Association between Statin Use and Cancer: Data Mining of a Spontaneous Reporting Database and a Claims Database

Mai Fujimoto, Tomoya Higuchi, Kouichi Hosomi and Mitsutaka Takada

Division of Clinical Drug Informatics, School of Pharmacy, Kinki University, 3-4-1, Kowakae, Higashi-osaka, Osaka, 577-8502, Japan

Purpose: In recent years, the potential risk of cancer associated with statin use has been a focus of much interest. However, it remains uncertain whether statin therapy is associated with cancer risk. To examine the association between statin use and the risk of cancer, we conducted data mining using the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and a large organized database of claims constructed by a database vendor (The Japan Medical Data Center Co., Ltd, Tokyo, Japan [JMDC]).

Methods: Relevant reports in the FAERS, which included data from the first quarter of 2004 through the end of 2012, were identified and analyzed. The reporting odds ratio (ROR) was used to detect spontaneous report signals and was calculated using the case/non-case method. Additionally, signals were detected via the information component (IC) using the IC025 metric. Furthermore, event sequence symmetry analysis (ESSA) was applied to identify the risk of cancer following treatment with statins over the period January 2005 to July 2013.

Results: In the FAERS database analyses, significant signals for colorectal cancer and pancreatic cancer were found for statins as a class. In the ESSA, significant associations between statin use and colorectal cancer and pancreatic cancer were found, with adjusted sequence ratios (95% confidence intervals) of 1.20 (1.08-1.34) and 1.31 (1.13-1.53), respectively, at an interval of 48 months.

Conclusions: Multi-methodological approaches using different algorithms and databases suggest that statin use is associated with an increased risk for colorectal cancer and pancreatic cancer.

Key words: statin use, cancer risk, FAERS database

Introduction

HMG-CoA reductase inhibitors (statins) are highly effective treatments for the primary and secondary prevention of cardiovascular diseases [1, 2]. Statin therapy was recently recommended for individuals with a wide range of cardiovascular risk factors, including those with average and below-average lipid levels [3]. Despite widespread and long-term use of statins, there is still a long-standing debate concerning their association with cancer at various sites.

Overall, statin-associated cancer risk is of major concern in clinical practice. There are many conflicting reports concerning the association between statin use and the risk of cancer. First, several preclinical studies have suggested that statins may have potential anticancer effects through the arrest of cell cycle progression [4], induction of apoptosis [5, 6], suppression of angiogenesis [7, 8], and inhibition of tumor growth and
metastasis [9, 10]. An experimental study found that statin therapy may be chemopreventive [11]. In contrast, other evidence suggests that statins may be carcinogenic [12]. Likewise, a number of clinical trials and epidemiologic studies have investigated the association between statin use and cancer risk [13-32]. These studies have reported inconsistent findings, with some studies reporting a reduced risk, some describing an increased risk, and others failing to identify any effect. Therefore, it remains uncertain whether statin therapy is associated with cancer risk.

Recently, data mining with different methodologies and algorithms has been applied to identify safety signals within medical databases, including spontaneous adverse drug reaction databases, claims databases, and prescriptions databases. To examine the association of statin use and the risks of common cancers, the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), a large and useful spontaneous database of adverse event reports, was analyzed. In addition, a large, well-organized claims database constructed by a database vendor (The Japan Medical Data Center Co., Ltd, Tokyo, Japan [JMDC]) was also analyzed. Our study aimed to examine the hypothesis that statin use is associated with cancer risk by employing different methodologies, algorithms, and databases.

Materials and Methods

FAERS data

Data source

The FAERS is a computerized information database designed to support the FDA’s post-marketing safety surveillance program for all approved drugs and therapeutic biological products. The system contains all reports of adverse events reported spontaneously by health care professionals, manufacturers, and consumers worldwide. The FAERS consists of seven data sets that include patient demographic and administrative information (file descriptor DEMO), drug and biologic information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), start of drug therapy and end dates (THER), and indications for use/diagnosis (INDI). A unique number for identifying a FAERS report allows all of the information from different files to be linked. The raw data of the FAERS database can be downloaded freely from the FDA website (http://www.fda.gov/Drugs/InformationOnDrugs/ucm135151.htm). The structure of the FAERS database is described elsewhere [33].

This study included data from the first quarter of 2004 through the end of 2012. A total of 4,052,885 reports were obtained. Reports with a common CASE number were identified as duplicate reports. We deleted all duplicates and excluded them from the analyses. Finally, a total of 54,841,322 drug-reaction pairs were identified among 3,308,116 reports. The Medical Dictionary for Regulatory Activities (MedDRA® version 17.0) preferred terms (PTs) was used to classify the adverse events.

Identifying statins and cancers

The FAERS permits the registration of arbitrary drug names including trade names, generic names, and abbreviations. All drug names were extracted from the DRUG file of the FAERS and recorded. A drug name archive that included the name of all preparations, generic names, and synonyms of drugs marketed in the world was created using the Martindale website (https://www.medicinescomplete.com/mc/login.htm). Simvastatin, rosuvastatin, atorvastatin, fluvastatin, pitavastatin, pravastatin, and lovastatin were identified by linking this archive with the FAERS database. All records including statins in the DRUG files were selected, and the relevant reactions from the REACTION files were then identified.

Adverse events in the FAERS database are coded using the MedDRA® PTs, which are grouped by defined medical conditions or areas of interest. We identified PTs related to cancer using the Standardized MedDRA® Queries (SMQ). PTs related to the 9 cancers (colorectal cancer, lung cancer, pancreatic cancer, gastric cancer, esophageal cancer, breast cancer, hemotological malignancies, melanoma, and prostate cancer) were identified in the SMQ category of malignant tumors.

Data mining (Disproportional analysis)

The reporting odds ratio (ROR) and the information component (IC) were utilized to detect spontaneous report signals. Signal scores were calculated using a case/non-case method [34, 35]. ROR and IC are widely used algorithms and have been employed by the Netherlands Pharmacovigilance Centre and the World Health Organization (WHO), respectively [36, 37]. Cases were defined as reports containing the event of interest (ie, cancers); all other reports comprised the non-cases.

Applying these algorithms and using a two-by-two table of frequency counts, we calculated signal scores to assess whether or not a drug was significantly associated with an adverse event. However, these calculations or algorithms, so-called disproportionality analyses or measures, differ from one another in that the ROR is frequentist (non-Bayesian), whereas the IC is Bayesian. For the ROR, a signal is detected if the lower limit of 95% two-sided confidence interval (95% CI) is >1 [36]. Signal detection
using the IC is performed using the IC025 metric, a lower limit of the 95% two-sided CI of the IC. In this method, a signal is detected if the IC025 value exceeds 0 [37]. In the current study, two methods were used to detect signals, and the adverse events were listed as drug-associated when the two indices met the criteria outlined above. Data management and analyses were performed using Visual Mining Studio software (version 8.0; Mathematical Systems, Inc. Tokyo, Japan).

