High Receipt of Statins Reduces the Risk of Lung Cancer in Current Smokers With Hypercholesterolemia: The National Health Insurance Service–Health Screening Cohort

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Abstract

Recent studies have presented conflicting data on the effect of the receipt of statins on lung cancer risk. This current study found that high statin receipt could prevent lung cancer in Korean men with hypercholesterolemia, especially those who are current smokers. A better understanding of statin receipt in the effects of lung cancer risk according to smoking status will help clinicians.

Background: The incidence and mortality of lung cancer have risen steadily with the increasing popularity of tobacco smoking. Observational studies suggest that statins, which are widely used to lower cholesterol, may prevent lung cancer; however, other studies have produced conflicting results. We investigated the effect of statin receipt on lung cancer risk in Korean men according to smoking status. **Patients and Methods:** We collected data from the 2002-2015 National Health Insurance Service–National Health Screening Cohort (NHIS-HEALS). We included a total of 16,588 men in the final analysis. We classified the participants as having high or low statin receipt or as not receiving statins. We used Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for lung cancer risk by statin receipt after adjusting for potential confounders. **Results:** We identified 363 patients with a new diagnosis of lung cancer from 2005 to 2015. Compared to participants who did not receive statins, high statin receipt resulted in a reduced lung cancer risk (HR = 0.64; 95% CI, 0.47, 0.85) after adjustment for confounders. Among current smokers, the fully adjusted HR for high statin receipt compared to those who did not receive statin therapy was 0.50 (95% CI, 0.32, 0.79). **Conclusion:** High statin receipt was associated with lower risk of lung cancer in Korean men with hypercholesterolemia, especially current smokers.

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Introduction

Cancer and cardiovascular disease are leading causes of death globally and in Korea.[1,2] In Korean men, lung cancer is the leading cause of cancer-related death, with a 5-year survival rate of 22.7%, which is much lower than that of other malignancies (62.8%).[2,3] There are many risk factors for lung cancer such as genetic susceptibility, poor diet, air pollution, occupational exposure, and lung diseases (eg, chronic obstructive pulmonary disease [COPD]).[4] However, tobacco smoking is the most crucial risk factor for lung cancer.[3,4] The carcinogenic effect of tobacco smoking on the lung

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has been well established by many studies.[5] Therefore, public health professionals and health authorities have implemented health promotion actions for smoking prevention and cessation.[6]

Statins are drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in the mevalonate pathway.[7] Statins are efficient cholesterol-lowering drugs that inhibit cholesterol synthesis and are widely used to prevent and treat cardiovascular disease.[8] Several experimental and preclinical studies have suggested that statins have anticancer properties as a result of their inhibition of the mevalonate pathway and impairment of geranylation and farnesylation involved in Ras superfamily signaling.[9,10] Emerging evidence supports the potential roles of statins in the prevention and treatment of cancer; however, a recent meta-analysis and randomized trials failed to show any significant benefit of statins for cancer prevention or treatment.[11-14] In contrast, results from several observational studies suggest that statin therapy may reduce the risk of lung cancer.[15-17] Although many researchers have searched for an association between receipt of statins and lung cancer risk, differences in study methodologies and study populations have led to inconsistent findings. Setoguchi et al[18] found that statins did not reduce the risk of lung cancer in a large elderly population, using glaucoma drug initiators as a comparison group. Likewise, Friis et al[19] did not find a significant reduction of lung cancer risk in those who receive statin therapy. Those two cohort studies were well designed, but they had relatively short follow-up time and did not consider possible confounders such as tobacco use and body mass index (BMI). After considering potential confounding factors, a recent large population-based cohort study with follow-up for 14 years showed that statin receipt before lung cancer diagnosis lowered lung cancer-specific mortality by up to 12%.[17] More studies with larger samples and longer duration are needed to determine if statins have an effect on lung cancer development.

We aimed to investigate the effect of statin receipt on the risk of lung cancer in Korean men with high cholesterol using a large population-based cohort. We stratified the cohort based on smoking status and medication possession ratio (MPR), the most common measure of medication adherence,[20] to examine the effects of those factors on the association between lung cancer risk and statin receipt.

Patients and Methods

Data Source

We collected data from the National Health Insurance Service–National Health Screening Cohort (NHIS-HEALS) conducted from 2002 to 2015 in Korea.[21] Seoung et al[21] previously provided detailed information about the NHIS-HEALS. The NHIS-HEALS is based on the national health screening program of Korea for the prevention and early detection of diseases. The screening program is conducted at least every 2 years and includes the whole population of Korea. We selected a sample cohort of participants aged > 40 years from the 2002-2003 health screening. The institutional review board of Chungbuk National University approved the present study (CBNU-201711-BMETC-564-01), which was conducted according to the guidelines of the Declaration of Helsinki.

