World Journal of Meta-Analysis

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.13105/wjma.v1.i3.130

World J Meta-Anal 2013 November 26; 1(3): 130-137
ISSN 2308-3840 (online)

META-ANALYSIS

Statin use and risk of liver cancer: A meta-analysis of 7 studies involving more than 4.7 million patients

Hui Zhang, Chun Gao, Long Fang, Shu-Kun Yao

Hui Zhang, Department of Gastroenterology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China
Chun Gao, Long Fang, Shu-Kun Yao, Department of Gastroenterology, China-Japan Friendship Hospital, Ministry of Health, Beijing 100029, China
Author contributions: Zhang H participated in the acquisition of data, statistical analysis and manuscript writing; Gao C and Fang L conceived the study and participated in the study design, acquisition of data, statistical analysis and manuscript writing; Yao SK participated in the critical revision of the manuscript for important intellectual content; and all authors have read and approved the final manuscript.
Supported by Beijing NOVA Programme, No. Z131107000413067; and the Research Fund of the China-Japan Friendship Hospital, Nos. 2013-QN-07 and 2013-QN-06
Correspondence to: Chun Gao, MD, Department of Gastroenterology, China-Japan Friendship Hospital, Ministry of Health, No. 2 Yinghua East Road, Beijing 100029, China. gaochun@bjmu.edu.cn
Telephone: +86-10-84205313 Fax: +86-10-84205313
Received: June 21, 2013 Revised: September 12, 2013
Accepted: November 20, 2013
Published online: November 26, 2013

Abstract

AIM: To pool data currently available to determine the association between statin use and the risk of liver cancer.

METHODS: A computerized literature search was conducted to identify those relevant studies between January 1966 and March 2013. Stata 11.0 (Stata Corp, College Station, Texas) was used for statistical analyses. Pooled relative risk (RR) estimates with 95%CI were calculated for overall analysis and subgroup analyses, using the random- and fixed-effects models. Heterogeneities between studies were evaluated by Cochran's *Q* test and I^2 statistic. The Begg's funnel plot and Egger's regression asymmetry test were used to detect the publication bias.

RESULTS: Seven studies were included in our meta-analysis according to the selection criteria, including four cohort studies and three case-control studies. These studies involved 4725593 people and 9785 liver cancer cases. The overall analysis showed that statin use was statistically associated with a significantly reduced risk of liver cancer (random-effects model, RR = 0.61, 95%CI: 0.49-0.76, $P < 0.001$; fixed-effects model, RR = 0.64, 95%CI: 0.57-0.71, $P < 0.001$); however, significant heterogeneity was found between studies (Cochran's Q statistic = 19.13, $P = 0.004$; $I^2 = 68.6\%$). All subgroup analyses provided supporting evidence for the results of overall analysis. Begg's ($Z = 0.15$, $P = 0.881$) and Egger's test ($t = -0.44$, $P = 0.681$) showed no significant risk of having a publication bias.

CONCLUSION: Statin use was associated with the reduced risk of liver cancer. To clearly clarify this relationship, more high quality studies are required.

Key words: Statin use; Liver cancer; Reduced risk; Meta-analysis

Core tip: Statin use has been suggested to be associated with the risk of liver cancer by some studies, but no consensus was reached among them. This meta-analysis involved 4725593 people, 9785 liver cancer cases, and found that statin use was associated with the reduced risk of liver cancer (RR = 0.67, 95%CI: 0.55-0.82, $P < 0.001$).

Zhang H, Gao C, Fang L, Yao SK. Statin use and risk of liver cancer: A meta-analysis of 7 studies involving more than 4.7 million patients. *World J Meta-Anal* 2013; 1(3): 130-137 Available from: URL: http://www.wjgnet.com/2308-3840/full/v1/i3/130.htm DOI: http://dx.doi.org/10.13105/wjma.v1.i3.130

INTRODUCTION

Liver cancer, with a mounting annual incidence of 4.9 per 100000 people, is the third most common cause of cancer death worldwide. For example in 2008, an estimated 748300 new liver cancer cases and 695900 cancer deaths occurred[1]. Despite some advances in treatment over the past several decades, the prognosis of liver cancer is unfavorable. Even in the most developed countries like the United States, the 1-year survival rate is less than 50%[2]. Because of its high fatality rate, it is very important to identify those risk and protective factors. Major risk factors that were identified include hepatitis B virus (HBV), hepatitis C virus (HCV), cirrhosis, heavy alcoholic consumption, non-alcoholic steatohepatitis, and alfatoxin exposure[3]. Recently, emerging evidence suggests that diabetes mellitus (DM) may be a potential risk factor for liver cancer[4,5], whereas metformin use in diabetic patients, coffee and tea consumption have been suggested as possible protective factors[6-8].

Statins have been widely used to lower the cholesterol level, which could inhibit the activity of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-COA), the rate-limiting enzyme in the mevalonate synthesis pathway[9]. The protective role of statin use in cardiovascular diseases has been confirmed by several large-scale randomized controlled trials (RCTs)[10-13]. Over the past several years, statins have been suggested to be associated with some varieties of cancers, including liver cancer[14-16]. For example, two epidemiological studies which were performed in Taiwan province of China found that statin use was associated with the reduced risk of liver cancer[17,18]. In addition, *in vitro* and *in vivo* studies showed that statins could enhance anti-proliferative effects of some antitumor agents in cancer treatment[19-21]. Moreover, combined treatment with pravastatin and chemoembolization had been reported to improve the survival rate of patients with hepatocellular carcinoma (HCC)[22].