**Claims data**

**Date source**

A large and chronologically organized claims database was employed, which was constructed by the JMDC using standardized disease classifications and anonymous record linkage [38]. In total, this database included about 1.2 million insured persons (approximately 1% of the population), comprised mainly of company employees and their family members. The JMDC claims database contained monthly claims from medical institutions and pharmacies submitted during the period from January 2005 to July 2013. The database provided information on the beneficiaries, including encrypted personal identifiers, age, sex, International Classification of Diseases, 10th revision (ICD-10) procedure and diagnostic codes, as well as the name, dose, and number of days' supplied for prescribed and/or dispensed drugs. All drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification of the European Pharmaceutical Market Research Association (EphMRA). An encrypted personal identifier was used to link claims data from different hospitals, clinics, and pharmacies. For the event sequence symmetry analysis (ESSA), we utilized cases extracted from the JMDC claims database for which statins were prescribed at least once during the study period and the patient was diagnosed with cancer.

This study was approved by the Ethics Committee of Kinki University School of Pharmacy. All researchers signed a written agreement declaring that they had no intention of attempting to obtain information from JMDC that could potentially violate the privacy of patients or care providers. In the JMDC claims database, all personal data (name and identification number) were replaced by a univocal numerical code, making the database anonymous at the source. Therefore, there was no need to obtain informed consent in the study.

**Definition of statins and cancers**

Six available statins (simvastatin, rosuvastatin, atorvastatin, fluvastatin, pitavastatin, and pravastatin) were analyzed. There were no data for lovastatin in this claims database. The ICD-10 codes of C18 (Malignant neoplasm of colon), C19 (Malignant neoplasm of rectosigmoid junction) and C20 (Malignant neoplasm of rectum) were selected as colorectal cancer. In addition, the ICD-10 codes of C34 (Malignant neoplasm of bronchus and lung), C25 (Malignant neoplasm of pancreas), C16 (Malignant neoplasm of stomach), C15 (Malignant neoplasm of esophagus), C50 (Malignant neoplasm of breast), C81-96 (Malignant neoplasms, stated or presumed to be primary, of lymphoid, hematopoietic and related tissue), C43 (Malignant melanoma of skin), and C61 (Malignant neoplasm of prostate) were selected as lung cancer, pancreatic cancer, gastric cancer, esophageal cancer, breast cancer, hematological malignancies, melanoma, and prostate cancer, respectively.

**Data mining (Symmetry analysis)**

Event sequence symmetry analysis (ESSA) was performed to test the hypothesis that statins increase the risk for cancer. The ESSA method has been described in detail in several published studies investigating the associations between the use of certain target drugs and potential adverse events [39, 40]. Briefly, the ESSA evaluates asymmetry in the distribution of an incident event before and after the initiation of a specific treatment. Asymmetry may indicate an association between the specific treatment of interest and the event. In this study, the association between statin use and diagnosis of cancer was analyzed.

The crude sequence ratio (SR) was defined as the ratio of the number of patients newly diagnosed with cancer after the initiation of statins versus the number of patients newly diagnosed with cancer before the initiation of statins. A SR >1 signified an association between statin use and an increased risk of cancer. The SR is sensitive to prescribing or event trends over time. Therefore, the SRs were adjusted for temporal trends in statins and events using the method proposed by Hallas [39]. The probability for the statins to be prescribed first, in the absence of any causal relationship, can be estimated in a so-called null-effect SR [39]. The null-effect SR produced by the proposed model may be interpreted as a reference value for the SR. Therefore, the null-effect SR is the expected SR in the absence of any causal association, after accounting for the incidence trends. By dividing the crude SR by the null-effect SR, an adjusted SR (ASR) can be obtained that is corrected for temporal trends. A slightly modified model was used to account for the limited time interval allowed between statin use and the diagnosis of cancer [40].

All incident users of statins and all cases newly diagnosed with cancer were identified during the period from January 2005 to July 2013. For this study,
patients included in the database were followed up to July 2013; therefore, different patients had different follow-up periods. Incidence was defined as the first prescription for statins. To exclude prevalent users of statins, the analysis was restricted to users who presented their first prescription on July 2005 or later (after a run-in period of 6 months). Likewise, the analysis was restricted to cases who presented their first diagnosis on July 2005 or later. To ensure that our analysis was restricted to incident users of statins and cases newly diagnosed with cancer, we also carried out a waiting time distribution analysis [41]. An identical run-in period was also applied to patients enrolled into the cohort after June 2005. Incident users were identified by excluding those patients who had received their first prescription for statins before July 2005, and cases newly diagnosed with cancer were identified by excluding those patients who had a first diagnosis of cancer before July 2005. All patients who initiated a new treatment with statins and had a first diagnosis within 48-month period were identified. Patients who had received their first prescriptions for statins and had a first diagnosis of cancer within the same month were not included in determining the SR.

The results of the analyses were expressed as the mean ± standard deviation (SD) for quantitative data and as frequency (percentage) for categorical data. Ninety-five percent confidence intervals (95% CI) for the ASRs were calculated using a method for exact confidence intervals for binomial distributions [42].

Results

FAERS database

A total of 8,270 PTs were found in reports for simvastatin, 5,923 for rosuvastatin, 9,014 for atorvastatin, 3,417 for fluvastatin, 1,258 for pitavastatin, 5,815 for pravastatin, and 4,196 for lovastatin. The total number of drug-reaction pairs for statins was 1,433,826; this included 487,237 for simvastatin, 177,763 for rosuvastatin, 556,579 for atorvastatin, 28,010 for fluvastatin, 5,424 for pitavastatin, 122,768 for pravastatin, and 56,045 for lovastatin. The number of drug-reaction pairs was 25,951 for colorectal cancer, 62,107 for lung cancer, 15,464 for pancreatic cancer, 8,439 for gastric cancer, 4,832 for esophageal cancer, 152,541 for breast cancer, 115,714 for hematological malignancies, 12,601 for melanoma, and 21,927 for prostate cancer.

