Statin use and risk of liver cancer: an update meta-analysis

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ABSTRACT

Objective: Statins are commonly prescribed cholesterol-lowering drugs. Preclinical studies suggest that statins may possess cancer preventive properties. The primary objective of this meta-analysis was to determine the association between statin use and risk of liver cancer.

Design: Meta-analysis.

Setting: International.

Participants: A comprehensive literature search of PubMed, BIOSIS Previews, Web of Science, EMBASE, EBSCO and Cochrane Library was conducted through March 2014. The effect estimate was reported as pooled relative risk (RR) with 95% CIs, using the random-effects model.

Results: A total of 12 studies (1 individual patient data analysis of 22 randomised controlled trials, 5 cohorts and 6 case-controls) were qualified for this meta-analysis, involving 5 640 313 participants including 35 756 liver cancer cases. Our results indicated a significant risk reduction of liver cancer among all statin users (RR=0.58, 95% CIs 0.51 to 0.67). The difference of the study designs can partly explain the significant heterogeneity found in the overall analysis (I²=65%, p=0.0006). No evidence of publication bias was observed in this meta-analysis. Similar risk reductions were found in the subgroups analysis of Western and Asian countries, lipophilic and hydrophilic statins. There was a trend towards more risk reductions in subgroups with higher baseline risk, inadequate adjustment and higher cumulative dosage of statin use.

Conclusions: This meta-analysis suggests that statin is associated with a significant risk reduction of liver cancer when taken daily for cardiovascular event prevention. However, this preventive effect might be overestimated due to the exposure period, the indication and contraindication of statins and other confounders. Statins might be considered as an adjuvant in the treatment of liver cancer.

INTRODUCTION

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, widely used to reduce plasma cholesterol levels and the risk of cardiovascular events.1 Although there is a concern over their possible carcinogenicity raised in rodent studies,2 preclinical studies indicate that statins have anticancer properties in vitro and in vivo, through inhibiting angiogenesis, inducing apoptosis, and suppressing tumour growth and metastasis.3-5

However, higher concentrations of statins are typically required to induce these effects, raising questions concerning the therapeutic relevance of statins on cancer.6 To date, clinical studies regarding the cancer incidence associated with statin administration have highlighted conflicting results. Moreover, a large number of meta-analyses have concluded that there was no association between statin use and risk of overall cancer or of cancer of breast, stomach or pancreas.13 There is only a modest protective effect of statins in prostate cancer14 and colorectal cancer.15

On the contrary, recent studies reported encouraging results for risk reduction of liver cancer among all statin users. Previous meta-analysis, conducted by Singh et al6 through including 10 studies, found that statin users were less likely to develop hepatocellular carcinoma (HCC) than statin non-users. However, Singh et al included the ALERT, LIPS and MEGA trials twice by including three individual patient data (IPD) analysis of randomised controlled trials (RCTs).17-19 Meanwhile, some factors of
stratification were not considered in their analyses, such as dose and timing of exposure to statins, and the selection of controls and confounders, which might limit the evaluation of cancer risk. Furthermore, lipophilic statins are accompanied by an extensive first-pass effect at the hepatic level. It is plausible that lipophilic statins may have better liver cancer preventive qualities than hydrophilic statins.

Therefore, we performed this updated meta-analysis to assess the association between statin use and risk of liver cancer, involving the recently published studies and conducting more subgroup analyses based on the factors aforementioned. Our results demonstrated that statin use was associated with an over 40% risk reduction in liver cancer, which may have a significant translational potential in clinical practice. However, there were some confounders that might overestimate this preventive effect of statins.

**MATERIALS AND METHODS**

**Literature search strategy**

This meta-analysis was conducted following the PRISMA guidelines. The systematic computerised search for eligible studies were performed on the database of PubMed, BIOSIS Previews, Web of Science, EMBASE, EBSCO and Cochrane Library, covering all studies published from their inception to 5 March 2014. The following terms were searched with the subjects (MeSH terms) as well as text-word search strategies: "(Statin OR HMG-CoA reductase inhibitors OR Atorvastatin OR Cerivastatin OR Fluvastatin OR Lovastatin OR Pravastatin OR Rosuvastatin OR Simvastatin) AND (Hepatocellular OR Hepatic OR Intrahepatic OR Interlobular OR Liver) AND (Carcinoma OR Sarcomas OR Angiosarcoma OR Cancer OR Neoplasm). Additionally, the relevant reviews and retrieved articles were searched manually for more eligible studies.

In study searching, only the original researches, published in the form of peer review articles or meeting abstracts, were included. No language restrictions were imposed. However, the studies we included were all published in English.

**Study selection**

The inclusion criteria were: (1) RCTs, cohort studies or case–control studies; (2) original studies that assessed the effect of statin use on the risk of liver cancer, compared with placebo or no treatment; (3) liver cancer cases identified according to the International Classification of Diseases codes (ICD) and (4) studies with estimate of relative risk (risk ratio, RR) of liver cancer, or with data sufficient to calculate it.

The exclusion criteria were: (1) study design not meeting the inclusion criteria; (2) studies without estimate of RR, or without sufficient data to calculate it or (3) studies with duplicated or overlap reports.

**Data extraction**

Two independent investigators (MS and XC) extracted data from the eligible studies using a predefined data collection form. The differences of data extraction were resolved by consensus referring back to the original article. The extracted information included: (1) studies: first author, year of publication, study design, location, patient populations, period and follow-up; (2) statins: type, dosage or duration of statin use and (3) liver cancer: case identification, number of liver cancers, crude RR with 95% CIs, adjusted RR reflecting the greatest degree of control for confounders and confounders for adjustment (including variables for matching). When the RR data were not available, the RR with 95% CIs were calculated from the raw data in original studies.

We extracted different measurements of effect estimates from original studies, such as RR, OR, HR and Observed/Expected ratio. Owing to the fact that the incidence of liver cancer was low in all studies, these different measurements can be used to provide similar estimates of RR.

**Methodological quality assessment**

Of note, the included RCT was pooled analysis of other RCTs, therefore it is inappropriate to assess the methodological quality. The methodological quality of cohort and case–control studies were assessed on the Newcastle-Ottawa Scale, including eight items that were categorised into three categories: selection (four items, one star each), comparability (one item, up to two stars) and exposure/outcome (three items, one star each). A ‘star’ presents a ‘high’-quality choice of each item.

**Statistical analysis**

The overall meta-analysis was first performed, followed by the subgroup analyses, based on study design, baseline risk of liver cancer, confounding adjustment, study location and pharmacokinetics. Meanwhile, we conducted subgroup analyses based on studies that reported RR estimates for higher cumulative dosage of statin use, when appropriate data were available.

To take into account the heterogeneity and provide a more conservative estimate, the inverse variance method was used to estimate the pooled RRs and corresponding 95% CIs, and data were pooled using a random effects model. Heterogeneity was assessed using the χ² statistic (P) together with the Higgins I² statistic (I²), a p value <0.10 was considered statistically significant for heterogeneity; and an I² value >50% was considered a measure of severe heterogeneity.