However, results from the limited number of RCTs were disappointing[23], which could not provide supportive evidence for those above-mentioned epidemiological and pre-clinical studies, although several limitations should be acknowledged in these RCTs. First, most of these studies were not designed to determine the association of statin use with the risk of liver cancer. Therefore, liver cancer was neither a primary end point nor a topic of interest in these studies, and selection bias may not be avoided[24]. The second limitation is that most of these studies were conducted in the United States or European countries, not in the areas with higher incidence of HCC, such as China and other Asian countries. Thus, the number of observed liver cancer cases was very limited[25], which could not be regarded as the representative for the overall study population. Considering that no consensus was reached among these studies, this meta-analysis was performed to pool data currently available to determine the association between statin use and the risk of liver cancer.

MATERIALS AND METHODS

Search strategy

A computerized literature search (Medline, Embase and the Cochrane library) was conducted to identify those relevant studies between January 1966 and March 2013. The Medical subject heading (MeSH) terms and/or the text words which were used included "statin(s)", "HMG-COA reductase inhibitor(s)", "atorvastatin", "cerivastatin", "fluvastatin", "lovastatin", "mevastatin", "pravastatin", "rivastatin", "rosuvastatin", or "simvastatin", combined with "carcinoma(s)", "hepatoma(s)", "cancer(s)", "neoplasm(s)", or "malignancy(ies)". Publication type was limited to "article". Data from abstracts, review articles, editorials, case reports, and letters were excluded. After scanning of the titles and abstracts, studies identified in the search clearly not relevant to our topic of interest were excluded. The full texts of the remaining studies were read to determine whether they were eligible for inclusion. Data from each eligible study were extracted. According to the retrieved original studies and relevant review articles, we also manually searched the reference lists to identify those possible eligible articles which were not found in our primary search.

Selection criteria

The studies would be included in our statistical analysis if they fulfilled these criteria as follows: (1) Epidemiologic studies on human subjects, including cohort study or case-control study; (2) The language was English and only full papers were included; (3) They were designed to evaluate the association between statin use and the risk of liver cancer; and (4) Risk estimates, including relative risks (RRs) for cohort studies or odds ratios (ORs) for case-control studies, and their corresponding 95% confidence intervals (95%CIs) were provided or could be calculated based on the available data. If more than one paper was derived from the same research, only the recently published paper which provided the most abundant information was included. When necessary, the authors were contacted to obtain the corresponding required information.

Data extraction

Each potentially eligible study was evaluated independently by at least two authors (HZ, CG and LF). If evaluation results diverged, agreement was reached in a joint session. The following information would be extracted and recorded, including the first author, the year of publication, study design, country or area which the study was conducted, study time or mean follow-up years, total participants, liver cancer cases, adjusted RR or OR with their 95%CIs, and the confounding factors which had been adjusted. The quality of included studies was not tried to be assessed, considering that no consensus standardized method could be obtained for the quality assessment of observational studies[26,27]. Instead, we performed several subgroup analyses to explore the source of heterogeneity and validate the results from overall analysis.

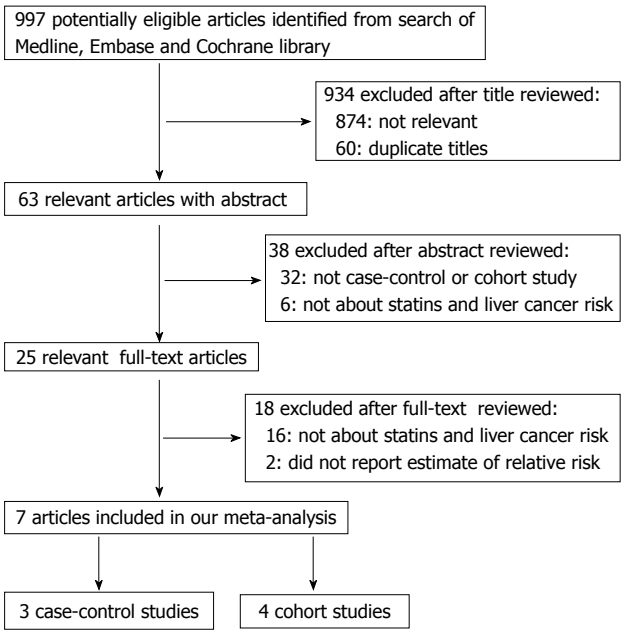

Figure 1 Flow chart of the selection of studies for inclusion.

Statistical analysis

For cohort studies, the value of RRs were used to assess the risk estimate; however, for case-control studies, those ORs would be regarded as approximate RRs in our meta-analysis, considering that the prevalence of liver cancer was relatively very low in these studies. We used the adjusted RRs (ARRs) to estimate the risk of liver cancer treated with statins, whereas for those studies in which no ARR was available, the unadjusted RRs were adopted. We also expressed the summary of results as the RR and the corresponding 95%CI. For all tests, $P < 0.05$ was considered statistically significant unless specially described and all P values quoted were two-sided.