The statistical data on statin-associated cancers are presented in Table 1. The signal scores suggested that the statins were associated with colorectal cancer (ROR: 1.29, 95% CI: 1.20-1.38; IC: 0.35, 95% CI: 0.25-0.45), pancreatic cancer (ROR: 1.35, 95% CI: 1.24-1.47; IC: 0.42, 95% CI: 0.30-0.55), and prostate cancer (ROR: 1.25, 95% CI: 1.17-1.34; IC: 0.31, 95% CI: 0.21-0.42). The signal scores of breast cancer (ROR: 0.48, 95% CI: 0.46-0.51; IC: -1.03 to -0.96) and hematological malignancies (ROR: 0.52, 95% CI: 0.49-0.54; IC: -0.93, 95% CI: -1.00 to -0.85) showed an inverse association with statins. In the analysis of individual statins, simvastatin showed significant signals for pancreatic cancer, rosvastatin for pancreatic cancer and prostate cancer, atorvastatin for colorectal cancer, lung cancer, pancreatic cancer, and prostate cancer, pitavastatin for lung cancer, gastric cancer, and prostate cancer, and lovastatin for prostate cancer. Meanwhile, significant inverse signals were found for lung cancer with simvastatin and lovastatin, for gastric cancer with simvastatin, for breast cancer with simvastatin, rosvastatin, atorvastatin, fluvastatin, pitavastatin, pravastatin, and lovastatin, for hematological malignancies with simvastatin, rosuvastatin, atorvastatin, fluvastatin, pravastatin, and lovastatin, and for prostate cancer with pravastatin.

Table 1. Signal scores for statin-associated cancers

|                | Case       | Non-cases  | ROR      | 95% CI     | IC        | 95% CI     |
|----------------|------------|------------|----------|------------|-----------|------------|
| **A: Colorectal cancer** |            |            |          |            |           |            |
| Statins        | 866        | 1,432,960  | 1.29     | 1.20-1.38  | 0.35      | 0.25-0.45  |
| Simvastatin    | 208        | 487,029    | 0.90     | 0.79-1.03  | -0.15     | -0.35 to 0.05 |
| Rosuvastatin # | 87         | 177,676    | 1.03     | 0.84-1.28  | 0.05      | -0.26 to 0.36 |
| Atorvastatin # | 464        | 556,115    | 1.78     | 1.62-1.95  | 0.81      | 0.68-0.95  |
| Fluvastatin    | 12         | 27,998     | 0.91     | 0.51-1.59  | -0.13     | -0.93 to 0.67 |
| Pitavastatin # | 4          | 5,420      | 1.56     | 0.58-4.16  | 0.49      | -0.80 to 1.78 |
| Pravastatin    | 68         | 122,700    | 1.17     | 0.92-1.49  | 0.22      | -0.12 to 0.57 |
| Lovastatin     | 23         | 56,022     | 0.87     | 0.58-3.13  | -0.20     | -0.79 to 0.39 |
| **B: Lung cancer** |            |            |          |            |           |            |
| Statins        | 1,566      | 1,432,260  | 0.96     | 0.92-1.01  | -0.05     | -0.13 to 0.02 |
| Simvastatin    | 440        | 486,797    | 0.90     | 0.72-0.87  | -0.33     | -0.46 to -0.19 |
| Rosuvastatin # | 184        | 177,679    | 0.91     | 0.79-1.06  | -0.13     | -0.34 to 0.08 |
| Atorvastatin # | 728        | 555,851    | 1.16     | 1.08-1.24  | 0.21      | 0.10-0.32  |
| Fluvastatin    | 28         | 27,982     | 0.88     | 0.61-1.28  | -0.17     | -0.71 to 0.36 |
| Pitavastatin # | 13         | 5,411      | 2.12     | 1.23-3.65  | 0.97      | 0.20-1.74  |
| Pravastatin    | 127        | 122,641    | 0.91     | 0.77-1.09  | -0.13     | -0.39 to 0.13 |
| Lovastatin     | 46         | 55,999     | 0.72     | 0.54-0.97  | -0.46     | -0.88 to -0.03 |
### C: Pancreatic cancer

| Statin | Case | Non-cases | ROR | 95% CI | IC | 95% CI |
|--------|------|-----------|-----|--------|----|--------|
| Atorvastatin | 219 | 556,360 | 1.40 | 1.23-1.60 | 0.48 | 0.28-0.67 |
| Fluvastatin | 28,001 | 1.14 | 0.59-2.19 | 0.17 | -0.74 to 1.08 |
| Pitavastatin | 5 | 5,421 | 1.96 | 0.63-6.09 | 0.66 | -0.78 to 2.10 |
| Pravastatin | 122,730 | 1.10 | 0.80-1.51 | 0.13 | -0.33 to 0.59 |
| Lovastatin | 56,029 | 1.01 | 0.62-1.65 | 0.02 | -0.68 to 0.72 |

### D: Gastric cancer

| Statin | Case | Non-cases | ROR | 95% CI | IC | 95% CI |
|--------|------|-----------|-----|--------|----|--------|
| Atorvastatin | 204 | 1,433,622 | 0.92 | 0.80-1.06 | -0.11 | -0.32 to 0.09 |
| Simvastatin | 40 | 487,197 | 0.53 | 0.39-0.72 | -0.89 | -1.34 to -0.44 |
| Fluvastatin | 28,001 | 1.06 | 0.74-1.53 | 0.08 | -0.45 to 0.61 |
| Pitavastatin | 10 | 5,414 | 12.01 | 6.46-22.35 | 2.58 | 1.71-3.46 |
| Pravastatin | 122,742 | 1.38 | 0.94-2.02 | 0.44 | -0.12 to 1.00 |
| Lovastatin | 56,041 | 0.46 | 0.17-1.24 | -0.94 | -2.24 to 0.35 |

### E: Esophageal cancer

| Statin | Case | Non-cases | ROR | 95% CI | IC | 95% CI |
|--------|------|-----------|-----|--------|----|--------|
| Atorvastatin | 134 | 1,433,692 | 1.06 | 0.89-1.26 | 0.08 | -0.17 to 0.34 |
| Simvastatin | 47 | 487,190 | 1.10 | 0.82-1.46 | 0.13 | -0.29 to 0.55 |
| Fluvastatin | 28,010 | 0.00 | - | -1.79 | -4.68 to 1.09 |
| Pravastatin | 122,754 | 1.30 | 0.77-2.19 | 0.34 | -0.40 to 1.09 |
| Lovastatin | 56,040 | 1.01 | 0.42-2.43 | 0.01 | -1.16 to 1.19 |

### F: Breast cancer (female)

| Statin | Case | Non-cases | ROR | 95% CI | IC | 95% CI |
|--------|------|-----------|-----|--------|----|--------|
| Atorvastatin | 1,777 | 749,094 | 0.48 | 0.46-0.51 | -1.03 | -1.10 to -0.96 |
| Simvastatin | 505 | 239,204 | 0.43 | 0.40-0.47 | -1.19 | -1.32 to -1.07 |
| Fluvastatin | 28,010 | 0.00 | - | -1.79 | -4.68 to 1.09 |
| Pravastatin | 122,754 | 1.30 | 0.77-2.19 | 0.34 | -0.40 to 1.09 |
| Lovastatin | 56,040 | 1.01 | 0.42-2.43 | 0.01 | -1.16 to 1.19 |