Publication bias was assessed using the Begg’s test and the Egger’s test. Influence analysis was performed to investigate the influence of a single study on the overall meta-analysis estimate, by omitting one study in each turn. Test for interaction was applied to identify the differences between pooled RRs from subgroup analysis using the method described by Altman and Bland. All statistical tests were two-sided and p<0.05 was considered statistically significant.
statistically significant, unless otherwise specified. Software Review Manager (RevMan5.2, Copenhagen) and STATA (Stata V.11.2, Texas, USA) were used for the statistical analysis.

RESULTS
Study selection
Figure 1 illustrates the process of study selection for the meta-analysis. Of the 1424 potentially relevant references identified by electric and manual search, 142 were selected for full-text review after screening titles and abstracts. Finally, a total of 12 studies were included, with one IPD analysis,19 five cohort studies,28–32 and six case–control studies.33–38 One case–control study was presented solely in abstract form.33

Of note, the cohort study conducted by Friedman et al29 reported RR estimates separately for different genders (male and female), we considered these two reports as separate studies. Therefore, a total of 13 reports were included for the present meta-analysis.

Study characteristics
Table 1 summarises the characteristics of qualified studies in this meta-analysis. The 12 studies, involving 5 640 313 participants with 35 756 liver cancer cases, were published between 2005 and 2013. The ‘RCT’ in the present study was pooled analysis of 22 clinical trials,19 which investigated statin therapy in cardiovascular event prevention and reported the occurrence of liver cancer as an adverse event. The observational studies were conducted with the local or national health databases, statin exposures were identified by linkage to prescription databases, and the controls were matched mainly by age, sex and index date. Except for one cohort, which adopted ICD-10 C29,28 all other studies identified liver cancer cases according to the ICD-9 155. Of note, two cohorts were restricted to patients with hepatitis B virus (HBV)31 and hepatitis C virus (HCV) infections32; one case–control only included patients with diabetes mellitus34; and two observational studies included patients aged at least 45 years.30 35

Table 2 summarises the data of the included studies. In the RCT19 and one cohort study,30 the RR with 95% CIs were calculated from the 2×2 tables defined by the incidence of liver cancer and statin use status. The observational studies reported different measurements of RR estimates with adjustment by confounders. Several observational studies adopted the important risk factors of liver cancer for adjustments31 32 34–36 such as HBV infection, HCV infection, cirrhosis and alcoholic liver disease or non-alcoholic fatty liver disease (NAFLD).39 Of note, only two studies adjusted for cholesterol level,30 38 and no study adjusted for metabolic syndrome, which might also influence the risk of liver cancer.39

Methodological quality
For the cohort and case–control studies, the median score was 7 on the Newcastle-Ottawa Scale, with a range 5–8 (see online supplementary table S1). These results indicated that the observational studies were of a reasonably good quality.

Overall meta-analysis
Figure 2 depicts the forest plot of RR estimate with 95% CIs from individual studies and overall meta-analysis. In the overall meta-analysis, pooled results showed a statistically significant decrease in liver cancer risk among all statin users (RR=0.58, 95% CIs 0.51 to 0.67). Of note, a statistically significant heterogeneity was observed (I²=65%, p=0.0006). The p values of Begg’s test and Egger’s test were 0.669 and 0.749, respectively, both suggesting there was no evidence of publication bias. In the influence analysis, the omission of any individual studies did not alter the direction and magnitude of the observed effect (see online supplementary figure S1).

Subgroup analyses and test for interaction
We first performed preplanned subgroup analyses based on study design, baseline risk of liver cancer, confounding adjustment and study location (table 3).

The RCT showed there is no significant association between statin use and risk of liver cancer (RR=1.06, 0.66 to 1.71). But the observational studies indicated a significant decrease of liver cancer risk among all statin users (RR=0.57, 0.50 to 0.64; I²=61%, p=0.003; figure 2). Furthermore, we found a greater risk reduction in the subgroup analysis of cohort studies (RR=0.51, 0.44 to 0.58; I²=18%, p=0.30) than in the case–control studies (RR=0.63, 0.54 to 0.73; I²=46%, p=0.10; see online supplementary figure S2).
| Studies                  | Study design | Patient population                                      | Study period | Cases defined | Follow-up (years) | Statin types                      | Dosage/duration of statin use |
|-------------------------|--------------|---------------------------------------------------------|--------------|---------------|-------------------|-----------------------------------|------------------------------|
| Emberson et al.         | RCT          | IPD analysis of 22 RCTs                                 | –            | ICD-9 155     | 5.1 (Me)          | A, F, L, P, R and S               | 5.1 years (Me)               |
| Friis et al.            | Cohort       | General population (CPR)                                | 1989–2002    | ICD-10 C22    | 3.3 (M)           | Unspecified                      | ≥2 Rx                        |
| Friedman et al.         | Cohort       | General population (KPMCP)                              | 1994–2003    | ICD-9-CM 155  | >2                | A, L and S (97.6%)               | ≥1 Rx                        |
| Marelli et al.          | Cohort       | General older population (men ≥45 and women ≥55 years; GE Centricity) | 1990–2009    | ICD-9 155     | 4.6 (M)           | Unspecified                      | ≥1 cDDD                     |
| Tsan et al.             | Cohort       | Patients with HBV infection (NHIRD)                     | 1997–2008    | ICD-9 155     | 9.9 (M)           | A, F, L, P, R and S               | ≥28 cDDDs                   |
| Tsan et al.             | Cohort       | Patients with HCV infection (NHIRD)                     | 1999–2010    | ICD-9 155     | 10.7 (M)          | A, F, L, P, R and S               | ≥28 cDDDs                   |
| Khurana et al.          | Case–control | General population (VISN)                               | 1997–2002    | ICD-9 155     | NR                | Unspecified                      | ≥1 Rx                        |
| El-Serag et al.         | Case–control | Diabetes patients (VA)                                  | 1997–2002    | ICD-9-CM 155  | 2.4 (M)           | A, C, F, L, P and S               | 1.6 years (M)               |
| Chiu et al.             | Case–control | Older patients (≥50 years; NHIRD)                       | 2005–2008    | ICD-9-CM 155  | NR                | A, F, L, P, R and S               | ≥1 cDDD                     |
| Lai et al.              | Case–control | General population (NHIRD)                              | 2000–2009    | ICD-9-CM 155  | 1.4 (M)           | A, F, L, P, R and S               | ≥1 Rx                        |
| Leung et al.            | Case–control | General population (NHIRD)                              | 2000–2008    | ICD-9-CM 155  | 4.1 (M)           | Unspecified                      | >0.5 years                   |
| Chaiteerakij et al.     | Case–control | Hyperlipidaemia patients (Mayo Clinic)                  | 2000–2010    | ICD-9-CM 155  | >1                | Unspecified                      | ≥1 Rx                        |

Duration of follow-up: When the follow-up periods of statin user and non-user were different, only the shorter period was shown, and all periods were transformed to years.