Study Population

The 2002-2003 sample cohort from the NHIS-HEALS included a total of 279,078 men. We set the inclusion criteria as participants with hypercholesterolemia (serum total cholesterol level ≥ 250 mg/dL at initial screening) or participants with use of antidyslipidemia drugs during 2002-2003. We excluded individuals who were diagnosed with malignant neoplasia (10th edition of the International Classification of Diseases [ICD-10] codes C00–C97 or D00–D09) between 2002 and 2004 (n = 1766); who died of any cause between 2002 and 2004 (n = 321); 3) who initiated therapy with a statin since January 1, 2004 (n = 14,927); who were diagnosed with ischemic heart disease (ICD-10 codes I20–I25) or cerebrovascular disease (ICD-10 codes I60–I69) between 2002 and 2003 (n = 3877); who were 79 or more years of age at the time of the initial screening (n = 34); or who had missing data (n = 1385). Thus, we finally included 16,588 men the analysis. The data management is illustrated in Figure 1.

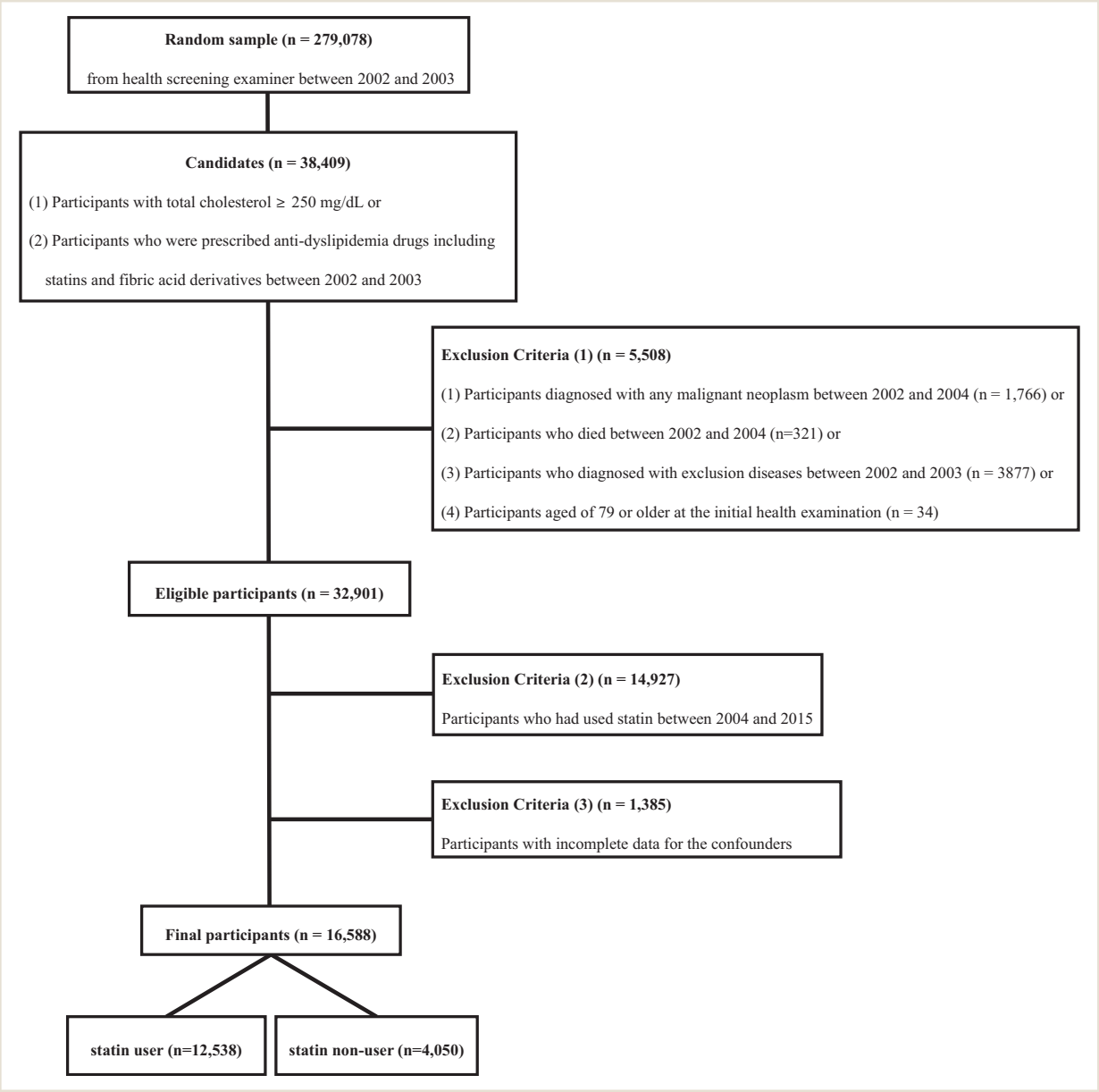
Definition of Lung Cancer

The outcome in our study was lung cancer incidence. To diminish any potential effects of latent cancer, we excluded participants who were diagnosed with lung cancer within 1 year after the entry date. For our analysis, we identified participants who were diagnosed with lung cancer as those who were newly diagnosed with ICD codes C34 (malignant neoplasm of bronchus and lung) and C39 (malignant neoplasm of upper respiratory tract, part unspecified) since January 1, 2005.

Assessment of Statin Receipt

To investigate the effect of statins on the incidence of lung cancer, we defined statin receipt as participants having been prescribed statins during 2002-2003. We excluded individuals who initiated statin therapy since January 1, 2004. We defined nonreceipt of statins as participants never having been prescribed a statin during the entire study period from 2002 to 2015. The statins prescribed were pravastatin, simvastatin, atorvastatin, cerivastatin, lovastatin, and fluvastatin. We classified those who received statins into 2 groups according to the degree of statin receipt. We evaluated the degree of statin receipt based on the MPR, the ratio of the total days during which the participant was prescribed a statin to the total days in the study period. We classified participants with an MPR