### G: Hematological malignancies

| Statin | Case | Non-cases | ROR | 95% CI | IC | 95% CI |
|--------|------|-----------|-----|--------|----|--------|
| Atorvastatin | 1,590 | 1,432,236 | 0.52 | 0.49-0.54 | -0.93 | -1.00 to -0.85 |
| Simvastatin | 544 | 486,693 | 0.53 | 0.48-0.57 | -0.92 | -1.04 to -0.79 |
| Fluvastatin | 28,010 | 0.00 | - | -1.79 | -4.68 to 1.09 |
| Pravastatin | 122,615 | 0.59 | 0.50-0.69 | -0.76 | -0.99 to -0.52 |
| Lovastatin | 56,032 | 0.56 | 0.44-0.71 | -0.83 | -1.18 to -0.48 |

### H: Melanoma

| Statin | Case | Non-cases | ROR | 95% CI | IC | 95% CI |
|--------|------|-----------|-----|--------|----|--------|
| Atorvastatin | 298 | 1,433,528 | 0.90 | 0.80-1.01 | -0.14 | -0.31 to 0.02 |
| Simvastatin | 103 | 487,134 | 0.92 | 0.76-1.12 | -0.12 | -0.40 to 0.16 |
| Fluvastatin | 28,005 | 0.78 | 0.32-1.87 | -0.31 | -1.49 to 0.87 |
| Pravastatin | 122,747 | 0.74 | 0.48-1.14 | -0.41 | -1.02 to 0.21 |
| Lovastatin | 56,032 | 1.01 | 0.59-1.74 | 0.01 | -0.76 to 0.78 |

### I: Prostate cancer (male)

| Statin | Case | Non-cases | ROR | 95% CI | IC | 95% CI |
|--------|------|-----------|-----|--------|----|--------|
| Atorvastatin | 823 | 642,806 | 1.25 | 1.17-1.34 | 0.31 | 0.21-0.42 |
| Simvastatin | 243 | 234,140 | 1.01 | 0.89-1.14 | 0.01 | -0.17 to 0.20 |
| Fluvastatin | 72,176 | 1.32 | 1.08-1.61 | 0.39 | 0.10-0.68 |
| Pravastatin | 12,013 | 1.21 | 0.73-2.01 | 0.26 | -0.46 to 0.98 |
| Lovastatin | 2,529 | 2.69 | 1.28-5.65 | 1.15 | 0.13-2.17 |

Case: Number of reports of cancer
Non-cases: All reports of adverse drug reactions other than cancer
ROR: Reporting odds ratio
CI: Confidence interval
The ESSA characteristics of the study population are summarized in Table 2. The numbers of claims including statins during the study period was 1,624,438. Among the 95,941 statin users, 38,402 incident users were identified. The mean age of statin incident users was 51.8±10.4 years. Table 3 shows the associations between statin use and the risk of cancer. Of the 38,402 incident statin users, 1,575 were identified as incident persons with a diagnosis of colorectal cancer, 818 with lung cancer, 804 with pancreatic cancer, 1,333 with gastric cancer, 125 with esophageal cancer, 373 with hematological malignancies, and 34 with melanoma, before or after the initiation of statins. Of the 15,694 female users and 22,708 male users of statins, 485 and 522 were identified as incident person with a diagnosis of breast cancer and prostate cancer before or after the initiation of statins, respectively. Statin use and the diagnoses of colorectal cancer, lung cancer, and pancreatic cancer were significantly associated with ASRs of 1.20 (95% CI: 1.08–1.34), 1.32 (1.13–1.53), and 1.31 (1.13–1.53), respectively. Statin use was inversely associated with the diagnosis of breast cancer, with an ASR of 0.81 (0.66–0.98). Analyses of the gastric cancer, esophageal cancer, hematological malignancies, prostate cancer, and melanoma showed no significant association. In the analyses of individual statins, significant associations were found for colorectal cancer with atorvastatin (1.33, 1.12–1.57), and pitavastatin (1.32, 1.06–1.65), for lung cancer with rosuvastatin (3.46, 2.80–4.28) and atorvastatin (1.28, 1.01–1.64), and for pancreatic cancer with atorvastatin (1.47, 1.14–1.90). Inverse associations were found for gastric cancer with simvastatin (0.51, 0.29–0.87), for breast cancer with simvastatin (0.25, 0.06–0.83) and rosuvastatin (0.74, 0.56–0.99), and for hematological malignancies with pravastatin (0.61, 0.38–0.97).

A summary of signal detection for statin-associated cancers is presented in Table 4.

Table 2. Characteristics of the study population for statin users (January 2005 to July 2013)

|                | Total       | Male         | Female        |
|----------------|-------------|--------------|---------------|
| Users, n       | 95,941      | 45,000       | 50,941        |
| Claims including statins, n | 1,624,438 | 803,751       | 820,687       |
| Incident users, n (%) | 38,402  | 22,708 (59.1) | 15,694 (40.9) |
| Age, years, n (%) |              |              |               |
| <20            | 78 (0.20)   | 39 (0.17)    | 39 (0.25)     |
| 20-39          | 4,696 (12.2) | 2,425 (6.5)  | 2,271 (5.4)   |
| 40-59          | 24,757 (64.0) | 14,674 (38.6) | 10,083 (23.5) |
| 60-79          | 8,790 (22.9) | 4,234 (11.2)  | 4,556 (10.7)  |
| ≥80            | 81 (0.21)   | 8 (0.04)     | 73 (0.18)     |
| Mean ±SD       | 51.8 ± 10.4 | 49.8 ± 10.1  | 54.8 ± 10.0   |

Incident users: Number of patients who received their first prescription for statins
SD: Standard deviation