For overall analysis, both random-effects model (DerSimonian and Laird method) and fixed-effects model (Mantel-Haenszel method) were used to calculate the pooled RR estimates[28,29], in order to provide accurate results and conclusions[30,31]. When significant heterogeneity between studies is not found, the two models would provide the similar results, whereas if significant heterogeneity is found, the random-effects model, which incorporates an estimate of between-study variance (heterogeneity) in the weighting, is more appropriate. The combined RR was displayed in Forest plot.

Moreover, subgroup analyses would be performed based on the study design, the country or area in which the study was conducted, the study population and whether the confounding factors had been controlled adequately, in order: (1) to validate the results and conclusion from the overall analysis in different conditions; (2) to further explore the stability and reliability of the overall analysis; and (3) to find the possible source of statistical heterogeneity among studies.

For the statistical heterogeneity among studies, Cochrane Q statistic test with a significance level of $P < 0.10$ was used[32]. I^2 statistic, which describes the percentage variation across studies that is due to heterogeneity rather than chance, was also calculated, considering the low power of Cochrane Q test when the number of included studies was very limited. The heterogeneity would be considered significant when $I^2 > 50\%$[33]. Finally, the publication bias for included studies would be detected using the Begg's funnel plot and Egger's regression asymmetry test[34,35]. We followed the guidelines for the meta-analysis of observational studies in epidemiology proposed by MOOSE group[36]. Stata 11.0 (Stata Corp, College Station, Texas) was used for the statistical analyses.

RESULTS

Search results

Seven studies were included in our meta-analysis according to the selection criteria using the defined MeSH terms and/or the text words, including 4 cohort studies and 3 case-control studies (Table 1 and Figure 1)[17,18,37-41]. Among them, four studies were conducted in European and American regions (United States and Denmark)[37,39-41], and others were in Asian country (Taiwan of China)[17-18,38].

Baseline characteristics of included studies

These studies involved 4725593 people and 9785 liver cancer cases. They were published between the years of 1966 and 2013. The confounding factors which had been controlled in these studies include age, sex, HBV infection, HCV infection, alcohol liver disease, DM, liver cirrhosis, other lipid-lowering drugs, nonsteroidal anti-inflammatory drugs/aspirin, angiotensin-converting enzyme inhibitors, the number of hospitalization, anti-HBV treatment, income, level of urbanization, calendar period, hormone replacement therapy, race, anti-HCV treatment, propensity to use statins, body mass index, and smoking[17,18,37-41]. For these factors, some were controlled by matching which had been indicated in Table 1, and others were controlled by multivariate analyses. When these 5 factors had been controlled, including age, sex, HBV infection, HCV infection and alcohol liver disease, the confounding factors would be regarded as been controlled adequately.

For the study population, most of the studies (5/7) were designed to aim at the general population, except for two studies: one case-control study limited their patients to those with DM[37], and another cohort study restricted to those with HBV infection[18]. In the study performed by Friedman *et al*[40] in the United States, 4222660 patients were observed and only 32 patients were diagnosed with liver cancer, including intrahepatic bile duct cancer cases. In addition, in this study[40] the RRs and their 95%CIs were reported by men and women, separately. Therefore, we had pooled the two risk estimates before statistical analysis, using random-effects model and fixed-effects model; and the two models yielded a same result (Table 1).

Table 1 Baseline characteristics and results of multivariate analysis in included studies

Ref.	Country	Study time/mean follow-up years	Total participants	Liver cancer cases	Adjusted RR(95%CI)	Confounding adjustment[1]
Case-control studies (n = 3)						
El-Serag *et al*[37]	United State	1997-2002	6515	1303	0.74 (0.64-0.87)	1[2], 2[2], 3-5, 6[2], 7, 9, 10, 17-19
Chiu *et al*[17]	Taiwan	2005-2008	2332	312	0.62 (0.45-0.83)	1, 2, 3[2], 4[2], 5-10
Leung et al[38]	Taiwan	2000-2008	34205	6841	0.44 (0.28-0.72)	1[2], 2[2], 6, 8, 9,
Cohort studies (n = 4)						
Friis *et al*[39]	Denmark	3.3 (exposure) 5.1 (control)	334754	171	1.16 (0.46-2.90)	1, 2, 9, 15, 16
Friedman *et al*[40]	United State	4.91	4222660	32	0.47 (0.34-0.64)	15
Marelli *et al*[41]	United State	4.7 (exposure) 4.6 (control)	91714	105	0.88 (0.60-1.28)	1[2], 2[2], 15[2], 17[2], 20[2], 21[2]
Tsan *et al*[18]	Taiwan	328196 (person-years)	33413	1021	0.47 (0.36-0.61)	1-14

[1]1: Age; 2: Sex; 3: HBV infection; 4: HCV infection; 5: Alcohol liver disease; 6: Diabetes mellitus; 7: Liver cirrhosis; 8: Other lipid-lowering drugs; 9: Nonsteroidal anti-inflammatory drugs/aspirin; 10: Angiotensin-converting enzyme inhibitors; 11: Number of hospitalization; 12: anti-HBV treatment; 13: Income; 14: Level of urbanization; 15: Calendar period; 16: Hormone replacement therapy; 17: Race; 18: Anti-HCV treatment; 19: Propensity to use statins; 20: Body mass index; 21: Smoking. [2]Variables which had been indicated were controlled by matching, and others were controlled by multivariate analyses. RR: Relative risk; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