above the sample median as having high statin receipt and those with an MPR below the sample median as having low statin receipt. To compute the MPR, we needed to identify the research period, which varied among participants. For participants who received statins, we defined the study start date as the first date of statin prescription in 2002-2003. For participants who did not receive statins, we defined the study start date as either the first screening date on which the participant had a total cholesterol level above 250 mg/dL or the first prescription date for any nonstatin antidyslipidemic drug. We defined the study end date differently for participants who were or were not diagnosed with lung cancer during 2005-2015. For the participants diagnosed with lung cancer during 2005-2015, we defined the study end date as the date of initial diagnosis of lung cancer. For the participants who were not

Figure 1 Flowchart of Study Population



diagnosed with lung cancer during 2002-2015, we defined the study end date as the last screening date.

Potential Confounders

The variables included in our analysis were age, BMI, blood pressure, blood glucose level, total cholesterol level, smoking status, alcohol consumption, physical activity, medical history of hypertension and diabetes, and income status. For those variables, we used the values measured at the time of screening in 2002-2003. For the participants who had screenings in both 2002 and 2003, we used the record from 2002. Age, BMI, blood glucose level, total cholesterol level, and blood pressure were continuous variables. The other variables were categorical. For smoking status, we categorized the participants as nonsmokers, ex-smokers, or current smokers. We categorized alcohol consumption into 3 groups as follows: rare, less than twice per month; sometimes, twice per month to twice per week; and often, more than twice per week. We categorized physical activity level in 3 groups: rare, did not exercise; sometimes, exercised 1 to 4 times per week; regular, exercised more than 5 times per week. We considered histories of hypertension and diabetes as binary variables based on a self-reported questionnaire. We categorized economic status in 3 groups on the basis of individual income percentile: low, 0 to 30th percentile; middle, 40th to 70th percentile; and high, 80th to 100th percentile.