Table 3. Symmetry analysis: Associations of statins with cancers

|                        | Incident users | Cases with cancer | Diagnosis of cancer last/first | Adjusted SR | 95% CI            |
|------------------------|---------------|-------------------|-------------------------------|-------------|------------------|
|                        |               |                   |                               |             | Lower    | Upper   |
| **A: Colorectal cancer** |               |                   |                               |             |         |         |
| Statins                | 38,402        | 1,575             | 747                            | 648         | 1.20     | 1.08    | 1.34    |
| Simvastatin            | 2,118         | 85                | 43                             | 32          | 1.06     | 0.66    | 1.73    |
| Rosuvastatin #         | 17,515        | 742               | 311                            | 353         | 0.95     | 0.81    | 1.11    |
| Atorvastatin #         | 14,359        | 611               | 295                            | 256         | 1.33     | 1.12    | 1.57    |
| Fluvastatin            | 1,678         | 81                | 35                             | 37          | 0.72     | 0.44    | 1.18    |
| Pitavastatin #         | 8,942         | 381               | 184                            | 154         | 1.32     | 1.06    | 1.65    |
| Pravastatin            | 9,327         | 473               | 224                            | 195         | 1.00     | 0.82    | 1.22    |
| **B: Lung cancer**     |               |                   |                               |             |         |         |
| Statins                | 38,402        | 818               | 396                            | 313         | 1.32     | 1.13    | 1.53    |
| Simvastatin            | 2,118         | 42                | 24                             | 13          | 1.46     | 0.72    | 3.13    |
| Rosuvastatin #         | 17,515        | 405               | 181                            | 177         | 3.46     | 2.80    | 4.28    |
| Atorvastatin #         | 14,359        | 312               | 144                            | 129         | 1.28     | 1.01    | 1.64    |
| Fluvastatin            | 1,678         | 48                | 22                             | 18          | 0.94     | 0.48    | 1.85    |
| Pitavastatin #         | 8,942         | 185               | 87                             | 75          | 1.28     | 0.93    | 1.77    |
| Pravastatin            | 9,327         | 225               | 113                            | 88          | 1.12     | 0.84    | 1.50    |
| **C: Pancreatic cancer** |               |                   |                               |             |         |         |
| Statins                | 38,402        | 804               | 388                            | 293         | 1.31     | 1.13    | 1.53    |
| Simvastatin            | 2,118         | 44                | 17                             | 18          | 0.71     | 0.34    | 1.46    |
| Rosuvastatin #         | 17,515        | 386               | 179                            | 156         | 1.17     | 0.94    | 1.46    |
| Atorvastatin #         | 14,359        | 303               | 147                            | 110         | 1.47     | 1.14    | 1.90    |
| Fluvastatin            | 1,678         | 45                | 22                             | 16          | 1.00     | 0.50    | 2.04    |
| Pitavastatin #         | 8,942         | 208               | 92                             | 92          | 1.05     | 0.78    | 1.42    |
| Pravastatin            | 9,327         | 221               | 113                            | 88          | 1.07     | 0.80    | 1.43    |
| **D: Gastric cancer**  |               |                   |                               |             |         |         |
| Statins                | 38,402        | 1,333             | 595                            | 568         | 1.04     | 0.93    | 1.17    |
| Simvastatin            | 2,118         | 72                | 25                             | 37          | 0.51     | 0.29    | 0.87    |
| Rosuvastatin #         | 17,515        | 626               | 257                            | 297         | 0.89     | 0.75    | 1.05    |
| Atorvastatin #         | 14,359        | 538               | 225                            | 239         | 1.04     | 0.86    | 1.25    |
| Fluvastatin            | 1,678         | 83                | 34                             | 40          | 0.62     | 0.38    | 1.01    |
| Pitavastatin #         | 8,942         | 307               | 122                            | 147         | 0.88     | 0.69    | 1.12    |

http://www.medsci.org
Table 4. Summary of signal detection for statin-associated cancers

| Incident users | Cases with cancer | Diagnosis of cancer last/first | Adjusted SR | 95% CI |
|----------------|------------------|-------------------------------|-------------|-------|
|                |                  |                               |             | Lower | Upper |
| Pravastatin    | 9,327            | 339                           | 107         | 80    | 1.12  | 0.83  | 1.51  |
| E: Esophageal cancer |            |                               |             |       |       |
| Statins        | 38,402           | 125                           | 68          | 45    | 1.38  | 0.93  | 2.05  |
| Simvastatin    | 2,118            | 3                             | 2           | 1     | 1.38  | 0.87  | 1.94  |
| Rosuvastatin   | 17,515           | 57                            | 32          | 21    | 1.42  | 0.79  | 2.58  |
| Atorvastatin   | 14,359           | 65                            | 28          | 30    | 0.95  | 0.55  | 1.54  |
| Fluvastatin    | 1,678            | 7                             | 4           | 2     | 1.34  | 0.19  | 14.76 |
| Pitavastatin   | 8,942            | 38                            | 22          | 14    | 1.52  | 0.74  | 3.21  |
| Pravastatin    | 9,327            | 24                            | 11          | 9     | 0.93  | 0.35  | 2.55  |
| F: Breast cancer (female) |          |                               |             |       |       |
| Statins        | 15,694           | 485                           | 195         | 239   | 0.81  | 0.66  | 0.98  |
| Simvastatin    | 971              | 18                            | 4           | 12    | 0.25  | 0.06  | 0.83  |
| Rosuvastatin#  | 7,075            | 227                           | 87          | 119   | 0.74  | 0.56  | 0.99  |
| Atorvastatin#  | 5,756            | 176                           | 68          | 85    | 0.90  | 0.64  | 1.25  |
| Fluvastatin    | 756              | 31                            | 17          | 11    | 1.12  | 0.50  | 2.65  |
| Pitavastatin#  | 3,542            | 118                           | 43          | 60    | 0.75  | 0.49  | 1.13  |
| Pravastatin    | 4,283            | 128                           | 54          | 63    | 0.73  | 0.50  | 1.07  |
| G: Hematological malignancies |          |                               |             |       |       |
| Statins        | 38,402           | 373                           | 156         | 171   | 0.90  | 0.72  | 1.12  |
| Simvastatin    | 2,118            | 21                            | 9           | 12    | 0.56  | 0.21  | 1.44  |
| Rosuvastatin#  | 17,515           | 161                           | 68          | 77    | 0.89  | 0.63  | 1.25  |
| Atorvastatin#  | 14,359           | 165                           | 64          | 84    | 0.83  | 0.59  | 1.16  |
| Fluvastatin    | 1,678            | 19                            | 10          | 9     | 0.80  | 0.29  | 2.22  |
| Pitavastatin#  | 8,942            | 80                            | 32          | 35    | 0.95  | 0.57  | 1.58  |
| Pravastatin    | 9,327            | 92                            | 35          | 47    | 0.61  | 0.38  | 0.97  |
| H: Melanoma    |                  |                               |             |       |       |
| Statins        | 38,402           | 34                            | 20          | 14    | 1.15  | 0.55  | 2.46  |
| Simvastatin    | 2,118            | 0                             | 0           | 0     | -     | -     | -     |
| Rosuvastatin#  | 17,515           | 18                            | 9           | 9     | 0.61  | 0.21  | 1.72  |
| Atorvastatin#  | 14,359           | 13                            | 7           | 5     | 1.26  | 0.35  | 5.05  |
| Fluvastatin    | 1,678            | 2                             | 0           | 2     | 0.00  | -     | -     |
| Pitavastatin#  | 8,942            | 12                            | 7           | 5     | 1.20  | 0.33  | 4.78  |
| Pravastatin    | 9,327            | 7                             | 4           | 3     | 0.90  | 0.15  | 6.15  |
| I: Prostate cancer (male) |          |                               |             |       |       |
| Statins        | 22,708           | 522                           | 231         | 231   | 1.16  | 0.96  | 1.40  |
| Simvastatin    | 1,147            | 33                            | 11          | 18    | 0.53  | 0.23  | 1.19  |
| Rosuvastatin#  | 10,440           | 247                           | 103         | 119   | 1.04  | 0.79  | 1.36  |
| Atorvastatin#  | 8,603            | 229                           | 100         | 105   | 1.20  | 0.90  | 1.60  |
| Fluvastatin    | 922              | 27                            | 13          | 12    | 0.92  | 0.38  | 2.19  |
| Pitavastatin#  | 5,400            | 154                           | 72          | 67    | 1.33  | 0.94  | 1.88  |
| Pravastatin    | 5,044            | 143                           | 66          | 58    | 1.08  | 0.74  | 1.56  |