≥1 cDDD = more than 1 cumulative defined daily dose before the diagnosis of liver cancer; A, atorvastatin; C, cerivastatin; CM, clinical modification; CRP, the Central Population Register of Danish citizens; F, fluvastatin; GE Centricity, the General Electric Centricity database; HBV, hepatitis B virus; HCV, hepatitis C virus; ICD-9 or ICD-10, International Classification of Diseases, Ninth Revision or Tenth Revision; IPD, individual patient data; KPMCP, the Kaiser Permanente Medical Care Program in northern California; L, lovastatin; M, mean; Mayo Clinic, Mayo Clinic (Rochester, MN); Me, median; NHIRD, the Taiwanese National Health Insurance research database; non-statin, non-statin cholesterol-lowering drug(s) only; NR, not reported; P, pravastatin; R, rosuvastatin; RCT, randomised controlled trials; Rx, prescriptions; S, simvastatin; VA, Veterans Affairs national databases; VISN, Veterans Integrated Service Networks 16 Veteran Affairs database.
| Studies                     | Intervention/cases | Control                        | Measurements of effect estimates | Crude RR with 95% CIs          | Adjusted RR with 95% CIs       | Confounders for adjustment |
|----------------------------|--------------------|--------------------------------|----------------------------------|--------------------------------|--------------------------------|----------------------------|
| Emberson et al,19 UK       | 35, 67 258         | 33, 67 279                     | RR                               | 1.06 (0.66 to 1.71)*           | 1.06 (0.66 to 1.71)*           | Randomisation               |
| Friis et al,28 North Jutland| 1, 12 251          | 166                            | OR                               | NA                             | 1.16 (0.46 to 2.90)             | 1, 2, 16, 21, 23            |
| Friedman et al (male),29 USA| 32, 192 598        | NA                             | HR                               | NA                             | 0.49 (0.34 to 0.70)             | 16                         |
| Friedman et al (female),29 USA| 10, 169 261        | NA                             | HR                               | NA                             | 0.40 (0.21 to 0.75)             |                            |
| Marelli et al,30 USA       | 13, 45 857         | 24                              | RR                               | 0.31 (0.14 to 0.68)*           | 0.31 (0.14 to 0.68)*           | 1–5, 14, 16–18, 26, 27     |
| Tsan et al,31 Taiwan       | 58, 2785           | 963                            | HR                               | 0.66 (0.51 to 0.86)            | 0.47 (0.36 to 0.61)             | 1, 2, 7, 8, 11, 12         |
| Tsan et al,32 Taiwan       | 1378, 35 023       | 26 505                         | HR                               | 0.42 (0.39 to 0.46)            | 0.53 (0.49 to 0.58)             | 1, 2, 7, 8, 11, 13         |
| Khurana et al,33 USA       | NA                 | NA                             | OR                               | NA                             | 0.52 (0.41 to 0.67)             | 1, 11, 13                  |
| El-Serag et al,34 USA      | 447, 1303          | 2766                           | OR                               | 0.46 (0.40 to 0.52)            | 0.74 (0.64 to 0.87)             | 1–3, 6, 8, 9, 11–13, 21, 24, 28 |
| Chiu et al,35 Taiwan       | 117, 1166          | 195                            | OR                               | 0.53 (0.41 to 0.69)            | 0.62 (0.45 to 0.83)             | 1, 2, 8, 9, 11, 12, 20, 29 |
| Lai et al,36 Taiwan        | 255, 3480          | 1635                           | OR                               | 0.61 (0.52 to 0.72)            | 0.71 (0.56 to 0.89)             | 1, 2, 8–13, 22, 24, 25     |
| Leung et al,37 Taiwan      | 26, 424            | 6851                           | HR                               | 0.45 (0.30 to 0.67)            | 0.44 (0.28, 0.72)              | 1, 2, 11, 15, 20, 21, 23   |
| Chaiteerakij et al,38 USA  | 72                 | 165                            | OR                               | NA                             | 0.6 (0.4 to 0.9)               | 1–3, 8, 11, 17, 22, 28, 30 |

The RR with an asterisk mark (*) was calculated based on the raw data. The others, crude or adjusted, were extracted from the original paper; confounders for adjustment: 1=age, 2=sex, 3=race, 4=Smoking status, 5=Ethanol intake, 6=Socioeconomic status, 7=Cirrhosis, 8=Alcoholic liver disease, 9=Non-alcoholic fatty liver disease, 10=Diabetes mellitus, 11=HCV infection, 12=HCV infection, 13=Concomitant diagnoses (unspecified), 14=Charlson score, 15=Cholesterol (total cholesterol, VLDL, LDL or triglycerides), 16=Prostate-specific antigen, 17=Resection extent, 20=Other lipid-lowering agents, 21=Cardiovascular medications (aspirin, non-steroidal anti-inflammatory medications or ACE inhibitors), 22=Metformin or thiazolidinedione, 23=Hormone-replacement therapy, 24=HCV treatment, 25=HBV treatment, 26=Medications taken (unspecified), 27=Number of office visits, 28=Propensity to use statins, 29=Hospital stay, 30=Biliary tract diseases.

BMI, body mass index; HCV, hepatitis C virus; LDL, low-density lipoprotein; NA, not applicable; RR, relative risk; VLDL, very low-density lipoprotein.
Test for interaction showed significant results between subgroups of the RCT and observational studies (P_{interaction}=0.01, Z=2.47), and between subgroups of the cohort and case–control studies (P_{interaction}=0.04, Z=−2.03). These results indicated that the difference of the study designs was partly the reason why there was severe heterogeneity in the overall analysis (table 3).

Figure 2  Overall meta-analysis of statin use and liver cancer risk.