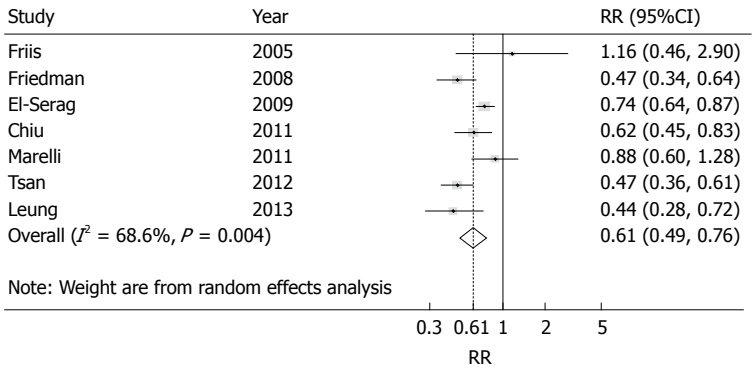

Figure 2 Forest plot of pooled relative risks and their 95%CI for statin use and the risk of liver cancer, when using random effects model. Studies are arranged based on the year of publication. Black boxes indicate the relative risks point estimate, and their areas are proportional to the weights of the studies. Horizontal lines represent the 95%CIs. The broken line and diamond represent the summary estimate and the unbroken vertical line is at the null value.

Overall analysis: Reduced risk of liver cancer with statin use

Table 1 shows the adjusted RRs, their corresponding 95%CIs, and the confounding adjustment in included studies. The RRs and their 95%CIs from the study by Friedman *et al*[40] had been pre-treated before the final statistical analysis. Of the total seven studies, reduced risk of liver cancer was observed in five studies by multivariate analysis, whereas the results with no statistical difference had been demonstrated in the left two studies. For all the three case-control studies, positive results were found; however, for the four cohort studies, half of them demonstrated no statistical difference. We used the random- and fixed-effects models to perform the overall analysis (Figure 2). The results showed that statin use was statistically significantly associated with the reduced risk of liver cancer (random-effects model, RR = 0.61, 95%CI: 0.49-0.76, $P < 0.001$; fixed-effects model, RR = 0.64, 95%CI: 0.57-0.71, $P < 0.001$); however, significant heterogeneity was found between studies (Cochran's Q statistic = 19.13, $P = 0.004$, $I^2 = 68.6\%$, Figure 2).

Subgroup analyses

We further performed subgroup analyses to validate the results from the overall analysis, and to find the possible source of statistical heterogeneity among studies. As shown in Table 2, subgroup analyses were performed according to the type of design of studies, the country or area in which the study was conducted, the study population and whether the confounding factors had been controlled adequately. Based on the results of Cochran's Q statistic, significant heterogeneities were not found only when the subgroup analysis was restricted into those studies which were conducted in Asian country. This may be because these three studies were conducted in the same area, Taiwan province of China (Table 2).

Fortunately, all of the subgroup analyses provided supporting evidence for the results of overall analysis, especially when the subgroup analysis was restricted into those cohort studies. The results from the four cohort studies also showed that statin use was associated with the reduced risk of liver cancer (random-effects model, RR = 0.62, 95%CI: 0.43-0.89, $P = 0.010$; fixed-effects model, RR = 0.56, 95%CI: 0.47-0.66, $P < 0.001$), although heterogeneity was also found (Cochran's Q = 10.74, $P = 0.013$, $I^2 = 72.1\%$).

Publication bias

Finally, we detected the publication bias using the Begg's funnel plot and Egger's regression asymmetry test. As shown

Table 2 Subgroup analyses of included studies

Subgroup	No. of studies	Fixed-effects model			Random-effects model			Heterogeneity		
		RR	95%CI	*P* value	RR	95%CI	*P* value	*Q*	*P*	I^2 (%)
Type of design of studies										
Case-control	3	0.69	0.60-0.79	< 0.001	0.63	0.49-0.82	< 0.001	4.75	0.093	57.9
Cohort	4	0.56	0.47-0.66	< 0.001	0.62	0.43-0.89	0.01	10.74	0.013	72.1
Country or area										
Asian	3	0.51	0.43-0.62	< 0.001	0.51	0.42-0.63	< 0.001	2.30	0.317	13.0
Euro- American	4	0.71	0.62-0.80	< 0.001	0.71	0.52-0.95	0.023	9.14	0.028	67.2
Confounding adjustment										
Adequately[1]	3	0.65	0.58-0.74	< 0.001	0.61	0.46-0.81	0.001	8.64	0.013	76.8
Inadequately	4	0.59	0.48-0.73	< 0.001	0.63	0.41-0.95	0.028	9.82	0.020	69.4
Study population										
General population	5	0.60	0.50-0.71	< 0.001	0.62	0.46-0.83	0.001	9.89	0.042	59.5
Restricted to specified patients[2]	2	0.66	0.58-0.75	< 0.001	0.60	0.38-0.93	0.023	8.50	0.004	88.2

[1]The confounding factors would be regarded as been controlled adequately when these 5 factors had been controlled, including age, sex, HBV infection, HCV infection and alcohol liver disease; [2]The study population of two studies was restricted to specified patients, including patients with diabetes mellitus (Ref. 37) and those with HBV infection (Ref. 18). RR: Relative risk; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