Incident users: Number of patients who received their first prescription for statins
Cases with cancer: Number of patients newly diagnosed with cancer
Diagnosis of cancer last: Diagnosis of cancer last indicates the number of patients with a diagnosis after statin use
Diagnosis of cancer first: Diagnosis of cancer first indicates the number of patients with a diagnosis before statin use
Adjusted SR: Adjusted sequence ratio
CI: Confidence interval
#: High potency statin

FAERS: The US Food and Drug Administration (FDA) Adverse Event Reporting System
 Claims: Claims database
↑ : A positive signal was detected (This means the statin may be associated with an increased risk of cancer).
↓ : A negative signal was detected (This means the statin may be associated with a decreased risk of cancer).
nd: A signal was not detected.
# : High potency statin

http://www.medsci.org
Discussion

Significant signals for colorectal cancer and pancreatic cancer were found for statins as a class in analyses of both the FAERS database and the JMDC claims database. Consistent findings from the independent analyses using different methodologies, algorithms, and databases suggest that statin use is associated with the risk of these two cancers. For lung cancer, a significant association was found with statins as a class in the analysis of the JMDC claims database, but not in the analysis of the FAERS database. In the analyses of individual statins, significant associations with lung cancer were found for atorvastatin and pitavastatin in the analysis of the FAERS database, and were found for rosuvastatin and atorvastatin in the analysis of the JMDC claims database. These findings may suggest that high potency statins including atorvastatin, rosuvastatin, and pitavastatin are associated with an increased risk of lung cancer.

For gastric cancer, no significant association was found for statins as a class. In the analyses of individual statins, significant associations were found for pitavastatin in the analysis of the FAERS database. However, simvastatin was inversely associated with gastric cancer in analyses of the FAERS database and the JMDC claims database. Overall, the association between statin use and gastric cancer is unclear. Given the contradictory findings, it may be reasonable that different statins are associated with different risks of gastric cancer.

For prostate cancer, a significant association was found for statins as a class in the analysis of the FAERS database, but not in the analysis of the JMDC claims database. In the analyses of individual statins, significant associations with prostate cancer were found for rosuvastatin, atorvastatin, pitavastatin and lovastatin in the analysis of the FAERS database, but not in the analysis of the JMDC claims database. Overall, the association between statin use and prostate cancer is unclear; however, high potency statins including rosuvastatin, atorvastatin, and pitavastatin should be noted and monitored in the future.

Of note, inverse associations of statin use were found for breast cancer and hematological malignancies. Statins as a class and individual statins were inversely associated with breast cancer in the analysis of the FAERS database and the JMDC claims database. There is debate concerning the association of statins with breast cancer. However, some studies reported that statins were associated with a decreased risk of breast cancer [43-45]. This accumulated evidence, including our study, supports the hypothesis that statin use may be associated with a decreased risk of breast cancer. In addition, statins were inversely associated with hematological malignancies in the analysis of the FAERS database. A series of nested case-control studies performed by Vinogradova et al. in 2011 suggested that prolonged use of statins was associated with a reduced risk of hematological malignancies [19]. Some experimental studies have suggested that statins may have chemopreventive potential against hematopoietic malignancies [46-48]. These findings support the hypothesis that statins may have a protective effect against the development of breast cancer and hematological malignancies. Further studies are needed to confirm these hypotheses. There was no significant association of statin use with esophageal cancer and melanoma in analyses of the FAERS database and JMDC claims database, suggesting that statins have no positive or negative effects on these cancers.

Although a plausible pharmacological mechanism for statin-associated cancer is unknown, there are several noteworthy potential explanations. The relationship between serum cholesterol levels and the risk of cancer is an area of considerable research and debate. The literature on cholesterol and cancer has demonstrated an inverse relationship between total serum cholesterol levels and incident cancer [49]. There are a number of studies suggesting that an excessively low level of total cholesterol might be an increased risk for cancer mortality [50-55]. Recently, some studies have reported that lower levels of LDL-C are associated with higher rates of incident cancers [56]. Kikuchi et al. suggested that lower serum levels of total cholesterol are associated with higher oxidative DNA damage and linking to an increased risk of cancer [50]. Oxidative DNA stress is thought to play a major role in carcinogenesis [57]. As our study did not examine serum levels of cholesterol, the association of the cholesterol level with cancer risk is unknown. However, it was noteworthy that significant associations with increased risks of cancers were predominantly found for high potency statins such as atorvastatin, rosuvastatin, and pitavastatin. Treatment with high potency statins may result in a lower level of cholesterol than other statin therapy.

Statins increase the number of regulatory T cells (Tregs) [58]. This effect might impair both the innate [59] and adaptive [60] host antitumour immune responses. The number of Tregs present in many solid tumors correlates inversely with patient survival [61]. The elderly are relatively immunosuppressed and are more likely to have occult cancers [62]. Therefore, it is highly plausible that the elderly are particularly sensitive to a statin-induced increase in Tregs, further impairing their immune response to cancer. Some statin trials revealed that statin therapy of the specific
populations including the elderly was associated with an increased risk for the development of incident cancer [63-65]. Given these findings, it is reasonable to assume that statin-induced impairment of the immune response may play an important role in the development of cancer.