| Study or Subgroup | log(Risk Ratio) | SE  | Weight | Risk Ratio IV, Random, 95% CI | Year |
|-------------------|----------------|-----|--------|-------------------------------|------|
| 1.1.1 Randomized Controlled Trials |
| Emberson 2012     | 0.05026691     | 0.24265939 | 5.4% | 1.06 [0.66, 1.71] | 2012 |
| Subtotal (95% CI) | 5.4%           | 1.06 [0.66, 1.71] |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 0.24 (P = 0.61) |

| 1.1.2 Observational studies |
|-------------------------------|
| Khurana 2005                 | -0.65392647     | 0.12526586 | 10.3% | 0.52 [0.41, 0.66] | 2005 |
| Friis 2005                   | 0.14842         | 0.46970396 | 1.9%  | 1.16 [0.46, 2.91] | 2005 |
| Friedman (Male) 2008         | -0.71334989     | 0.18421894 | 7.4%  | 0.49 [0.34, 0.70] | 2008 |
| Friedman (Female) 2008       | -0.91629073     | 0.32473614 | 3.5%  | 0.40 [0.21, 0.76] | 2008 |
| El-Serag 2009               | -0.30110059     | 0.07832271 | 13.0% | 0.74 [0.63, 0.86] | 2009 |
| Chiu 2011                   | -0.47803585     | 0.15616789 | 8.7%  | 0.62 [0.46, 0.84] | 2011 |
| Marelli 2011                | -1.17118298     | 0.40317612 | 2.5%  | 0.31 [0.14, 0.68] | 2011 |
| Tsan 2012                   | -0.75502258     | 0.13452932 | 8.8%  | 0.47 [0.36, 0.61] | 2012 |
| Tsan 2013                   | -0.63487827     | 0.043016   | 14.7% | 0.53 [0.49, 0.58] | 2013 |
| Leung 2013                  | -0.82098055     | 0.24053408 | 5.4%  | 0.44 [0.27, 0.71] | 2013 |
| Chaiakajik 2013             | -0.51082582     | 0.20686995 | 6.5%  | 0.60 [0.40, 0.90] | 2013 |
| Lai 2013                    | -0.34249031     | 0.11818487 | 10.7% | 0.71 [0.56, 0.90] | 2013 |
| Subtotal (95% CI)           | 94.6%           | 0.57 [0.50, 0.64] |
| Heterogeneity: Tau^2 = 0.02; Chi^2 = 27.92, df = 11 (P = 0.003); I^2 = 61% |
| Test for overall effect: Z = 8.60 (P < 0.00001) |

Table 3  Subgroup analyses of included studies

| Subgroup                                      | Number of studies (reports) | Summary RR (95% CIs) | Heterogeneity, I^2 (%) | Heterogeneity, p value | P_{interaction} |
|-----------------------------------------------|-----------------------------|----------------------|------------------------|------------------------|-----------------|
| RCT                                           | 1                           | 1.06 (0.66 to 1.71)  | –                      | –                      | 0.01            |
| Observational studies                         | 11 (12)                     | 0.57 (0.50 to 0.64)  | 61                     | 0.003                  |                 |
| Observational studies                         | 5 (6)                       | 0.51 (0.44 to 0.58)  | 18                     | 0.30                   | 0.04            |
| Cohort studies                                | 6                           | 0.63 (0.54 to 0.73)  | 46                     | 0.10                   |                 |
| Baseline risk of liver cancer                 | 4                           | 0.52 (0.47 to 0.59)  | 16                     | 0.31                   | 0.08            |
| General population                            | 8 (9)                       | 0.63 (0.52 to 0.75)  | 59                     | 0.01                   |                 |
| Confounding adjustment                        | 6                           | 0.64 (0.53 to 0.77)  | 81                     | 0.0001                 | 0.08            |
| Adequate adjustment                          | 6 (7)                       | 0.51 (0.43 to 0.60)  | 3                      | 0.40                   |                 |
| Inadequate adjustment                        |                             |                      |                        |                        |                 |
| Study location                                | 7 (8)                       | 0.61 (0.48 to 0.76)  | 64                     | 0.007                  | 0.54            |
| Western studies                               | 5                           | 0.56 (0.48 to 0.64)  | 51                     | 0.09                   |                 |
| Asian studies                                 |                             |                      |                        |                        |                 |
| Pharmacokinetic                               | 5 (6)                       | 0.57 (0.50 to 0.65)  | 50                     | 0.08                   | 0.86            |
| Lipophilic statins                            | 3                           | 0.59 (0.41 to 0.84)  | 50                     | 0.13                   |                 |
| Hydrophilic statins                           | 6                           | 0.53 (0.36 to 0.79)  | <0.0001                |                        |                 |

RR higher baseline risk of liver cancer: patients with older age, HBV or HCV infection. Adequate adjustment: RCT or studies, which adjusted for at least four of seven important confounders, such as HBV infection, HCV infection, cirrhosis, alcoholic liver disease, NAFLD, HBV treatment or HCV treatment; lipophilic statins: atorvastatin, fluvastatin, lovastatin or simvastatin; hydrophilia statins: pravastatin or rosuvastatin; higher cumulative dosage of statin use: >180 cumulative defined daily dose or duration of statin use >0.5 years before the diagnosis of liver cancer. HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; RCT, randomised controlled trials; RR, relative risk.
In the subgroup analysis of the four studies with higher baseline risk of liver cancer,30–325 defined as patients with older age, HBV or HCV infection, there was a trend towards more decrease of liver cancer risk (RR=0.52, 0.47 to 0.59; I²=16%, p=0.31) than in the other eight studies with general population19 28 29 33 34 36–38 (RR=0.63, 0.52 to 0.75; I²=59%, p=0.01; see online supplementary figure S3).

We defined the RCT or studies adjusted for at least four of seven important confounders, such as HBV infection, HCV infection, cirrhosis, alcoholic liver disease, NAFLD, HBV treatment or HCV treatment,39 were adjusted adequately. Subgroup analysis of these six studies19 31 32 34–36 found a trend towards less decrease of liver cancer risk (RR=0.64, 0.53 to 0.77; I²=81% p=0.0001) than the other six studies28–30 33 37 38 (RR=0.51, 0.43 to 0.60; I²=3%, p=0.40; see online supplementary figure S4).

Subgroup analyses based on study location found a similar risk reduction of liver cancer in Western countries (RR=0.61, 0.48 to 0.76; I²=64%, p=0.007) and in Asian countries (RR=0.56, 0.48 to 0.64; I²=51%, p=0.09; see online supplementary figure S5).

Besides the overall RR estimates, some studies reported different RR estimates for different pharmacokinetics and dosage of statin use (see online supplementary table S2). We conducted further subgroup analyses based on these available data.

According to the different pharmacokinetics, statins can be classified as lipophilic statins (atorvastatin, fluvastatin, lovastatin and simvastatin) and hydrophilic statins (pravastatin and rosuvastatin).21 Subgroup analysis of lipophilic statins29 31 34–36 found a significant decrease of liver cancer risk (RR=0.57, 0.50 to 0.65; I²=50%, p=0.08). There was a similar result among users of hydrophilia statins31 35 36 (RR=0.59, 0.41 to 0.84; I²=50%, p=0.13; see online supplementary figure S6).

Test for interaction showed non-significant results for subgroups with different baseline risk, confounding adjustment, study location or pharmacokinetics (Pinteraction=0.08, 0.08, 0.54 and 0.86, respectively; table 3). Therefore, there is no strong evidence to support a different preventive effect of statins on liver cancer in these subgroups.

Subgroup analysis of six studies with higher cumulative dose of statin use, defined as statin use over 180 cumulative defined daily doses (cDDD) or 0.5 years (cumulative duration), showed a trend towards more risk reduction of liver cancer (RR=0.53, 0.36 to 0.79), but with a high degree of heterogeneity (I²=90%, p<0.00001; see online supplementary figure S7).