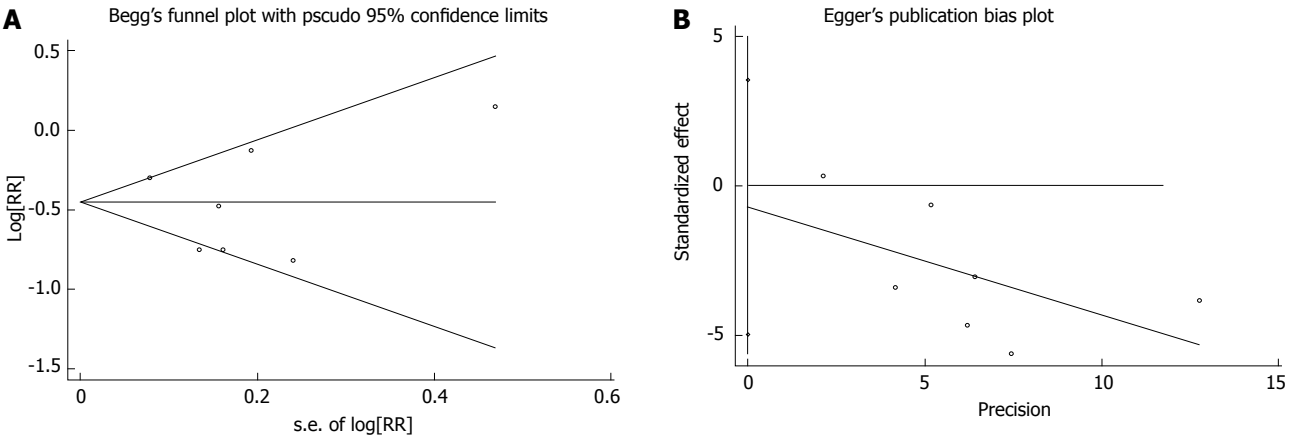

Figure 3 Publication bias detected by the Begg's funnel plot (A) and Egger's regression asymmetry test (B).

in Figure 3 by Begg's (Z = 0.15, P = 0.881) and Egger's test (t = -0.44, P = 0.681), no statistically significant publication bias was noted.

DISCUSSION

Our meta-analysis, which involved 4725593 people and 9785 liver cancer cases, was designed to determine the association between statin use and the risk of liver cancer. The results showed that statin use was associated with a 36%-39% reduction in liver cancer risk. Moreover, all subgroup analyses provided supporting evidence for the results of overall analysis. In addition, no significant risk of having a publication bias was observed by using Begg's plot and Egger's regression test.

Statins have been widely and successfully used in patients with hypercholesterolemia and cardiovascular diseases for more than 30 years[42]. In the past few years, some studies have been designed to determine the association between statins use and the risk of cancer, including liver cancer, taking into account the large number of patient population treated with statins. Besides the epidemiological studies, preclinical studies also suggested that statins may inhibit the growth of cancer cells by promoting apoptosis, suppressing angiogenesis and inhibiting the metastatic process[43-45]. Considering that no consensus was reached among these studies, our meta-analysis was performed to pool data currently available to determine this relationship.

Some issues or questions, which could be regarded as the drawbacks or limitations, should be acknowledged, before acceptance of these results and conclusion. The first was about the observational designs of included studies, which could not provide definite evidence to clarify the causal association. Of the total seven studies, four were population-based cohort designs, three were case-control designs, and none was prospective intervention study. Unfortunately, for the four cohort studies, half of them were shown as without statistical difference. From the viewpoint of basic principle, cohort study is better than case-control study to explain the causal association[24]. However, even when the study population

was limited to those from cohort studies, consistent results were obtained which showed that statin use was associated with the reduced risk of liver cancer, providing supporting evidence for the results of overall analysis. To clarify this relationship between statin use and liver cancer risk, more cohort studies, especially prospective intervention studies, are required.

The second was about the very limited number of included studies. To include all the possibly relevant studies in which the study population could represent the majority of the general population, we added case-control studies in the statistical analysis and treated the ORs as approximate RRs, which may have some effect on the final results. However, when the study population was restricted to those either from cohort studies or from case-control studies, the results remained unchanged. Be that as it may, we also hope that these results and conclusions could be validated in more patients, more hospitals and more countries with higher quality.

The third was about the study population and the general population. The seven studies were conducted in three countries, including the United States, Denmark and Taiwan (China), which could not be regarded as the representative of the general population. Mainland China has the higher incidence of liver cancer with nearly 40 per 100000 people per year, which is more than eight times compared with the average incidence worldwide. In addition, risk factors, including the subtype of HBV, in Taiwan are different from those in mainland China. Therefore, for the general study population, more studies are required, such as prospective intervention study in China.

The fourth limitation was about the confounding factors which could not be controlled adequately because of the original nature of observational epidemiological studies. These studies did not have the process of random allocation, and complete controlling of the confounding factors was seemingly impossible. Some important factors, such as age, sex, HBV/HCV infection, cirrhosis and alcohol drinking, were not controlled adequately in some of these studies. Others included: the exposure time of statins was not long enough, leading to one possibility that the positive association may be affected by other factors, such as high socioeconomic status[46,47]; different units and different kind of statins were used in these studies, whereas different statins may have different effects on liver cancer risk, for example, the effect of hydrophilic statins was different from that of hydrophobic statins[48-50]; and statin use was contraindicated in the presence of liver diseases[40], which may have effects on the results and conclusions.