The analysis of spontaneous reports is a useful method for identifying signals, and the FAERS database is considered a large source of these data. However, there are several potential limitations that should be taken into account when interpreting results obtained from the FAERS database [66]. First, there is no certainty that the reported event (adverse event or medication error) was actually due to the drug. Second, the FDA does not receive reports on every adverse event or medication error that occurs with a product. Third, the database has missing data and also frequent misspelling of drug names. Fourth, there are a number of duplicate entries in the database. To overcome problems with data quality, we deleted duplicates. Fifth, slightly increased ROR and IC values do not imply an unmistakable risk of cancer in clinical practice. These data mining algorithms and criteria may be helpful to provide further information on the adverse event, and many studies in this area have been reported [67-71]. However, no individual algorithm to detect signals is adequate, and the concurrent use of other algorithms is essential. Therefore, the ROR and IC algorithms were used in the analysis of FAERS database, and our study detected weak but reliable signals for colorectal and pancreatic cancer. Furthermore, in the current study, a different methodology, the ESSA of the JMDC claims database, was used to confirm the findings of FAERS database analyses. Of course, the ESSA is associated with several potential limitations due to its use of a claims database. First, our study population was selected from beneficiaries covered by the employees’ health insurance system. Because most beneficiaries are working adults or their family members, the proportion of elderly patients aged ≥65 years is low. This may make it difficult to detect cancer risk in an analysis of the JMDC claims database. Second, the diagnoses listed in the claims were not validated. We generally needed to consider the diagnosis contained in the claim, which is listed for health insurance claims. However, it is obvious that serious diseases such as cancer may not be listed in the claim only for health insurance claims. In the present study, individual cases were not reviewed, and other causes were not considered. Finally, potential confounding factors, including smoking history, health history, race/ethnicity, body mass index and occupation, which are associated with cancer, could not be controlled in this study. Lack of data on these potential confounding factors should be considered as a limitation when interpreting our findings. Although these potential limitations should be taken into account when interpreting results obtained from the study, it is noteworthy that the multi-methodological approaches using different algorithms and databases detected significant signals for cancer.

Conclusions

Multi-methodological approaches using different methodologies, algorithms, and databases suggest that statin use is associated with an increased risk for colorectal and pancreatic cancer. Although there are many conflicting reports concerning the association between statin use and the risk of these cancers, our study definitely demonstrated this association. An association of lung cancer, gastric cancer, and prostate cancer with statin use is uncertain, because different statins are associated with different risks of these cancers. Of note, significantly increased risks of cancers were found predominantly for high potency statins, such as atorvastatin, rosuvastatin and pitavastatin. Further studies are needed to confirm our findings and elucidate the mechanism for statin-induced cancers.

Abbreviations

FAERS: FDA Adverse Event Reporting System; FDA: Food and Drug Administration; MedDRA: Medical Dictionary for Regulatory Activities; SMQ: Standardized MedDRA Queries; PT: preferred term; ROR: reporting odds ratio; IC: information component; JMDC: The Japan Medical Data Center; ICD-10: International Classification of Disease, 10th Revision; ESSA: Event sequence symmetry analysis; SR: Sequence ratio.

Acknowledgements

The authors thank the Japan Medical Data Center Co., Ltd for providing the claims database.

Competing Interests

Mai Fujimoto, Tomoya Higuchi, Kouichi Hosomi, and Mitsutaka Takada, have no conflicts of interest that are directly relevant to the content of this study.

References

1. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. The New England journal of medicine. 1995; 333: 1301-1307.
2. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. The Cochrane database of systematic reviews. 2013: 1:CD004816.
3. NCEP. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood
Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002; 106: 3143-3421.

4. Keyomarsi K, Sandeol V, Band V, et al. Synchronization of tumor and normal cells from G1 to multiple cell cycles by lovastatin. Cancer research. 1991; 51: 3602-3609.

5. Wong WW, Dimitroulakos J, Minden MD, et al. HMG-CoA reductase inhibitors and the malignant cell: the statin family of drugs as triggers of tumour-specific apoptosis. Leukemia. 2000; 14: 508-519.

6. Dimitroulakos J, Marthin WH, Lukanga J, et al. Microarray and biochemical analysis of lovastatin-induced apoptosis of squamous cell carcinomas. Neoplasia (New York, NY). 2002; 4: 337-346.

7. Pasi HK, Kong D, Iruela-Arispe L, et al. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors interfere with angiogenesis by inhibiting the geranylgeranylation of RhoA. Circulation research. 2002; 91: 143-150.

8. Weis M, Heeschen C, Glassford AJ, et al. Statins have biphasic effects on angiogenesis. Circulation. 2002; 105: 739-747.

9. Alonso DF, Farina HG, Skilton G, et al. Reduction of mouse mammary tumor formation and metastasis by lovastatin, an inhibitor of the mevalonate pathway of cholesterol synthesis. Breast cancer research and treatment. 1998; 50: 83-95.

10. Kusama T, Muki M, Iwasaki T, et al. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors reduce human pancreatic cancer cell invasion and metastasis. Gastroenterology. 2002; 122: 308-317.

11. Kamat AM, Netkin GM. Alorvastatin: a potential chemopreventive agent in breast cancer. Oncology. 2005; 66: 1290-1296.

12. Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. JAMA. 1990; 257: 55-60.

13. Denis M, Boudreau OY, Jeannes J, et al. Statin Use and Cancer Risk: A Critical Review. Expert opinion on drug safety. 2010; 9: 603-621.

14. Haukka J, Sankila R, Klaukka T, et al. Incidence of cancer and statin usage—record linkage study. International journal of cancer Journal international du cancer. 2010; 126: 279-284.

15. Steinberg D. Statin Treatment Does Not Cause Cancer. Journal of the National Cancer Institute. 2008; 100: 134-139.

16. Kuoppala J, Lamminpaa A, Pukkala E. Statins and cancer: A systematic review and meta-analysis. European journal of cancer (Oxford, England : 1990). 2008; 44: 3212-3219.

17. Karp I, Behbouli H, Lelorier J, et al. Statins and cancer risk. The American journal of medicine. 2008; 121: 302-309.

18. Friedman GD, Feussner J, Habel LA, et al. Screening strategies for possibly carcinogenic risk: up to 9 years of follow-up of 361 895 recipients. Pharmacoepidemiology and drug safety. 2008; 17: 27-36.

19. Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to statins and risk of common cancers: a series of nested case-control studies. BMC cancer. 2011; 11: 400.

20. Sato S, Aiki K, Kobayashi T, et al. Pravastatin use and the five-year incidence of cancer in coronary heart disease patients: from the prevention of coronary sclerosis study. Journal of epidemiology / Japan Epidemiological Association. 2006; 16: 201-206.