DISCUSSION

This present meta-analysis represents the most comprehensive review to date on the association between statin use and liver cancer risk, by including 12 studies (1 IPD analysis of 22 RCTs, 5 cohort studies and 6 case–control studies) and involving 5 640 313 participants with 35 756 liver cancer cases. Overall, we found that statin use was associated with an over 40% risk reduction in liver cancer compared with non-users (RR=0.58, 95% CIs 0.51 to 0.67). This result was in line with the previous three meta-analyses: Singh et al16 included 10 studies and suggested statin users were less likely to develop HCC (OR 0.63, 95% CIs 0.52 to 0.76), Pradelli et al30 and Zhang et al41 included 5 and 7 observational studies and found a summary RR of 0.58 (95% CIs 0.46 to 0.74) and 0.61 (95% CIs 0.49 to 0.76), respectively.

The IPD analysis of 22 RCTs showed there is no significant association between statin use and risk of liver cancer. The significant risk reduction of liver cancer among all statin users was seen primarily in the observational studies, and this preventive effect was relatively more convincing in the cohorts than in the case–controls. There were some reasons to explain the different findings between RCTs and observational studies.

First, the exposure period to statins might be shorter than the period to carcinogenesis and the latency to diagnosis in the cohorts and the case–controls. The observational studies defined statin use varying in dosage and duration, from patients who received ≥1 cDDD or >1 Rx of statins to more than 0.5 years (table 1). On the other hand, the median period of statin use was 5.1 years in the RCTs. Although there was a trend towards more risk reduction of liver cancer with higher cumulative dose of statin use, this defect might still result in overestimating the cancer-preventive effect of statins in the observational studies.

Second, clinical studies demonstrated that higher serum total cholesterol concentration was associated with decreased risk of liver cancer (see online supplementary table S3).42–44 Meanwhile, there were inverse associations between use of non-statin lipid-lowering drugs and risk of liver cancer.35 36 Meanwhile, because of the contraindication, statins might not be prescribed to patients with chronic liver disease, which is a known risk factor of liver cancer. Unfortunately, the observational studies included in this analysis seldom adopted these factors for adjustment. Actually, subgroup analysis of studies with adequate adjustment showed a trend towards less risk reduction, indicating the potential of overestimation of this preventive effect by confounders.

Third, the RCTs including a lower risk population (patients with cardiovascular disease rather than HBV/HCV infection), might not be powerful enough to investigate the liver cancer outcomes, which were much rarer than cardiovascular events. In addition, subgroup analysis of studies with higher baseline risk showed a trend towards a greater decrease of liver cancer risk.

These reasons suggested that the observed modulation of cancer incidence cannot be ascribable to a direct statin-mediated effect20; the exposure period, the indication (eg, hyperlipidaemia) and contraindication (eg, chronic liver disease) of statins might overestimate its cancer-preventive effect.

We found similar results in Western and Asian countries, which were different from the meta-analysis conducted by Singh et al, which concluded that the inverse
association of statins with HCC was stronger in the Asian population. Considering four more studies we included, this difference might be caused by the insufficient data in their meta-analysis. Based on the pharmacokinetics, it is plausible that lipophilic and hydrophilic statins will differ in their liver cancer prevention qualities. However, subgroup analysis of lipophilic and hydrophilic statins showed similar results.

Besides the limitations described previously, there were some other limitations that should be noted. First, a significant heterogeneity was observed in the present meta-analysis, which might result from the difference in study design. Results of subgroup analyses would also be limited by this heterogeneity. Second, the adherence to statin therapy is known to be associated with a healthy lifestyle, which might affect the cancer outcome. Such information is hard to capture in databases or medical records in the observational studies. Third, five observational studies were conducted using the Taiwanese National Health Insurance Research Database (NHIRD). Although they were not all in the same period, these studies might contain overlapping groups of patients. These limitations aforementioned could lead to confounding of overall results from the present study, and should be considered in future studies aiming at confirming the protective effects of statins on human cancer risk.

The strengths of our meta-analysis were as follows: First, we performed a much more comprehensive search and more subgroup analyses, compared with the previous meta-analyses; second, the methodological quality of the included studies was reasonably good; third, publication bias, due to the tendency of not publishing small studies with null results, was not found in our meta-analysis.

Of note, preclinical studies have indicated that statins possess synergism with other therapeutic agents in vitro and in vivo for liver cancer. Some clinical studies have also demonstrated that statins would prolong survival in patients with advanced liver cancer (see online supplementary table S4), and are associated with risk reduction of recurrence after curative surgery in patients of HBV-related HCC. Therefore, considerable interest exists in adjunctive therapy with statins for liver cancer. In fact, there were some RCTs ongoing to determine the effectiveness of pravastatin, when used in combination with sorafenib, in the treatment of liver cancer (see online supplementary table S5).

Currently, physicians are less likely to prescribe statins for patients with chronic liver disease, based on the concerns about statin-induced liver injury. However, there were number of studies that have demonstrated their safe use and even salutary effects. Meanwhile, the risk of serious statin-related liver injury appears to be no greater than the background incidence of this rare event. Therefore, considering their benefits for cardiovascular event prevention and the potential effect in liver cancer prevention and treatment, statins should not be denied to these patients.

In conclusion, our results suggest that statin use is associated with significant risk reduction of liver cancer when taken daily for cardiovascular event prevention. However, this preventive effect might be overestimated due to the exposure period, indication and contraindication of statins, and other confounders. Statins might be considered as an adjuvant in the treatment of liver cancer.

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Contributors XC had the original idea. MS, XC and WG worked together to develop an appropriate theoretical framework and design. XC developed the search. MS and XC were involved in the selection process. MS and XC extracted relevant data. XC and WG performed the statistical analysis and all authors were involved in the data interpretation. MS and BN wrote the manuscript draft and revised the draft based on input from the other authors. All authors revised it critically for content and approved the final version.

