidemia. Matching was performed until the baseline characteristics of the two groups were equivalent; however, given the larger number of patients in the control group than that in the pravastatin group, only one round of matching was required. PSM was performed at a 1:4 ratio. We performed a statistical analysis to confirm that there were no significant differences in sex or age between the two groups after PSM.

Statistical analysis

Descriptive statistics are presented as mean±standard deviation or percentage of participants. For the basic table, the t-test was performed for continuous variables and the chi-square test was used for nominal variables. In addition, during 5 years of follow-up, the occurrence of outcomes (cancer or death) in the pravastatin and control groups was determined and factors affecting the dependent variable were analyzed using a Cox proportional hazard model.

RESULTS

The total number of patients included in the NHIS database was 1,108,369. Among them, 267,955 patients were diagnosed with diabetes after the age of 50 years, and 78,580 patients took antidiabetic medication twice or more after the diagnosis of diabetes. Patients with a history of cancer and those taking statins other than pravastatin were also excluded. In total, 18,478 participants were included in this study (557 in pravastatin group and 17,921 in control group). Because age, sex, dyslipidemia, and hypertension

may affect the study results, the control group was matched at a 1:4 ratio considering those variables. Finally, 557 and 2,221 individuals were included in the pravastatin and control groups, respectively.

In the pravastatin group, of the 557 patients, 240 (43.1%) were female and 317 (56.9%) were male, while in the control group, of the 2,221 patients, 979 (44.1%) were female and 1,242 (55.9%) were male (Table 1). The difference in the sex ratio between the two groups was not statistically significant (P=0.709). The average age in both groups was 63.2±8.3 years, with no significant difference observed (P=0.982). Patients were classified by age according to whether they were in their 50s, 60s, or 70s, and there was no statistically significant difference between the two groups in this regard (P=0.976). The number of patients diagnosed with hypertension and taking antihypertensive drugs were 158 (28.4%) in the pravastatin group and 602 (27.1%) in the control group.

During the 5-year follow-up, the incidence of cancer was 16.7% (93 of 557) in the pravastatin group and 19.9% (442 of 2,221) in the control group (Table 2). After correcting for age, sex, hypertension, and dyslipidemia, the cancer incidence rate in the control group was approximately 22% higher than that of the pravastatin group (hazard ratio [HR], 1.22; 95% confidence interval [CI], 0.97–1.52; P=0.09). During the surveillance period, the incidence of cancer in patients in their 50s was 13.9% (30 of 216) in the pravastatin group and 17.2% (148 of 861) in the control group. After adjusting for age, sex, hypertension, and dyslipidemia, the cancer incidence rate in the control group was approximately 28% higher than that in the pravastatin group, but the difference was not statistically significant (HR, 1.28; 95% CI, 0.86–1.89; P=0.22). During the follow-up, the incidence of cancer in patients in their 60s was 16.3% (33 of 202) in the pravastatin group and 20.2% (160 of 794) in the control group. After correcting for age, sex, hypertension, and dyslipidemia, the cancer incidence rate in the control group was 29% higher than that in the pravastatin group, but the difference was not statistically significant (HR, 1.29; 95% CI, 0.89–1.88; P=0.18). For patients in their 70s, the incidence of cancer during the 5-year follow-up period was 24.0% (29 of 121) in the pravastatin group and 24.4% (122 of 499) in the control group. After adjusting for age, sex, hypertension, and dyslipidemia, the cancer incidence rate in the control group was approximately 1% higher than that in the pravastatin group (HR, 1.01; 95% CI, 0.68–1.52; P=0.94).

During the 5-year follow-up period, the overall death rate was 5.6% (31 of 557) in the pravastatin group and 8.1% (179 of 2,221) in the control group (Table 3). After adjusting for age, sex, hypertension, and dyslipidemia, the mortality rate in the control group was approximately 45% higher than that in the pravastatin group (HR, 1.45; 95% CI, 0.99–2.12; P=0.06). During the surveillance period, the mortality in patients in their 50s was 3.2% (7 of 216) in the pravastatin group and 4.4% (38 of 861) in the control group. After adjusting for age, sex, hypertension, and dyslipidemia, the mortality rate in the control group was 5% higher than that in the pravastatin group, but the difference was not statistically significant (HR, 1.45; 95% CI, 0.65–3.24; P=0.37). During the 5-year follow-up, the mortality rate in patients in their 60s was 4.0% (8 of 202) in the pravastatin group and 7.2% (57 of 794) in the control group. After adjusting for age,

