Original Article

Can statins reduce risk of lung cancer, especially among elderly people? A meta-analysis

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Objective: As the most common cause of cancer mortality throughout the world, lung cancer has drawn people's attention on how to reduce the risk with chemopreventive ways. Many epidemiological studies have shown inconsistent effects of statins on lung cancer, but some observational studies have showed that statins had protective effect on lung cancer among elderly people. So we preformed this meta-analysis to find whether statins were chemopreventive.

Methods: We searched MEDLINE, EMBASE and Web of Science databases from inception to September, 2013. A total of 23 studies were selected, including 15 observational studies and 8 randomized controlled trials (RCTs). Both fixed and random-effects models were used to calculate pooled estimates in primary and sensitivity analyses. We used Q and I^2 statistics to assess statistical heterogeneity, and evaluated publication bias by Begg's test and Egger's test.

Results: No association between statins and lung cancer risk was identified either in the meta-analysis among RCTs [relative risk (RR): 0.95, 95% confidence interval (95% CI): 0.85-1.06] or observational studies (RR: 0.89, 95% CI: 0.77-1.04). We also selected 6 observational studies that all researched on elderly people. The result of meta-analysis showed that there was still no protective effect between statins and lung cancer among elderly people (RR: 1.03, 95% CI: 0.96-1.11).

Conclusions: Our results did not support a protective effect of statins on the overall lung cancer risk and the lung cancer risk among elderly people. More well-designed RCTs are needed to enhance our understanding of the chemopreventive effect of statins on lung cancer.

Keywords: Statins; lung cancer; meta-analysis; elderly people; risk

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Introduction

Statins are commonly used as a kind of cholesterol-lowering agents (1,2). They were reported to suppress tumor cell growth in several *in vitro* studies (3,4) and animal experiments (5,6). Recently, statins have become the most popular drugs used for high cholesterol because of their efficacy and few side effects. Besides, some studies have shown that statins have antiproliferative, proapoptotic and antiinvasive effects (7,8). Thus, many scholars show increasing interest in the antitumor effect of statins.

Among so many cancers, lung cancer is the most common cause of cancer mortality throughout the world with poor prognosis (9). In 2008, there were 1.61 million new cases, and 1.38 million deaths due to lung cancer, especially in Europe and North America (10). Common treatments include palliative care, surgery, chemotherapy, and radiation therapy. So people have tried to find out effective ways in preventing lung cancer.

Some meta-analyses (11-14) have yielded inconsistent results on chemopreventive effect of statins on lung cancers.

In vitro data have supported a potential role for statins in preventing cancer risk. HMG-CoA reductase overexpressed in cancer cells (15), and statins have been found to induce apoptosis in cancer cell lines (16,17). In contrast, Newman and Hulley (18) reported that lipid-lowering therapy might cause cancers in rodents. So there is no final conclusion about the anticancer effect of statins. The aim of this meta-analysis was to evaluate the protective association between statins and lung cancer risk, especially among elderly people.

Materials and methods

Search strategy

We conducted a computer-assisted systematic search of MEDLINE, EMBASE, and Web of Science databases from their commencement to September, 2013, attempting to find all publications on the effect of statins on lung cancer. Key words and medical subject heading (MeSH) terms for the search of MEDLINE were as follows: ["Lung cancer" (MeSH)] AND ["statins" (MeSH) OR "HMG-CoA-reducatase-inhibitor" OR pravastatin OR simvastatin OR lovastatin OR atorvastatin OR cerivastatin OR rosuvastatin OR fluvastatin]. We used similar strategies to search EMBASE. Web of Science was searched mainly for the abstracts of additional oncology society meetings. We also reviewed the bibliographies of relevant articles to identify additional studies that might have been missed.

Selection criteria

We screened titles and abstracts of identified papers to exclude studies that clearly did not meet the inclusion criteria. Full texts of those selected studies for further review were retrieved and evaluated. The studies included in this meta-analysis evaluated the statin use on lung cancer risk, but the statin use on the lung cancer mortality was excluded. The studies must test on human except specific population (e.g., patients after heart transplantation) (19), and *in vitro* experiments and animal trials were not included. To make sure the comparability of all the included studies, we made some other criteria to study selection and data extraction. Inclusion criteria were: publications in English; full texts can be found; an original study comparing statins group with placebo group or no statins group; follow up for over one year; lung cancer must be included in the cancer outcomes; and the strength of the association between statins and lung cancer must have measured in the form of odds ratio (OR), risk ratio (RR) or hazard ratio (HR), or could be calculated from the original data presented in the studies.