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REFERENCES

1. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
2. Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. JAMA 1996;275:55–60.
3. Demierre MF, Higgins PD, Gruber SB, et al. Statins and cancer prevention. Nat Rev Cancer 2005;5:830–42.
4. Zeiher SN, Mihos CG, Santoro O. The pleiotropic effects and therapeutic potential of the hydroxy-methyl-glutaryl-CoA reductase inhibitors in malignancies: a comprehensive review. J Cancer Res Ther 2012;8:176–83.
5. Londoño A, Moria P. Potential for statins in the chemoprevention and management of hepatocellular carcinoma. J Gastroenterol Hepatol 2012;27:1654–64.
6. Shimoyama S. Statins are logical candidates for overcoming limitations of targeting therapies on malignancy: their potential application to gastrointestinal cancers. Cancer Chemother Pharmacol 2011;67:729–39.
7. Dale KM, Coleman CI, Henyan NN, et al. Statins and cancer risk: a meta-analysis. JAMA 2006;295:74–80.
8. Browning DRL, Martin RM. Statins and risk of cancer: a systematic review and metaanalysis. Int J Cancer 2007;120:833–43.
9. Kuoppala J, Lamminpaa A, Pukkala E. Statins and cancer: a systematic review and meta-analysis. Eur J Cancer 2008;44:2122–32.
10. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–81.
11. Undelika K, Srikant V, Bansal D. Statin use and risk of breast cancer: a meta-analysis of observational studies. Breast Cancer Res Treat 2012;135:261–8.
12. Shimoyama S. Statins and gastric cancer risk. Hepatogastroenterology 2011;58:1057–61.
13. Cui X, Xie Y, Chen M, et al. Statin use and risk of pancreatic cancer: a meta-analysis. Cancer Causes Control 2012;23:1099–111.
14. Bansal D, Undelika K, O'Cruz S, et al. Statin use and risk of prostate cancer: a meta-analysis of observational studies. PLoS ONE 2012;7:e46691.
15. Bardou M, Barkun A, Martel M. Effect of statin therapy on colorectal cancer. Gut 2010;59:1572–85.

16. Singh S, Singh PP, Singh AG, et al. Statins are associated with a reduced risk of hepatocellular carcinoma: a systematic review and meta-analysis. Gastroenterology 2013;144:323–32.

17. Stein EA, Corsini A, Gimpelwick CW, et al. Fluavastatin treatment is not associated with an increased incidence of cancer. Int J Clin Pract 2006;60:1028–34.

18. Matsushita Y, Suphthara M, Kaburagi J, et al. Pravastatin use and cancer risk: a meta-analysis of individual patient data from long-term prospective controlled trials in Japan. Pharmacoeconomics 2010;19:196–202.

19. Emerson Jr JR, Kearney PM, Blackwell L, et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS ONE 2012;7:e29849.

20. Gazzerro P, Bifulco M. Statins and cancer in gastroenterology: new insight? Gastroenterology 2013;145:1572–3.

21. Gazzerro P, Proto MC, Gangemi G, et al. Pharmacological actions of statins: a critical appraisal in the management of cancer. Pharmacol Rev 2012;64:102–46.

22. Gronich N, Rennert G, Statsin and cancer in gastroenterology: new insight? Gastroenterology 2013;145:1572–3.

23. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

24. Wells GA, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

25. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

26. METABIAS: Stata module to test for small-study effects in meta-analysis [program], 2009.

27. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ 2003;326:219.

28. Friis S, Poulsen AH, Jørgensen SP, et al. Cancer risk among statin users: a population-based cohort study. Int J Cancer 2005;114:643–7.

29. Friedman GD, Flick ED, Udaltsova N, et al. Fluavastatin treatment is not associated with an increased incidence of cancer. Int J Clin Pract 2006;60:1028–34.

30. Matsumoto Y, Sugihara M, Kaburagi J, et al. Pravastatin use and cancer risk: a meta-analysis of individual patient data from long-term prospective controlled trials in Japan. Pharmacoeconomics 2010;19:196–202.

31. Matsushita Y, Suphthara M, Kaburagi J, et al. Pravastatin use and cancer risk: a meta-analysis of individual patient data from long-term prospective controlled trials in Japan. Pharmacoeconomics 2010;19:196–202.

32. Matsushita Y, Suphthara M, Kaburagi J, et al. Pravastatin use and cancer risk: a meta-analysis of individual patient data from long-term prospective controlled trials in Japan. Pharmacoeconomics 2010;19:196–202.
SUPPLEMENTARY FIGURES:

**Supplementary Figure 1.** Influence analysis.

| Study or Subgroup | Log(Risk Ratio) | SE | Weight | IV | Random | 95% CI | Year | Risk Ratio (IV, Random, 95% CI) |
|-------------------|----------------|----|--------|----|--------|--------|------|---------------------------------|
| Friis 2005        | 0.14842        | 0.6970396 | 2.0%  |    |        | 1.18   | 0.46, 2.91 | 2005                           |
| Friedman (Male) 2008 | -0.91529073   | 0.1247614 | 4.1%  |    |        | 0.40   | 0.21, 0.70 | 2008                           |
| Friedman (Femal) 2008 | -0.71324999   | 0.1241894 | 11.6% |    |        | 0.49   | 0.34, 0.70 | 2008                           |
| Marelli 2011      | -1.1718308    | 0.4031761 | 2.7%  |    |        | 0.31   | 0.14, 0.68 | 2011                           |
| Tsan 2012         | -0.75002258   | 0.1345283 | 19.3% |    |        | 0.47   | 0.36, 0.61 | 2012                           |
| Tsan 2013         | -0.65497627   | 0.040816  | 66.2% |    |        | 0.63   | 0.45, 0.85 | 2013                           |
| Subtotal (95% CI) |                |      | 100.0%|    |        | 0.61   | 0.44, 0.80 |                  |

Heterogeneity: $I^2 = 0.01$, $Q = 6.01$, $df = 6$ ($P = 0.30$), $P = 10\%$

Test for overall effect: $Z = 9.96$ ($P < 0.00001$)

**Supplementary Figure 2.** Subgroup analyses based on study design.
### Supplementary Figure 3.
Subgroup analyses based on baseline risk of liver cancer.

| Study or Subgroup | Log(Risk Ratio) | SE | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
|-------------------|----------------|----|--------|-------------------|------|-------------------|
| Chu 2011          | -0.4709039     | 0.15915739 | 12.4% | 0.62 [0.46, 0.84] | 2011 |                  |
| Marebj 2011       | -1.17110288    | 0.00317612 | 2.1%  | 0.31 [0.14, 0.69] | 2011 |                  |
| Tsan 2012         | -0.7502238     | 0.13452932 | 18.1% | 0.47 [0.36, 0.61] | 2012 |                  |
| Tsan 2013         | -0.64867827    | 0.0403616   | 69.4% | 0.63 [0.46, 0.88] | 2013 |                  |
| **Subtotal (95% CI)** |              |     | **100.0%** |                      |      | 0.52 [0.47, 0.59] |

Heterogeneity: $T^2=0.01$, Chi$^2=3.81$, df = 3 ($P = 0.31$), $P=19%$

Test for overall effect: $Z = 11.05$ ($P < 0.00001$)

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### Supplementary Figure 4.
Subgroup analyses based on confounder adjustment.