Table 1. Baseline characteristics

Characteristic	Before matching			After matching		
	Pravastatin group (n=557)	Control group (n=17,921)	P-value	Pravastatin group (n=557)	Control group (n=2,221)	P-value
Sex			0.377			0.709
Female	240 (43.1)	7,370 (41.1)		240 (43.1)	979 (44.1)	
Male	317 (56.9)	10,551 (58.9)		317 (56.9)	1,242 (55.9)	
Age (yr)	63.2±8.3	58.9±11.1	0.650	63.2±8.3	63.2±8.3	0.982
50–59	216 (38.8)	6,909 (38.6)	0.731	216 (38.8)	861 (38.8)	0.976
60–69	202 (36.3)	6,362 (35.5)		202 (36.3)	794 (35.7)	
70–79	121 (21.7)	3,899 (21.8)		121 (21.7)	499 (22.5)	
≥80	18 (3.2)	751 (4.2)		18 (3.2)	67 (3.0)	
Hypertension	158 (28.4)	5,106 (28.5)	0.986	158 (28.4)	602 (27.1)	0.586

Values are presented as number (%) or mean±standard deviation. Matching was conducted at a 1:4 ratio for age, sex, dyslipidemia, and hypertension.

Table 2. Comparison of the incidence of cancer between the pravastatin and control groups after 5 years

Variable	Pravastatin group	Control group	P-value
All age	557	2,221	
No. of incidence	93 (16.7)	442 (19.9)	-
Duration (person-years)	2,366	9,322	-
Incidence rate per 1,000 person-years	39.31	47.41	-
Model 1	1 (Reference)	1.21 (0.96–1.51)	0.11
Model 2	1 (Reference)	1.21 (0.97–1.52)	0.09
Model 3	1 (Reference)	1.22 (0.97–1.52)	0.09
50–59 yr	216	861	
No. of incidence	30 (13.9)	148 (17.2)	-
Duration (person-years)	920	3,605	-
Incidence rate per 1,000 person-years	32.61	41.05	-
Model 1	1 (Reference)	1.25 (0.84–1.85)	0.27
Model 2	1 (Reference)	1.27 (0.86–1.88)	0.23
Model 3	1 (Reference)	1.28 (0.86–1.89)	0.22
60–69 yr	202	794	
No. of incidence	33 (16.3)	160 (20.2)	-
Duration (person-years)	861	3,364	-
Incidence rate per 1,000 person-years	38.33	47.56	-
Model 1	1 (Reference)	1.25 (0.86–1.81)	0.25
Model 2	1 (Reference)	1.26 (0.86–1.83)	0.23
Model 3	1 (Reference)	1.29 (0.89–1.88)	0.18
70–79 yr	121	499	
No. of incidence	29 (24.0)	122 (24.4)	-
Duration (person-years)	510	2,075	-
Incidence rate per 1,000 person-years	56.86	58.80	-
Model 1	1 (Reference)	1.04 (0.69–1.55)	0.86
Model 2	1 (Reference)	1.03 (0.69–1.55)	0.88
Model 3	1 (Reference)	1.01 (0.68–1.52)	0.94

Values are presented as number (%) or hazard ratio (95% confidence interval). Model 1, unadjusted. Model 2, adjusted for age and sex. Model 3, additionally adjusted for hypertension and dyslipidemia.

sex, hypertension, and dyslipidemia, the mortality rate in the control group was 102% higher than that in the pravastatin group, but the difference was not statistically significant (HR, 2.02; 95% CI, 0.96–4.25; P=0.06). For patients in their 70s, the mortality rate during the 5-year follow-up period was 9.9% (12 of 121) in the pravastatin group and 13.6% (68 of 499) in the control group. After correcting for age, sex, hypertension, and dyslipidemia, mortality in the control group was approximately 29% higher than that in the pravastatin group. However, the difference was not statistically significant (HR, 1.29; 95% CI, 0.70–2.39; P=0.41).