We evaluated the methodological quality of all randomized controlled trials (RCTs) by using Jadad scoring system (20). Studies would be regarded as good methodological quality with scores not less than three points. Besides, we used a subgroup analysis to evaluate some influencing factors for the effect of statins on lung cancer risk (21,22).

Data extraction

All data were extracted according to the criteria. Discrepancies were discussed and resolved by consensus. Data extracted from each study included the first author, year of publication, regions of the population investigated, lung cancer cases/No. of all the participants, follow-up, age, the percentage of women, cancer outcomes, adjustment for smoking, adjusted OR/RR/HR, and 95% confidence interval (95% CI).

STATA Statistical Software was used for all the analyses (version 12.0, STATA Corporation, College Station, TX, USA). The measure of estimated effect of interest was RR with 95% CI. Because the risk of lung cancer is relatively low, the RR mathematically approximates the OR, or HR in case-control and cohort studies. We therefore reported all results as the RR for simplicity. Summary RR estimates were calculated using RR, OR, or HR reported in each study.

Meta-analysis

We used two models to calculate the pooled RR estimates with 95% CI: a fixed-effects model known as Mantel-Haenszel method (23) and a random-effects model known as DerSimonian-Laird method (24). When RR <1 and upper limit of 95% CI was lower than 1, we considered statin use could reduce the risk of lung cancer with statistical significance. We used the Cochran Q test to evaluate the heterogeneity of the studies (25) and the quantity I^2 was also calculated (26,27). I^2 is the proportion of total variation contributed by between-study variation, and values of 25%, 50%, and 75% have been regarded as representing low, moderate, and high heterogeneity respectively.

Publication bias was evaluated to find whether the results of the studies were homogeneous. The funnel

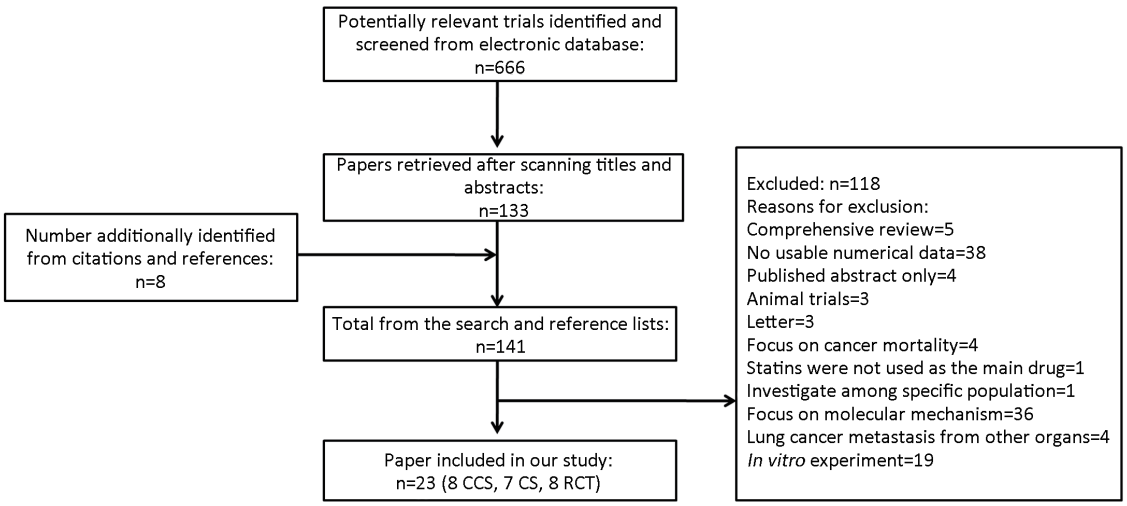

Figure 1 Search strategy. CCS, case-control study; CS, cohort study; RCT, randomized controlled trail.

graph, the Egger regression asymmetry test (28) and the Begg-Mazumdar adjusted rank correlation test (29) were used. When the P value of the Egger's test and Begg's test was <0.05, we considered obvious bias among the studies.