Besides these aforementioned weaknesses, some strengths were made in this meta- analysis to ensure the accuracy and reliability of our results, based on the available literature and current knowledge. The first was about the subgroup analysis which was designed to validate the results from the overall analysis, and to find the possible source of statistical heterogeneity among studies. Fortunately, all of the subgroup analyses provided supporting evidence for the results of overall analysis, especially when the subgroup analysis was restricted into those cohort studies. The second was that our meta-analysis was designed to pool the data currently available to determine the association between statin use and liver cancer risk. For example, in one study[40] the RRs and their 95%CIs were reported by men and women, separately. We had pooled the two risk estimates before statistical analysis, using random-effects model and fixed-effects model, and the two models yielded a same result.

In conclusion, our meta-analysis showed that statin use was associated with the reduced risk of liver cancer. To clearly clarify this relationship, more high quality epidemiological studies, especially prospective intervention studies, are required. *In vitro* data and animal studies are also required to clarify the relevant mechanisms.

COMMENTS

Background

Statin use has been suggested to be associated with the risk of liver cancer by some studies, but no consensus was reached among them.

Research frontiers

Over the past several years, statins have been suggested to be associated with some varieties of cancers, including liver cancer. For example, two epidemiological studies which were performed in Taiwan province of China found that statin use was associated with the reduced risk of liver cancer. In addition, *in vitro* and *in vivo* studies showed that statins could enhance anti-proliferative effects of some antitumor agents in cancer treatment. However, results from the limited number of randomized controlled trials (RCTs) were disappointing, which could not provide supportive evidence for those above-mentioned epidemiological and pre-clinical studies

Innovations and breakthroughs

This meta-analysis involved seven studies with 4725593 people and 9785 liver cancer cases. The authors found that statin use was associated with the reduced risk of liver cancer (RR = 0.67, 95%CI: 0.55-0.82, $P < 0.001$).

Applications

Statins may potentially be used for the therapy of liver cancer; however, more high quality studies, especially prospective intervention studies are required.

Peer review

The authors determined the association between statin use and the risk of liver cancer by a meta-analysis. This analysis involved 7 studies with 4725593 people and 9785 liver cancer cases from 2005 to 2013. The results showed a 36%-39% reduction in liver cancer risk when statins were used. This study is very interesting.

REFERENCES

1 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]

2 **Altekruse SF**, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009; **27**: 1485-1491 [PMID: 19224838 DOI: 10.1200/JCO.2008.20.7753]

3 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127 [PMID: 21992124 DOI: 10.1056/NEJMra1001683]

4 **El-Serag HB**, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004; **126**: 460-468 [PMID: 14762783 DOI: 10.1053/j.gastro.2003.10.065]

5 **Lai MS**, Hsieh MS, Chiu YH, Chen TH. Type 2 diabetes and hepatocellular carcinoma: A cohort study in high prevalence area of hepatitis virus infection. *Hepatology* 2006; **43**: 1295-1302 [PMID: 16729295 DOI: 10.1002/hep.21208]

6 **Bravi F**, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, Franceschi S, La Vecchia C. Coffee drinking and hepatocellular carcinoma risk: a meta-analysis. *Hepatology* 2007; **46**: 430-435 [PMID: 17580359 DOI: 10.1002/hep.21708]

7 **Fon Sing M**, Yang WS, Gao S, Gao J, Xiang YB. Epidemiological studies of the association between tea drinking and primary liver cancer: a meta-analysis. *Eur J Cancer Prev* 2011; **20**: 157-165 [PMID: 21403523 DOI: 10.1097/CEJ.0b013e3283447497]

8 **Lai SW**, Chen PC, Liao KF, Muo CH, Lin CC, Sung FC. Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. *Am J Gastroenterol* 2012; **107**: 46-52 [PMID: 22085817 DOI: 10.1038/ajg.2011.384]

9 **Goldstein JL**, Brown MS. Regulation of the mevalonate pathway. *Nature* 1990; **343**: 425-430 [PMID: 1967820 DOI: 10.1038/343425a0]

10 **Hsia J**, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol & lt; 50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *J Am Coll Cardiol* 2011; **57**: 1666-1675 [PMID: 21492764 DOI: 10.1016/j.jacc.2010.09.082]

11 **Bulbulia R**, Bowman L, Wallendszus K, Parish S, Armitage J, Peto R, Collins R. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. *Lancet* 2011; **378**: 2013-2020 [PMID: 22115874 DOI: 10.1016/S0140-6736(11)61125-2]

12 **Baigent C**, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011; **377**: 2181-2192 [PMID: 21663949 DOI: 10.1016/S0140-6736(11)60739-3]

13 **Walley T**, Folino-Gallo P, Schwabe U, van Ganse E. Variations and increase in use of statins across Europe: data from administrative databases. *BMJ* 2004; **328**: 385-386 [PMID: 14962875 DOI: 10.1136/bmj.328.7436.385]