| Study or Subgroup | Log(Risk Ratio) | SE | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
|-------------------|----------------|----|--------|-------------------|------|-------------------|
| Kurnaan 2005      | -0.06392674    | 0.12325396 | 15.8% | 0.52 [0.41, 0.68] | 2005 |                  |
| Friis 2005        | 0.143012      | 0.01970386 | 3.2%  | 1.16 [0.46, 2.97] | 2005 |                  |
| Friedman (Female) 2008 | -0.91229073   | 0.12378146 | 11.7% | 0.40 [0.14, 0.79] | 2008 |                  |
| Friedman (Male) 2008 | -0.71343898   | 0.13001894 | 11.7% | 0.40 [0.22, 0.77] | 2008 |                  |
| El-Serag 2009     | -0.3110639     | 0.07852271 | 10.2% | 0.74 [0.53, 0.96] | 2009 |                  |
| Emberson 2012     | 0.06366651     | 0.24265366 | 8.7%  | 1.08 [0.85, 1.37] | 2012 |                  |
| Loung 2013        | -0.20298855    | 0.24095493 | 8.8%  | 0.44 [0.27, 0.71] | 2013 |                  |
| Lai 2013          | -0.32449331    | 0.10818949 | 18.3% | 0.71 [0.56, 0.99] | 2013 |                  |
| Chertizos 2013    | -0.51892582    | 0.25060996 | 10.8% | 0.60 [0.44, 0.83] | 2013 |                  |
| **Subtotal (95% CI)** |              |     | **100.0%** |                      |      | 0.63 [0.52, 0.75] |

Heterogeneity: $T^2=0.04$, Chi$^2=12.39$, df = 8 ($P = 0.01$); $P=56%$

Test for overall effect: Z = 5.13 ($P < 0.00001$)

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Favours statin use | Favours control

0.1 | 0.2 | 0.5 | 1 | 2 | 3 | 5 | 10

- Supplementary Figure 3. Subgroup analyses based on baseline risk of liver cancer.
- Supplementary Figure 4. Subgroup analyses based on confounder adjustment.
Supplementary Figure 5. Subgroup analyses based on study location.

Supplementary Figure 6. Subgroup analyses based on pharmacokinetic of statins.

Supplementary Figure 7. Subgroup analysis of higher cumulative dose of statin use.
**SUPPLEMENTARY TABLES:**

**Supplementary Table 1.** Assessment of methodological quality of the cohort and case-control studies according to the Newcastle–Ottawa Scale

| Cohort Studies | Selection | Comparability | Outcome | Total Score |
|----------------|-----------|---------------|---------|-------------|
|                 | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Outcome of present at start of study | Control for important factor | Assessment of outcome | Follow-up long enough | Adequacy of follow up |
| Friis, 2005     | ☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆ | -       | -           | ☆☆☆☆☆☆☆ | - | ☆ | 7 |
| Friedman, 2008  | ☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆ | -       | -           | ☆☆☆☆☆☆☆ | - | ☆ | 7 |
| Marelli, 2011   | ☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆ | -       | -           | ☆☆☆☆☆☆☆ | - | ☆ | 8 |
| Tsan, 2012      | ☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆ | -       | -           | ☆☆☆☆☆☆☆ | - | ☆ | 8 |
| Tsan, 2013      | ☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆ | -       | -           | ☆☆☆☆☆☆☆ | - | ☆ | 8 |

| Case–Control Studies | Selection | Comparability | Exposure | Total Score |
|----------------------|-----------|---------------|----------|-------------|
|                      | Adequate definition of cases | Representativeness of cases | Selection of controls | Definition of controls | Control for important factor | Ascertainment of Exposure | Same method for cases and controls | Non-response rate | Total Score |
| Khurana, 2005        | -         | ☆☆☆☆☆☆☆ | -       | -           | ☆☆☆☆☆☆☆ | - | ☆ | 6 |
| El-Serag, 2009       | -         | ☆☆☆☆☆☆☆ | -       | -           | ☆☆☆☆☆☆☆ | - | ☆ | 7 |
| Chiu, 2011           | -         | ☆☆☆☆☆☆☆ | -       | -           | ☆☆☆☆☆☆☆ | - | ☆ | 7 |
| Lai, 2013            | -         | ☆☆☆☆☆☆☆ | -       | -           | ☆☆☆☆☆☆☆ | - | ☆ | 7 |
| Leung, 2013          | ☆☆☆☆☆☆☆ | ☆☆☆☆☆☆☆ | -       | -           | ☆☆☆☆☆☆☆ | - | ☆ | 8 |
| Chaiteerakij, 2013   | -         | ☆☆☆☆☆☆☆ | -       | -           | ☆☆☆☆☆☆☆ | - | ☆ | 5 |

Control for important factor: ☆Reported relative risk have been adjusted for at least 4 of 7 important factors: HBV infection, HCV infection, cirrhosis, NAFLD, HCV treatment, HBV treatment, anti-diabetic medications; ☆ Study controls for any additional factor. Assessment of outcome: ☆ record linkage. Follow-up long enough: ☆ follow up period ≥ 4 years. Adequate definition of cases: ☆ The case is defined with independent validation. Non-response rate: ☆ Same rate for both groups.
### Supplementary Table 2. Studies reporting RR for use of lipophilic or hydrophilia statins, and for higher cumulative dosage of statin use

| Studies                  | Measurements of effect estimates | Statins type | Dosage/Duration of Statin use | Crude RR with 95% CIs | Adjusted RR with 95% CIs |
|--------------------------|----------------------------------|--------------|------------------------------|-----------------------|--------------------------|
| Tsan, 2012, Taiwan 31    | HR                               | A, F, L, P, R, and S | >365 cDDDs                  | 0.50 (0.26-0.96)      | 0.34 (0.33-0.59)         |
|                          | HR                               | Lipophilia statin | ≥28 cDDDs                   | 0.62 (0.47-0.83)      | 0.44 (0.33-0.59)         |
|                          | HR                               | Hydrophilia statin| ≥28 cDDDs                   | 0.65 (0.39-1.09)      | 0.51 (0.31-0.85)         |
| Tsan, 2013, Taiwan 32    | HR                               | A, F, L, P, R, and S | >180 cDDDs                  | NA                    | 0.33 (0.25-0.42)         |
| El-Serag, 2009, USA 34   | OR                               | Simvastatin     | 1.6 years (M)               | 0.47 (0.41-0.54)      | 0.64 (0.55-0.75)         |
|                          | OR                               | A, F, L, P, R, and S | >215.4 cDDDs                | 0.47 (0.30-0.72)      | 0.63 (0.37-1.06)         |
| Chiu, 2011, Taiwan 35    | OR                               | Lipophilia statin| ≥1 cDDD                      | NA                    | 0.56 (0.45-0.69)*        |
|                          | OR                               | Hydrophilia statin| ≥1 cDDD                      | NA                    | 0.46 (0.29-0.71)*        |
| Lai, 2013, Taiwan 36     | OR                               | Lipophilia statin| ≥1 Rx                        | 0.54 (0.48-0.61)*     | 0.67 (0.57-0.79)*        |
|                          | OR                               | Hydrophilia statin| ≥1 Rx                        | 0.63 (0.47-0.83)*     | 0.80 (0.55-1.16)*        |