Table 1 General Characteristics According to Lung Cancer Status in Korean Men

Characteristic	Control	Lung Cancer	*P*
No. of subjects	16,225	363	
Age (years)	52.4 ± 0.1	60.5 ± 0.5	< .001
BMI (kg/m^2)	24.9 ± 0.0	24.3 ± 0.1	< .001
SBP (mm Hg)	131.4 ± 0.1	134.2 ± 1.1	.003
Glucose (mg/dL)	108.0 ± 0.4	110.3 ± 2.4	.387
Total cholesterol (mg/dL)	247.2 ± 0.4	243.7 ± 2.6	.169
Diabetes	1249 (7.7)	38 (10.5)	.064
Hypertension	1913 (11.8)	52 (14.3)	.163
Smoking Status			.001
Nonsmoker	6746 (41.6)	123 (33.9)	
Ex-smoker	2707 (16.7)	52 (14.3)	
Current smoker	6772 (41.7)	188 (51.8)	
Drinking Status			< .001
Rare	5530 (34.1)	160 (44.1)	
Sometimes	7488 (46.2)	12 (33.6)	
Often	3207 (19.8)	81 (22.3)	
Physical Activity			< .001
Rare	7606 (46.9)	217 (59.8)	
Sometimes	6961 (42.9)	111 (30.6)	
Regular	1658 (10.2)	35 (9.6)	
Income Status			< .001
Low	2959 (18.2)	121 (33.3)	
Middle	5082 (31.3)	111 (30.6)	
High	8184 (50.4)	131 (36.1)	

Data are presented as n (%) or mean ± standard error.
Abbreviations: BMI = body mass index; SBP = systolic blood pressure.

Statistical Analysis

We presented all data as the number and percentage of participants, or as mean ± standard error as appropriate for each variable. To compare the individuals who were not diagnosed with lung cancer with those who were diagnosed with lung cancer, we conducted independent 2-sample *t* tests for continuous variables and chi-square tests for categorical variables. To evaluate the difference among those who did not receive statins, those with low statin receipt, and those with high statin receipt, we performed 1-way ANOVA for continuous variables and chi-square tests for categorical variables. To compare the overall survival rates depending on the level of statin receipt, we used Kaplan-Meier estimates with the log-rank test. We determined the hazard ratio (HR) and 95% confidence interval (CI) for lung cancer incidence using Cox proportional hazards regression models after adjusting confounding factors. We adjusted for age in model 1; and age, BMI, systolic blood pressure, glucose, total cholesterol, smoking status, drinking status, physical activity, income status, history of hypertension, and history of diabetes in model 2. To further investigate the relationship between statin receipt and lung cancer incidence according to smoking status, we conducted subgroup analyses by smoking status (nonsmoker, ex-smoker, and current smoker). All *P* values are 2 sided, and we considered $P < .05$ to be statistically significant. We used the statistical package SAS enterprise guide 7.1 (SAS Institute, Cary, NC) and R studio 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/) to perform the analyses.

Results

A total of 16,588 male NHIS-HEALS participants met the entry criteria. The baseline characteristics of the case (diagnosed with lung cancer) and control (not diagnosed with lung cancer) populations are described in Table 1. Of the 16,588 participants, 363 (2.2%) were diagnosed with lung cancer since January 1, 2005. The mean age of the control and case populations was 52.4 and 60.5 years, respectively. The median follow-up duration was 12.7 years. The cholesterol level was not significantly different between the case and control populations. The case population smoked and drank more, exercised less, and had lower income status than the control population. The baseline characteristics of the population according to the degree of statin receipt are shown in the Table 2. A total of 8100 men (48.8%) were prescribed statins. The mean values of BMI, systolic blood pressure (SBP), and glucose were higher among those with high statin receipt than among those with low statin receipt and those who did not receive statin therapy (all $P < .001$). The total cholesterol level was lower among those with high statin receipt than among the other groups ($P < .001$). Those with high statin receipt smoked and drank less and exercised more than the

Table 2 General Characteristics According to Receipt of Statins

Characteristic	No Statin Receipt	Low Statin Receipt	High Statin Receipt	*P*
No. of subjects	8488	4050	4050	
Age (years)	51.2 ± 0.1	53.4 ± 0.1	54.5 ± 0.1	< .001
BMI (kg/m^2)	24.5 ± 0.0	25.0 ± 0.0	25.5 ± 0.0	< .001
SBP (mm Hg)	129.6 ± 0.2	131.9 ± 0.3	135.0 ± 0.3	< .001
Glucose (mg/dL)	104.4 ± 0.6	107.8 ± 0.7	116.1 ± 0.8	< .001
Total cholesterol (mg/dL)	263.2 ± 0.5	226.6 ± 0.7	234.0 ± 0.8	< .001
Diabetes	249 (2.9)	381 (9.4)	657 (16.2)	< .001
Hypertension	422 (5.0)	585 (14.4)	958 (23.7)	< .001
Smoking Status				
Nonsmoker	3243 (38.2)	1789 (44.2)	1837 (45.4)	< .001
Ex-smoker	1316 (15.5)	705 (17.4)	738 (18.2)	
Current smoker	3929 (46.3)	1556 (38.4)	1475 (36.4)	
Drinking Status				
Rare	2793 (32.9)	1412 (34.9)	1485 (36.7)	< .001
Sometimes	3964 (46.7)	1816 (448)	1830 (45.2)	
Often	1731 (20.4)	822 (20.3)	735 (18.1)	
Physical Activity				
Rare	4119 (48.5)	1951 (48.2)	1753 (43.3)	< .001
Sometimes	3654 (43.0)	1667 (41.2)	1751 (43.2)	
Regular	715 (8.4)	432 (10.7)	546 (13.5)	
Income Status				
Low	1746 (20.6)	695 (17.2)	639 (15.8)	< .001
Middle	2737 (32.2)	1291 (31.9)	1165 (28.8)	
High	4005 (47.2)	2064 (51.0)	2246 (55.5)	