14 **Mück AO**, Seeger H, Wallwiener D. Inhibitory effect of statins on the proliferation of human breast cancer cells. *Int J Clin Pharmacol Ther* 2004; **42**: 695-700 [PMID: 15624286]

15 **Yasuda Y**, Shimizu M, Shirakami Y, Sakai H, Kubota M, Hata K, Hirose Y, Tsurumi H, Tanaka T, Moriwaki H. Pitavastatin inhibits azoxymethane-induced colonic preneoplastic lesions in C57BL/KsJ-db/db obese mice. *Cancer Sci* 2010; **101**: 1701-1707 [PMID: 20398056 DOI: 10.1111/j.1349-7006.2010.01579.x]

16 **Björkhem-Bergman L**, Acimovic J, Torndal UB, Parini P, Eriksson LC. Lovastatin prevents carcinogenesis in a rat model for liver cancer. Effects of ubiquinone supplementation. *Anticancer Res* 2010; **30**: 1105-1112 [PMID: 20530415]

17 **Chiu HF**, Ho SC, Chen CC, Yang CY. Statin use and the risk of liver cancer: a population-based case–control study. *Am J Gastroenterol* 2011; **106**: 894-898 [PMID: 21157439 DOI: 10.1038/ajg.2010.475]

18 **Tsan YT**, Lee CH, Wang JD, Chen PC. Statins and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. *J Clin Oncol* 2012; **30**: 623-630 [PMID: 22271485 DOI: 10.1200/JCO.2011.36.0917]

19 **Bocci G**, Fioravanti A, Orlandi P, Bernardini N, Collecchi P, Del Tacca M, Danesi R. Fluvastatin synergistically enhances the antiproliferative effect of gemcitabine in human pancreatic cancer MIAPaCa-2 cells. *Br J Cancer* 2005; **93**: 319-330 [PMID: 16052215 DOI: 10.1038/sj.bjc.6602720]

20 **Kodach LL**, Jacobs RJ, Voorneveld PW, Wildenberg ME, Verspaget HW, van Wezel T, Morreau H, Hommes DW, Peppelenbosch MP, van den Brink GR, Hardwick JC. Statins augment the chemosensitivity of colorectal cancer cells inducing epigenetic reprogramming and reducing colorectal cancer cell 'stemness' via the bone morphogenetic protein pathway. *Gut* 2011; **60**: 1544-1553 [PMID: 21551187 DOI: 10.1136/gut.2011.237495]

21 **Wang W**, Le W, Cho DY, Hwang PH, Upadhyay D. Novel effects of statins in enhancing efficacy of chemotherapy in vitro in nasopharyngeal carcinoma. *Int Forum Allergy Rhinol* 2011; **1**: 284-289 [PMID: 22287433 DOI: 10.1002/alr.20039]

22 **Graf H**, Jüngst C, Straub G, Dogan S, Hoffmann RT, Jakobs T, Reiser M, Waggershauser T, Helmberger T, Walter A, Walli A, Seidel D, Goke B, Jüngst D. Chemoembolization combined with pravastatin improves survival in patients with hepatocellular carcinoma. *Digestion* 2008; **78**: 34-38 [PMID: 18797167 DOI: 10.1159/000156702]

23 **Emberson JR**, Kearney PM, Blackwell L, Newman C, Reith C, Bhala N, Holland L, Peto R, Keech A, Collins R, Simes J, Baigent C. 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 [PMID: 22276132 DOI: 10.1371/journal.pone.0029849]

24 **Bonovas S**, Filioussi K, Flordellis CS, Sitaras NM. Statins and the risk of colorectal cancer: a meta-analysis of 18 studies involving more than 1.5 million patients. *J Clin Oncol* 2007; **25**: 3462-3468 [PMID: 17687150 DOI: 10.1200/JCO.2007.10.8936]

25 **Clearfield M**, Downs JR, Weis S, Whitney EJ, Kruyer W, Shapiro DR, Stein EA, Langendorfer A, Beere PA, Gotto AM. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): efficacy and tolerability of long-term treatment with lovastatin in women. *J Womens Health Gend Based Med* 2001; **10**: 971-981 [PMID: 11788107 DOI: 10.1089/152460901317193549]

26 **Lang S**, Kleijnen J. Quality assessment tools for observational studies: lack of consensus. *Int J Evid Based Healthc* 2010; **8**: 247 [PMID: 21091888 DOI: 10.1111/j.1744-1609.2010.00195.x]

27 **Mallen C**, Peat G, Croft P. Quality assessment of observational studies is not commonplace in systematic reviews. *J Clin Epidemiol* 2006; **59**: 765-769 [PMID: 16828667 DOI: 10.1016/j.jclinepi.2005.12.010]

28 **DerSimonian R**, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177-188 [PMID: 3802833 DOI: 10.1016/0197-2456(86)90046-2]

29 **Mantel N,** Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; **22**: 719-748 [PMID: 13655060]

30 **Schmidt FL**, Oh IS, Hayes TL. Fixed- versus random-effects models in meta-analysis: model properties and an empirical comparison of differences in results. *Br J Math Stat Psychol* 2009; **62**: 97-128 [PMID: 18001516]

31 **Villar J**, Mackey ME, Carroli G, Donner A. Meta-analyses in systematic reviews of randomized controlled trials in perinatal medicine: comparison of fixed and random effects models. *Stat Med* 2001; **20**: 3635-3647 [PMID: 11746343 DOI: 10.1002/sim.1096]