DISCUSSION

This study used NHIS data to determine whether pravastatin use affects the occurrence of cancer. Although the pravastatin group had a lower incidence of cancer than the control group, this difference was not statistically significant. However, the cause of this phenomenon is difficult to determine. Thus, outcomes of randomized controlled trials (RCTs), rather than real-world evidence (RWE), should be utilized to establish a causal relationship between low-intensity statins, such as pravastatin, and the occurrence of cancer [15]. This is because only correlations, and not causality, can be identified from RWE. Nevertheless, this study was conducted using real-world data to explore correlations

Table 3. Comparison of death rates between the pravastatin and control groups after 5 year

	Pravastatin group	Control group	P-value
All age	557	2,221	
No. of incidence	31 (5.6)	179 (8.1)	-
Duration (person-years)	2,593	10,315	-
Incidence rate per 1,000 person-years	11.96	17.35	-
Model 1	1 (Reference)	1.45 (0.99–2.12)	0.06
Model 2	1 (Reference)	1.44 (0.98–2.11)	0.06
Model 3	1 (Reference)	1.45 (0.99–2.12)	0.06
50–59 yr	216	861	
No. of incidence	7 (3.2)	38 (4.4)	-
Duration (person-years)	1,001	3,986	-
Incidence rate per 1,000 person-years	6.99	9.53	-
Model 1	1 (Reference)	1.36 (0.61–3.05)	0.45
Model 2	1 (Reference)	1.41 (0.63–3.15)	0.41
Model 3	1 (Reference)	1.45 (0.65–3.24)	0.37
60–69 yr	202	794	
No. of incidence	8 (4.0)	57 (7.2)	-
Duration (person-years)	966	3,755	-
Incidence rate per 1,000 person-years	8.28	15.18	-
Model 1	1 (Reference)	1.83 (0.87–3.84)	0.11
Model 2	1 (Reference)	1.85 (0.88–3.88)	0.10
Model 3	1 (Reference)	2.02 (0.96–4.25)	0.06
70–79 yr	121	499	
No. of incidence	12 (9.9)	68 (13.6)	-
Duration (person-years)	559	2,302	-
Incidence rate per 1,000 person-years	21.47	29.54	-
Model 1	1 (Reference)	1.38 (0.75–2.54)	0.31
Model 2	1 (Reference)	1.38 (0.75–2.55)	0.30
Model 3	1 (Reference)	1.29 (0.70–2.39)	0.41

Values are presented as number (%) or hazard ratio (95% confidence interval). Model 1, unadjusted. Model 2, adjusted for age and sex. Model 3, additionally adjusted for hypertension and dyslipidemia.

among pravastatin use, death, and cancer occurrence in clinical practice. Therefore, the occurrence of cancer, rather than the occurrence of cardiovascular disease, was chosen as the outcome for this correlational analysis using RWE.

According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, the prevention of atherosclerotic cardiovascular disease is the main treatment goal, and active high-intensity statin treatment is recommended for this purpose [16] because of its low-density lipoprotein cholesterol (LDL-C)-reducing effect. A recent clinical study of statins related to the primary and secondary prevention of cardiovascular and cerebrovascular diseases emphasized that lower LDL-C levels were associated with fewer cardiovascular disease events [17]. In 2019, the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) recommended that the LDL-C target level should be lower in the presence of comorbidities such as diabetes mellitus and major cardiovascular diseases [18]. The 2021 Clinical Practice Guidelines for Diabetes Mellitus of the Korean Diabetes Association recommend a lower LDL-C control target of up to 70 mg/dL in patients with diabetes mellitus, chronic kidney disease, or hypertension, or who smoke [19]. The fifth edition of the dyslipidemia treatment guidelines of the Korean Society of Lipid and Arteriosclerosis, published on September 15, 2022, also recommend lower LDL-C target levels [20]. In patients with coronary artery disease, the target LDL-C level has been reduced to 55 mg/dL. Consequently, "the lower, the better"

is consistently emphasized in the selection of statins [21]. Accordingly, the opportunity to prescribe a low-intensity statin, as mentioned in the guidelines, is relatively limited, since high-risk groups receive a moderate- or high-intensity statin prescription. Both pravastatin (10 mg) and pravastatin (20 mg) are classified as low-intensity statins, whereas pravastatin (40 mg) is classified as a moderate-intensity statin. Therefore, the instances of pravastatin prescriptions remained low.