Data are presented as n (%) or mean ± standard error.
Abbreviations: BMI = body mass index; SBP = systolic blood pressure.

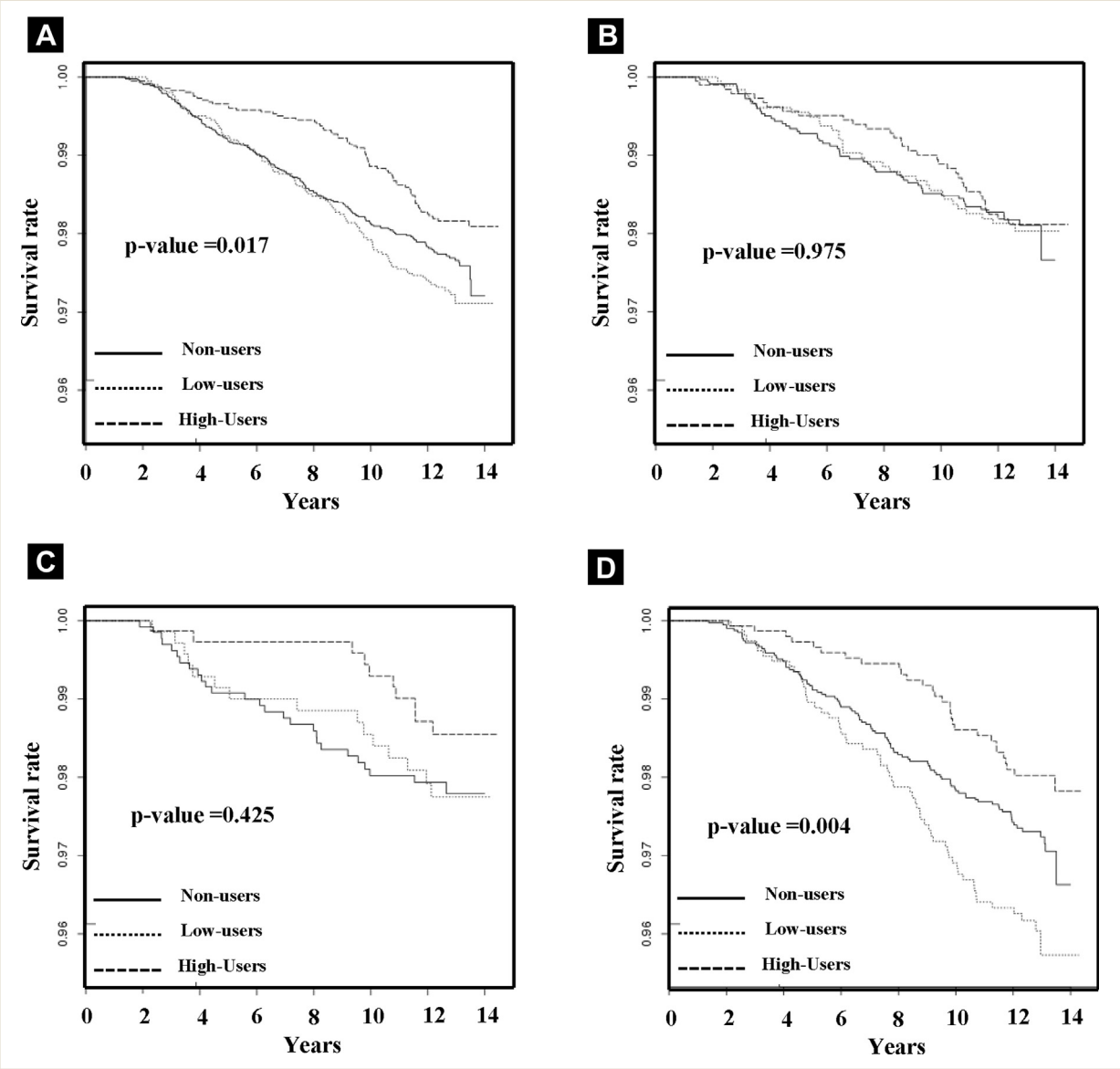
other groups (all $P < .001$). Income status was higher among those with high statin receipt than among the other groups ($P < .001$). Those with high statin receipt were more likely to have a history of diabetes and hypertension than the other groups (all $P < .001$). Figure 2A provides a Kaplan-Meier survival curve demonstrating the association between statin receipt and incidence of lung cancer in the cohort (log-rank test, $P = .017$). Figure 2B, C, and D provide Kaplan-Meier survival curves demonstrating the association between statin receipt and incidence of lung cancer according to smoking status. Cox proportional hazards regression models revealed that high statin receipt was independently associated with a lower risk of lung cancer (Table 3). The HR was 0.94 (95% CI, 0.74, 1.19) for participants with low statin receipt and 0.56 (95% CI, 0.43, 0.74) for high statin receipt after adjustment for age. The HR was 1.03 (95% CI, 0.80, 1.33) for those with for low statin receipt and 0.64 (95% CI, 0.47, 0.85) for high statin receipt after adjustment for age, BMI, SBP, glucose, total cholesterol, smoking status, drinking status, physical activity, income status, history of hypertension, and history of diabetes.