The RR with an asterisk mark (*) was calculated based on the raw data in the original study. The others, crude or adjusted, were extracted from the original paper.
**Supplementary Table 3. Published studies of the total cholesterol and the risk of liver cancer**

| Studies         | Study design                                      | cases/participants | Follow-up | Reference (mg/dL) | Index (mg/dL) | Adjusted HR (95% CIs) | P for trend* | Confounders for adjustment |
|-----------------|---------------------------------------------------|--------------------|-----------|-------------------|---------------|------------------------|-------------|---------------------------|
| Iso, 2009, Japan | Population-based cohort (JPHC Study)              | 125 /33,368        | 12.4 years| 180–199           | <160          | 2.62 (1.44–4.76)        | Men < 0.0001| 1-10                      |
|                 |                                                   |                    |           |                   | 160–179       | 1.04 (0.52–2.07)        | Women < 0.0001|                           |
|                 |                                                   |                    |           |                   | 180–199       | 1.99 (0.82–4.85)        |             |                           |
|                 |                                                   |                    |           |                   | 200–219       | 0.56 (0.24–1.28)        |             |                           |
|                 |                                                   |                    |           |                   | 200–239       | 1.99 (0.82–4.85)        |             |                           |
|                 |                                                   |                    |           |                   | > 240         | 0.80 (0.28–2.27)        |             |                           |
| Ahn, 2009, Finland | Placebo-controlled, double-blinded primary prevention trial in male smokers (ATBC) | 191/29,093         | 18.0 years | < 203.9           | < 203.9       | 0.69 (0.46–1.05)        | P=0.0007    | 1-5, 11-17                |
|                 |                                                   |                    |           |                   | 203.9–227.6   | 0.63 (0.41–0.97)        |             |                           |
|                 |                                                   |                    |           |                   | 227.7–249.2   | 0.63 (0.41–0.97)        |             |                           |
|                 |                                                   |                    |           |                   | 249.3–276.6   | 0.56 (0.36–0.88)        |             |                           |
|                 |                                                   |                    |           |                   | > 276.7       | 0.66 (0.43–1.01)        |             |                           |
| Kitahara, 2011, Korea | Prospective study of Korean men and women (Korean NHIC) | 10,161/1,189,719 | 12.7 years | < 160             | < 160         | 0.69 (0.65–74)          | Men < 0.001 | 2-5, 13, 18               |
|                 |                                                   |                    |           |                   | 160–179       | 0.63 (0.54–0.72)        | Women < 0.001|                           |
|                 |                                                   |                    |           |                   | 180–199       | 0.50 (0.44–0.58)        |             |                           |
|                 |                                                   |                    |           |                   | 200–239       | 0.37 (0.32–0.42)        |             |                           |
|                 |                                                   |                    |           |                   | > 240         | 0.32 (0.27–0.39)        |             |                           |

JPHC Study = The Japan Public Health Center-based Prospective Study, ATBC = The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Korean NHIC = The Korean National Health Insurance Corporation Medical Evaluation. *Tests for linear trend were conducted by treating the total cholesterol as a continuous variable in the multivariable models. Confounders for adjustment: 1 = age, 2 = BMI, 3 = smoking, 4 = ethanol intake, 5 = hypertension, 6 = diabetes, 7 = hyperlipidemia medication use, 8 = total vegetable intake, 9 = coffee intake, 10 = public health center, 11 = intervention, 12 = level of education, 13 = physical activity, 14 = Saturates fat intake, 15 = polyunsaturated fat intake, 16 = total calorie, 17 = serum HDL cholesterol, 18 = fasting serum glucose.
### Supplementary Table 4. Published trials of statin use as adjuvant in treatment of liver cancer

| Studies       | Study design       | Patients population                                      | Intervention                  | Control                             | Overall survival of intervention (months) | Overall survival of control (months) | Kaplan-Meier and log-rank test |
|---------------|--------------------|----------------------------------------------------------|-------------------------------|-------------------------------------|------------------------------------------|--------------------------------------|---------------------------------|
| Kawata, 2001, Japan ⁴⁹ | Prospective, randomized, open label study | Patients with advanced liver cancer after TAE procedure, n = 83 | Pravastatin 20-40 mg + 5-FU 200 mg QD, n = 41 | 5-FU 200 mg QD, n = 42 | Median 18 | Median 9 | P = 0.006 |
| Lersch, 2004, Germany ⁵⁰ | Prospective study | Patients with advanced liver cancer, n = 58 | Pravastatin 40-80 mg QD, n = 20 | A: Octreotide, n = 30; B: Gemcitabine, n = 8 | Median 7.2 (95% CIs 2.9-11.5) | Median 5 (95% CIs 2.2-7.8); B: Median 3.5 (95% CIs 2.2-4.9) | A: P = 0.09; B: P = 0.03 |
| Graf, 2008, Germany ⁵¹ | Prospective, non-randomized, open label study | Patients with advanced liver cancer after TACE, n = 183 | Pravastatin 20-40 mg QD, n = 52 | No treatment, n = 131 | Median 20.9 (95% CIs 15.5-26.3) | Median 20.9 (95% CIs 15.5-26.3) | P = 0.003 |
| Georgescu, 2011, Romania ⁵² | Prospective, randomized, open label study | Patients with advanced liver cancer, n = 72 | Lovastatin 40 mg + Sorafenib 400 mg QD, n = 39 | Sorafenib 400 mg QD, n = 33 | Mean 12.15±0.76 | Mean 10.85±0.82 | Non-significant |

TAE = Transcatheter Arterial Embolization; TACE = Transhepatic Arterial Chemotherapy and Embolization.
**Supplementary Table 5.** Ongoing clinical trials of statin use as adjuvant in treatment of liver cancer

| Studies       | Year | Location | Phase | Study design                                                                 | Condition          | Intervention                                                                 | Control                                   | Estimated Enrollment | Resist number        | Status    |
|---------------|------|----------|-------|------------------------------------------------------------------------------|--------------------|-----------------------------------------------------------------------------|-------------------------------------------|----------------------|---------------------|-----------|
| ESTAHEP-2010  | 2011 | Spain    | II    | Multicenter, prospective, randomized, double-blind, placebo-controlled study | Advanced liver cancer | Sorafenib 400 mg BID + Pravastatin 40 mg, QD | Sorafenib 400 mg BID + placebo QD | 216                  | NCT01418729; EUCTR2010-024421-21-ES | Recruiting |
| PRODIGE 21    | 2011 | France   | II    | Multicenter, prospective, randomized, open label study                      | Liver cancer with Child-Pugh Cirrhosis | A: Sorafenib 400 mg BID; B: Pravastatin 40 mg, QD; C: Sorafenib 400 mg BID + Pravastatin 40 mg, QD | Best supportive care | 160                  | NCT01357486         | Recruiting |
| JOUVE PHRCK 2009 | 2013 | France   | III   | prospective, randomized, open label study                                | Liver cancer with Child-Pugh Cirrhosis | A: Sorafenib 800 mg BID + Pravastatin 40 mg, QD | Sorafenib 800 mg BID | 474                  | NCT01903694; NCT01075555 | Recruiting |