32 **Cochran WG.** The combination of estimates from different experiments. *Biometrics* 1954; **10**: 101-129 [DOI: 10.2307/3001666]

33 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560

[PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]
34 **Begg CB**, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088-1101 [PMID: 7786990]
35 **Egger M**, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634 [PMID: 9310563 DOI: 10.1136/bmj.315.7109.629]
36 **Stroup DF**, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-2012 [PMID: 10789670 DOI: 10.1001/jama.283.15.2008]
37 **El-Serag HB**, Johnson ML, Hachem C, Morgana RO. Statins are associated with a reduced risk of hepatocellular carcinoma in a large cohort of patients with diabetes. *Gastroenterology* 2009; **136**: 1601-1608 [PMID: 19208359 DOI: 10.1053/j.gastro.2009.01.053]
38 **Leung HW**, Chan AL, Lo D, Leung JH, Chen HL. Common cancer risk and statins: a population-based case-control study in a Chinese population. *Expert Opin Drug Saf* 2013; **12**: 19-27 [PMID: 23199231 DOI: 10.1517/14740338.2013.744392]
39 **Friis S**, Poulsen AH, Johnsen SP, McLaughlin JK, Fryzek JP, Dalton SO, Sørensen HT, Olsen JH. Cancer risk among statin users: a population-based cohort study. *Int J Cancer* 2005; **114**: 643-647 [PMID: 15578694 DOI: 10.1002/ijc.20758]
40 **Friedman GD**, Flick ED, Udaltsova N, Chan J, Quesenberry CP, Habel LA. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. *Pharmacoepidemiol Drug Saf* 2008; **17**: 27-36 [PMID: 17944002 DOI: 10.1002/pds.1507]
41 **Marelli C**, Gunnarsson C, Ross S, Haas S, Stroup DF, Cload P, Clopton P, DeMaria AN. Statins and risk of cancer: a retrospective cohort analysis of 45,857 matched pairs from an electronic medical records database of 11 million adult Americans. *J Am Coll Cardiol* 2011; **58**: 530-537 [PMID: 21777752 DOI: 10.1016/j.jacc.2011.04.015]
42 **Bielinska A**, Gluszko P. [Statins--are they potentially useful in rheumatology?]. *Pol Arch Med Wewn* 2007; **117**: 420-425 [PMID: 18062565]
43 **Mehta N**, Hordines J, Sykes D, Doerr RJ, Cohen SA. Low density lipoproteins and Lovastatin modulate the organ-specific transendothelial migration of primary and metastatic human colon adenocarcinoma cell lines in vitro. *Clin Exp Metastasis* 1998; **16**: 587-594 [PMID: 9932605]
44 **Wong WW**, Dimitroulakos J, Minden MD, Penn LZ. HMG-CoA reductase inhibitors and the malignant cell: the statin family of drugs as triggers of tumor-specific apoptosis. *Leukemia* 2002; **16**: 508-519 [PMID: 11960327 DOI: 10.1038/sj.leu.2402476]
45 **Park HJ**, Kong D, Iruela-Arispe L, Begley U, Tang D, Galper JB. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors interfere with angiogenesis by inhibiting the geranylgeranylation of RhoA. *Circ Res* 2002; **91**: 143-150 [PMID: 12142347 DOI: 10.1161/01.RES.0000028149.15986.4C]
46 **Thomsen RW**, Johnsen SP, Olesen AV, Mortensen JT, Bøggild H, Olsen J, Sørensen HT. Socioeconomic gradient in use of statins among Danish patients: population-based cross-sectional study. *Br J Clin Pharmacol* 2005; **60**: 534-542 [PMID: 16236044 DOI: 10.1111/j.1365-2125.2005.02494.x]
47 **Mamdani MM**, Tu K, Austin PC, Alter DA. Influence of socioeconomic status on drug selection for the elderly in Canada. *Ann Pharmacother* 2002; **36**: 804-808 [PMID: 11978155 DOI: 10.1345/aph.1A044]
48 **Lakshminarayana Reddy CN**, Vyjayanti VN, Notani D, Galande S, Kotamraju S. Down-regulation of the global regulator SATB1 by statins in COLO205 colon cancer cells. *Mol Med Rep* 2010; **3**: 857-861 [PMID: 21472326 DOI: 10.3892/mmr.2010.338]
49 **Bergman M**, Salman H, Djaldetti M, Bessler H. Statins as modulators of colon cancer cells induced cytokine secretion by human PBMC. *Vascul Pharmacol* 2011; **54**: 88-92 [PMID: 21440087 DOI: 10.1016/j.vph.2011.03.002]
50 **Menter DG**, Ramsauer VP, Harirforoosh S, Chakraborty K, Yang P, Hsi L, Newman RA, Krishnan K. Differential effects of pravastatin and simvastatin on the growth of tumor cells from different organ sites. *PLoS One* 2011; **6**: e28813 [PMID: 22216116 DOI: 10.1371/journal.pone.0028813]

P- Reviewers: Liu JR, Limpaiboon T **S- Editor**: Song XX
L- Editor: Wang TQ **E- Editor**: Lu YJ

百世登
Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com