In the subgroup analysis according to smoking status, the HR was 0.71 (95% CI, 0.46, 1.10) for nonsmokers, 0.49 (95% CI, 0.24, 1.01) for ex-smokers, and 0.53 (95% CI, 0.35, 0.80) for current smokers with high statin receipt after adjustment for age. The HR was 0.83 (95% CI, 0.52, 1.31) for nonsmokers, 0.59 (95% CI, 0.27, 1.29) for ex-smokers, and 0.50 (95% CI, 0.32, 0.79) for current smokers with high statin receipt after adjustment for age, BMI, SBP, glucose, total cholesterol, drinking status, physical activity, income status, history of hypertension, and history of diabetes.

Discussion

We found that high levels of statin receipt reduced the lung cancer risk in men with hypercholesterolemia, especially those who were current smokers. Cholesterol is a key structure of mammalian cell membranes and is essential for maintaining cellular homeostasis.[22] Cancer cells tend to show altered lipid metabolic pathways with excessive lipogenesis and cholesterol synthesis.[23] However, the association between serum cholesterol level and cancer risk is still unclear. Results from a large population-based study in Korea showed that the relationship between total cholesterol level and cancer risk varied by cancer-specific site.[24] Our study included participants with hypercholesterolemia who may or may not have been receiving statin therapy at the time of initial screening. The baseline mean cholesterol level was not significantly different between the participants who were diagnosed with lung cancer and those who were not diagnosed with lung cancer (247.2 vs. 243.7 mg/dL, $P = .169$). Therefore, we could rule out the baseline cholesterol level as a potential confounding factor in differences

Figure 2 Kaplan-Meier Estimates for Lung Cancer Risk. Shown are Estimates According to Statin Receipt (A) Overall, (B) in Nonsmokers, (C) in Ex-Smokers, and (D) in Current Smokers. *P* Values are From Log-rank Tests



between the case and control populations. According to statin receipt, the baseline mean cholesterol level was significantly higher in people who did not receive statins, despite the presence of hypercholesterolemia.

We restricted our analysis to individuals who received statins before a diagnosis of lung cancer. We also included only individuals who were free of cancer for at least 1 year before the study start date to diminish any potential effects of latent cancer.

Adherence to medication is an important part of patient care, especially for noncommunicable diseases such as hypertension, diabetes, and dyslipidemia. Nonadherence leads to poor outcomes and wasteful health costs.[25] It is important to measure adherence in order to assess treatment efficacy. We measured adherence using the MPR, which is the most common tool for measuring adherence.[20,25]

Lung cancer is the most common cancer and the most common cause of cancer death worldwide.[3] Because of the high fatality rate of lung cancer, the US Preventive Service Task Force recommends annual screening for lung cancer by low-dose computed tomography in adults 55 to 80 years of age who currently smoke.[26] The National Cancer Center and Korea Centers for Disease Control and Prevention have also proposed cancer screening guidelines including lung cancer in September 2015.[27]