21. Downs JR, Clearfield M, Tyrolean HA, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAP/TEXCAP): additional perspectives on tolerability of long-term treatment with lovastatin. The American journal of cardiology. 2001; 87: 1074-1079.

22. Graaf MR, Beiderbeck AB, Egberts AC, et al. The risk of cancer in users of statins. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2004; 22: 2388-2394.

23. Kavour JA, Jick H. Statin use and cancer risk in the General Practice Research Database. British journal of cancer. 2004; 90: 635-637.

24. Strandberg TE, Pyorala K, Cook TJ, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). Lancet. 2004; 364: 771-777.

25. Group HPS3. The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: a randomised placebo-controlled trial [ISRCTN48490393]. BMJ Med. 2005; 3 6: 44.

26. Coogan PF, Rosenberg L, Strom BL, et al. Statin use and the risk of 10 cancers. Pharmacoepidemiology and drug safety. 2007; 18: 483-491.

27. Hallas J, Gaist D, Bjerum L. The waiting time distribution as a graphical approach to epidemiologic measures of drug utilization. European journal of clinical pharmacology. 2007; 63: 821-826.

28. Morris JA, Gardner MJ. Calculating confidence intervals for relative risks (odds ratios) and standardised ratios and rates. British medical journal (Clinical research ed). 1998; 296: 1313-1316.

29. Cauley JA, McTaman A, Budohou R, et al. Statin use and breast cancer: prospective results from the Women's Health Initiative. Journal of the National Cancer Institute. 2006; 98: 700-707.

30. Brewer TM, Masuda H, Liu DD, et al. Statin use in primary inflammatory breast cancer: a cohort study. British journal of cancer. 2013; 109: 318-324.

31. Sendur MA, Aksoy S, Yazici O, et al. Statin use may improve clinicopathologic characteristics and recurrence risk of invasive breast cancer. Medical oncology (Northwood, London, England). 2014; 31: 835.

32. Gross H, Drucker L, Shapira M, et al. Simvastatin induces death of multiple myeloma cells. Journal of investigative medicine : the official publication of the American Federation for Clinical Research. 2004; 52: 335-344.

33. Xia Z, Tan MM, Wong WW, et al. Blocking protein geranylgeranylation is essential for lovastatin-induced apoptosis of human acute myeloid leukemia cells. Leukemia. 2001; 15: 1398-1407.

34. Matar P, Rozados VR, Binda MM, et al. Inhibitory effect of Lovastatin on spontaneous metastases derived from a rat lymphoma. Clinical & Experimental Metastasis. 1997; 17: 19-25.

35. Jacobs D, Blackburn H, Higgins M, et al. Report of the Conference on Low Blood Cholesterol: Mortality Associations. Circulation. 1992; 86: 1046-1060.

36. Kikuchi H, Nanri A, Hori A, et al. Lower serum levels of total cholesterol are essential for lovastatin-induced apoptosis of human acute myeloid leukemia cells. Journal of internal medicine. 2013; 273: 549-574.

37. Alshehhi-Al A, Maddukuri PV, Van H, et al. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: insights from large randomized statin trials. Journal of the American College of Cardiology. 2007; 50: 409-418.

38. Hittat RF, Fireman BH. Serum cholesterol and the incidence of cancer in a large cohort. Journal of chronic diseases. 1986; 39: 861-870.

39. Knoet P, Reunanen A, Aromaa A, et al. Serum cholesterol and risk of cancer in a cohort of 39,000 men and women. Journal of clinical epidemiology. 1998; 41: 519-530.

40. Alshehhi-Al A, Trikalinos TA, Kent DM, et al. Association of low plasma cholesterol with mortality for cancer at various sites in men: 17-year follow-up of the prospective Basel study. The American journal of clinical nutrition. 2000; 72: 1047-1052.

41. Alshehhi-Al A, Trikalinos TA, Kent DM, et al. Statins, low-density lipoprotein cholesterol, and risk of cancer. Journal of the American College of Cardiology. 2008; 52: 1144-1147.

42. Alshehhi-Al A, Trikalinos TA, Kent DM, et al. Statins, low-density lipoprotein cholesterol, and risk of cancer. Journal of the American College of Cardiology. 2008; 52: 1144-1147.

43. Ames BN. Endogenous DNA damage as related to cancer and aging. Mutation research. 1989; 214: 41-46.

44. Mausner-Fainberg K, Luboshits G, Mor A, et al. The effect of HMG-CoA reductase inhibitors on naturally occurring CD4+CD25+ T cells. Atherosclerosis. 2008; 197: 829-839.

45. Tiemessen MM, Jagger AL, Evans HG, et al. CD4+CD25+Foxp3+ regulatory T cells induce alternative activation of human monocytes/macrophages. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104: 19446-19451.

46. Curiel TJ. Tregs and rethinking cancer immunotherapy. The Journal of clinical investigation. 2007; 117: 1167-1174.
61. Yakirevich E, Resnick MB. Regulatory T lymphocytes: pivotal components of the host antitumor response. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2007; 25: 2506-2508.
62. Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of ageing. The Journal of pathology. 2007; 211: 144-156.
63. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002; 360: 1623-1630.
64. Hunt D, Young P, Simes J, et al. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: Results from the LIPID trial. Ann Intern Med. 2001; 134: 931-940.
65. Wenger NK, Lewis SJ, Herrington DM, et al. Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. Annals of internal medicine. 2007; 147: 1-9.
66. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiology and drug safety. 2009; 18: 427-436.
67. Tamura T, Sakaeda T, Kadoyama K, et al. Aspirin- and clopidogrel-associated bleeding complications: data mining of the public version of the FDA adverse event reporting system, AERS. International journal of medical sciences. 2012; 9: 441-446.
68. Murakami H, Sakaeda T, Kadoyama K, et al. Gender Effects on Statin-Associated Muscular Adverse Events: An Analysis of the FDA AERS Database. Pharmacology & Pharmacy. 2013; 4: 340-346.
69. Moore N, Kreft-Jais C, Haramburu F, et al. Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. British journal of clinical pharmacology. 1997; 44: 513-518.
70. Poluzzi E, Raschi E, Moretti U, et al. Drug-induced torsades de pointes: data mining of the public version of the FDA Adverse Event Reporting System (AERS). Pharmacoepidemiology and drug safety. 2009; 18: 512-518.
71. Poluzzi E, Raschi E, Motola D, et al. Antimicrobials and the risk of torsades de pointes: the contribution from data mining of the US FDA Adverse Event Reporting System. Drug safety: an international journal of medical toxicology and drug experience. 2010; 33: 303-314.