In our study, patients who took pravastatin uninterruptedly were included in the pravastatin group. Patients who switched from pravastatin to another statin were excluded. For example, if a patient developed cardiovascular disease, belonged to a high-risk group (increased age), and had switched to a higher-intensity statin, they were excluded from the study, although this would reflect common practice. As mentioned previously, the range of pravastatin prescriptions in clinical practice is gradually narrowing. In particular, a higher-intensity statin regimen than pravastatin is recommended for patients with diabetes [19]. Although we did not examine the incidence of cardiovascular disease in this study, many patients with low cardiovascular risk were likely to have been included in the pravastatin group. Therefore, our study did not focus on the effect of pravastatin on the incidence of cardiovascular disease. Instead, we opted to study the incidence of cancer, since the clinical interpretability of research findings is important and we deemed this outcome to be more reflective of actual clinical experience, which highlights the difference between RCTs and RWE [15,22].

To test our hypothesis of the cancer-preventive effects of pravastatin, we examined the occurrence of cancer and death. Our results showed that these events were not affected by pravastatin use. Low-potency statins have previously been shown to affect the incidence of cancer [12], but changes in clinical statin use due to the occurrence of cancer are uncommon. More commonly, prescriptions are changed to a relatively low-potency statin because of side effects caused by high-intensity statins [23]. In this study, despite the absence of statistical significance, the incidence of cancer and death was lower in the pravastatin group than in the control group. This is considered to be because pravastatin showed positive impacts on cancer occurrence after adjusting for selection biases presumed to affect the occurrence of cardiovascular and cerebrovascular diseases in RWE. Since these results approached, but did not reach, the threshold for statistical significance, a larger scale study designed to minimize bias is required.

Statins have been reported to prevent many cancers, such as colorectal and prostate cancers [24,25]. In a meta-analysis of 14 studies in China, statins reduced the overall number of deaths and other cancer-related deaths in patients with colorectal cancer [26]. Other study has also shown that statins can reduce the risk of other cancers, including prostate and ovarian cancers [27]. Although these findings are interesting, the effectiveness of statins in preventing cancer and its metastasis requires further investigation.

An important issue to consider when prescribing moderate- or high-intensity statins is their side effects [23]. Adverse reactions including elevated blood glucose levels, muscle pain, and damaged liver function can occur during high-dose statin therapy [28,29]. These side effects are most common in Asian patients and are dose-dependent [30]. Pravastatin is safer than other statins that cause blood glucose elevation or myalgia [31]; therefore, it can be prescribed for elderly patients [32]. In our study, the incidence of cancer and death in the pravastatin group was consistently low across all age groups above 50 years. Therefore, although more large-scale RCTs are required, the results of this study are meaningful.

This retrospective cohort study has several limitations [33]. First, pravastatin doses were not analyzed separately. Because the use of pravastatin in this study tended to have a positive effect on the occurrence of cancer, it would be desirable to test the results through a subanalysis. Second, the inclusion of only patients taking pravastatin, which is known to have a relatively low LDL-C-lowering effect [12], could have introduced bias. However, this was unavoidable, as we aimed to investigate the effect of pravastatin on the occurrence of cancer. Finally, we could not account for some confounding variables, such as lifestyle and other underlying diseases, associated with the occurrence of cancer.

Owing to the limitations of the study design, pravastatin administration did not show a significant causal relationship with cancer incidence; however, the incidence of cancer was numerically lower in the pravastatin group than in the control group. An explanation for this finding may be that the advantage of RWE disappears with low-intensity statins, which are relatively likely to be changed to prescriptions of other statins, potentially introducing additional

bias. In the future, an RCT rather than an RWE-based study should be conducted to investigate the correlation between pravastatin and cardiovascular disease (in light of recent guidelines stating that the lower the LDL-C level, the better). Further large-scale studies are required to confirm these findings.

ARTICLE INFORMATION

Ethics statements

This study was approved by the Institutional Review Board of The Catholic University of Korea (No. KC21ZISI0545). The requirement for informed consent was waived due to the retrospective nature of the study.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Author contributions

Conceptualization: JY, HSK; Data curation: all authors; Formal analysis: JY, RK, MYP, HSK; Funding acquisition: HSK; Investigation: HSK; Methodology: HSK; Project administration: HSK; Resources: HSK; Software: HSK; Supervision: HSK; Validation: HSK; Visualization: JY; Writing–original draft: JY; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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