Although many studies have tried to find an association between statin receipt and lung cancer risk, the results are conflicting. Findings from a number of observational studies need to be

Table 3 Risk of Lung Cancer According to Receipt of Statins

Characteristic	Adjusted HR (95% CI) for:		
	No Statin Receipt	Low Statin Receipt	High Statin Receipt
Overall			
Model 1	1	0.94 (0.74, 1.19)	0.56 (0.43, 0.74)*
Model 2	1	1.03 (0.80, 1.33)	0.64 (0.47, 0.85)*
Nonsmoker			
Model 1	1	0.83 (0.54, 1.27)	0.71 (0.46, 1.10)
Model 2	1	0.93 (0.59, 1.47)	0.83 (0.52, 1.31)
Ex-Smoker			
Model 1	1	0.81 (0.43, 1.52)	0.49 (0.24, 1.01)
Model 2	1	0.95 (0.49, 1.85)	0.59 (0.27, 1.29)
Current Smoker			
Model 1	1	1.18 (0.85, 1.63)	0.53 (0.35, 0.80)*
Model 2	1	1.13 (0.79, 1.61)	0.50 (0.32, 0.79)*

Model 1 is adjusted for age. Model 2 is adjusted for age, body mass index, systolic blood pressure, glucose, total cholesterol, smoking status, drinking status, physical activity, income status, history of hypertension, and history of diabetes.
Abbreviations: CI = confidence interval; HR = hazard ratio.
*$P < .01$.

interpreted with caution because of factors such as residual confounding and exposure assessment.

Several randomized controlled trials and observational studies did not find a significant positive association between statin receipt and lung cancer incidence.[28-31] Some of those studies had few participants with lung cancer, had difficulty adjusting for smoking status, or had a relatively short follow-up period.[28,31] In addition, some studies were originally designed to test the potential of lipid-lowering agents for preventing coronary heart disease.[29,30] Therefore, they did not consider excluding subjects who were diagnosed with lung cancer within 1 year after the entry date. After the first designed trials ended, participants could be treated with a lipid-lowering drug, usually a statin. Therefore, the results of 10-year follow-up on the association between statin receipt and lung cancer were analyzed, regardless of the actual subsequent use of lipid-lowering therapy during the posttrial period.

Meanwhile, several case−control and observational studies found a significant association between statin receipt and lung cancer risk.[15-17,32] Khurana et al[15] found a 45% reduction of lung cancer risk in patients who received statins for more than 6 months compared to participants who did not receive statin therapy in a large population-based study. Farwell et al[32] showed that those who received statins had a lower risk of lung cancer than those who did not receive statins (HR = 0.70; 95% CI, 0.60, 0.81) after adjustment for multiple potential confounding factors. That association remained for various doses of simvastatin (≤10 mg, 11-39 mg, and ≥ 40 mg). In both studies, men accounted for most of the study population. A recent large population-based study investigated the association between statin receipt before and after cancer diagnosis and lung cancer−specific mortality.[17] Stain use before lung cancer diagnosis was associated with reduced cancer-specific mortality (HR = 0.88; 95% 95% CI, 0.83, 0.93). Statin use after lung cancer diagnosis was weakly associated with reduced cancer-specific mortality (HR = 0.89; 95% 95% CI, 0.78, 1.02). A large Danish populaton study demostrated a weak but protective effect of statin receipt before diagnosis of lung cancer (HR = 0.87; 95% 95% CI, 0.83, 0.92).[16] A recent randomized controlled trial did not report a significant benefit of statin receipt in combination with standard therapy for small-cell lung cancer (SCLC) in patients already diagnosed with lung cancer.[14]

The positive findings are supported by results from experimental and preclinical studies.[9,10,33] The inhibition of mevalonate and cholesterol synthesis via HMG-CoA is a key pathway to prevent cancer development. Downstream products of the mevalonate pathway play a key role in the maintenance of cellular function, cell membrane integrity, signaling, and cell-to-cell progression.[34] Mevalonate is a precursor of geranyl pyrophosphate and subsequent farnesyl pyophosphate.[10] Impairment of the prenylation of low molecular-weight guanosine triphosphate (GTP)ases, in particular Ras and Rho, prevents cell differentiation and proliferation.[35] Statins also affect apoptosis by depleting geranylgeranylated proteins.[9,36] An in vitro study demonstrated that lovastatin treatment decreased Bcl-2 (an antiapoptotic protein) and increased Bax (a proapoptotic protein).[34] Statins also exert antiproliferative effects by blocking the G_1-S transition in the cell cycle.[37]

Smoking is the most important risk factor for lung cancer.[4,38] A number of studies investigating the effect of statins on lung cancer have attempted to adjust for smoking status; however, other studies have had difficulty fully adjusting for tobacco smoking. We had information about smoking status for all of our study population. We excluded individuals with missing data at the entry stage, and we investigated the effect of statin receipt on lung cancer risk after stratifying according to smoking status. Statin use only had a significant effect in current smokers with high statin receipt. Statin use did not reduce the lung cancer incidence in nonsmokers and ex-smokers. Our findings could be explained by the results of previous studies.[39]

Han et al[39] showed that simvastatin receipt with chemotherapy had a beneficial effect only in heavy smokers with extensive SCLC. Chronic inflammation and increased reactive oxygen species

induced by tobacco smoking play crucial roles in the pathogenesis of lung cancer.[38] Statins have anti-inflammatory and immunomodulatory effects. A PRINCE (pravastatin inflammation/C-reactive protein evaluation) trial demonstrated that pravastatin reduced C-reactive protein levels regardless of low-density lipoprotein cholesterol level.[40] Another study found that simvastatin prevented tobacco smoke–induced inflammatory cell recruitment to the lung and acute bronchial epithelial damage.[41]

Associations between smoking, COPD, and lung cancer represent another possible mechanism that supports our results.[42] Lung cancer and COPD share a common etiology and are caused by tobacco smoking.[43,44] A pooled analysis by the International Lung Cancer Consortium demonstrated that the risk of SCLC caused by tobacco smoking was mediated by COPD.[42] The beneficial effects of statins on COPD are also supported by a meta-analysis of 238,459 patients.[45]

Our results should be interpreted with caution because of several limitations. First, we had no information about the histology of lung cancer. Smoking is a major risk factor for SCLC.[46] However, lung cancer in nonsmokers was estimated to increase in Korea.[47] In the current study, the number of lung cancer in Korean men was 123 (33.9%) in nonsmokers, 52 (14.3%) in ex-smokers, and 188 (51.7%) in current smokers. Lung cancer in never-smokers was regarded as a distinct biology.[48] Further study is needed to examine the relationship between statins and lung cancer based on histology through matching with national cancer registry information of National Cancer Center. Further study to examine the relationship between statins and lung cancer on the basis of histology is needed. Second, we could not distinguish the types of statin (ie, lipophilic, hydrophilic, or mixed) or the statin dose. A number of studies reported that different statin types have diverse effects on cancer development.[17] Third, we could not quantify the amount of smoking and could not consider the effect of secondhand smoke. Finally, we used MPR to evaluate statin adherence and use. Individuals who are more adherent to treatments tend to seek healthy lifestyles. In our study, participants with high statin receipt had more history of diabetes and hypertension but also more exercise, less drinking, less smoking, and higher income. Therefore, our results may not be free from healthy user effects and might have a selection bias.

Despite the drawbacks, our study has several strengths. First, we restricted the analysis to patients with high cholesterol, thus eliminating potential confounding effects of differences in baseline serum cholesterol level. Second, the cohort data set provided by the NHIS-HEALS was large and population based, and had a long follow-up of up to 14.5 years. Third, our study is the first to investigate the effect of statin receipt on lung cancer incidence in Korean men. Finally, our study used information about physical measurements (BMI and blood pressure), biochemical measurements (total cholesterol and glucose), and health-related behaviors (smoking, exercise, and drinking).

Conclusion

High statin receipt significantly lowered the lung cancer incidence in Korean men with hypercholesterolemia. The effect was strongest in current smokers. Presently, statins cannot be recommended for the prevention of lung cancer until their effects are demonstrated in well-designed clinical trials. Further clinical trials are needed to confirm the effects of statins on lung cancer incidence.

Clinical Practice Points

- Observational studies suggest that statins may prevent lung cancer; however, other studies have produced conflicting results.
- We included a total of 16,588 men using data from the 2002-2015 NHIS-HEALS.
- We investigated the effect of statin receipt on lung cancer risk in Korean men according to smoking status.
- The HRs (95% CIs) for lung cancer risk were 0.64 (0.47,0.85) in overall and 0.50 (0.32, 0.79) in current smokers with high statin receipt after adjusting for confounding factors.
- High statin receipt was associated with lower risk of lung cancer in Korean men with hypercholesterolemia, especially current smokers.

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Disclosure

The authors have stated that they have no conflict of interest.

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