Subgroup analysis

We performed subgroup analysis according to: (I) study design: case-control study and cohort study; (II) regions of the investigated population: Asia, America and Europe; (III) the percentage of women: the group ≥50% and the group <50%; (IV) the mean follow-up of the studies: group ≥5 years and the group <5 years (we chose 5 years as the boundary because in some studies (30,31), long-term effect of statin therapy was considered for more than 5 years); and (V) adjustment for smoking, because the risk of lung cancer is obviously associated with smoking.

Results

Search results

We found 561 records in EMBASE Database, 69 records in Web of Science Database and 36 records in MEDLINE Database. Eight references were found from the reference lists. With our selection criteria, we identified 23 studies to our meta-analysis, including 15 observational studies (8,9,30-42) (8 case-control studies, 7 cohort studies) and 8 randomized-controlled studies (43-50) (*Figure 1*). *Table 1* summarizes the characteristics of all the included studies.

Meta-analysis of statin use and risk of lung cancer

The meta-analysis of 15 observational studies showed no evidence for a protective association between statin use and the risk of lung cancer with obvious heterogeneity (RR: 0.89, 95% CI: 0.77-1.04, I^2=94.9%, P=0) (*Figure 2*, *Table 2*). Begg's test (P=0.235) and Egger's test (P=0.356) showed no obvious publication bias (*Figure 3*, *Table 2*). The assessment of methodological quality of RCTs by using Jadad scoring system was illustrated in *Table 3*, and 5 RCTs scored 5, 2 RCTs scored 4 and 1 RCT scored 3. All the RCTs were regarded as studies with good methodological quality. And the meta-analysis of 8 RCTs also showed no association between statins use and lung cancer risk (RR: 0.95, 95% CI: 0.85-1.06, I^2=0, P=0.483) (*Figure 2*, *Table 2*). No obvious publication bias was found (Begg's test: P=0.536; Egger's test: P=0.743) (*Figure 3*, *Table 2*).

Because the heterogeneity of all the observational studies was very obvious and obvious heterogeneity made the results less credible, we used an age limitation among all the 15 observational studies. And then we selected six observational studies that all the participants were elderly people (age >50 years old) (32-34,38,40,42), meta-analysis of this 6 studies still showed no protective effect on lung cancer among elderly people with no heterogeneity (RR: 1.03, 95% CI: 0.96-1.11, I^2=0, P=0.759) (*Figure 2*, *Table 2*). And no obvious publication bias was found (Begg's test: P=0.707; Egger's test: P=0.312) (*Figure 3*, *Table 2*). So we could draw the conclusion that there was no protective effect between statin use and lung cancer risk among elderly

Table 1 Studies included in the meta-analysis

Study	Year	Study design	Areas	Case/total	Follow-up (years)	Age (years)	Woman%	Adjust for smoking	RR	95% CI	Cancer outcomes measured
Observational study											
Cheng *et al*. (32)	2012	CCS	AS (Taiwan, China)	297/1,485	0-3	>50	100.0	No	0.82	0.58-1.15	Lung cancer
Lai *et al*. (33)	2012	CCS	AS (Taiwan, China)	1,117/5,585	>10	>50	100.0	No	1.07	0.90-1.27	Lung cancer
Vinogradova *et al*. (8)	2011	CCS	EU (UK)	10,163/450,379	NR	30-100	47.1	Yes	1.07	0.99-1.16	Any
Jacobs *et al*. (34)	2011	CS	AM (US)	297/1,485	NR	>60	54.9	Yes	1.04	0.95-1.14	Any
Hippisley-Cox *et al*. (35)	2010	CS	EU (UK)	6,001/2,121,786	NR	30-84 (mean, 50.8)	50.6	Yes	1.03	0.94-1.21	Any
Haukka *et al*. (31)	2009	CS	EU (Finland)	5,129/944,962	Mean, 8.8	Mean, 60	NR	No	0.81	0.77-0.86	Any
Friedman *et al*. (30)	2008	CS	AM (US)	1,042/361,859	NR	20-79	NR	No	1.09	0.96-1.23	Lung cancer
Farwell *et al*. (36)	2008	CS	AM (US)	867/62,842	NR	Mean, 66.5	2.8	Yes	0.70	0.60-0.81	Any
Coogan *et al*. (37)	2007	CCS	AM (US)	464/8,813	NR	40-79	52.8	Yes	0.70	0.40-1.10	Breast, prostate, colorectum, lung cancer
Setoguchi *et al*. (38)	2007	CS	AM (US)	216/31,723	Mean, 2.9	>65	82.2	No	1.11	0.77-1.60	Lung, breast, colorectal cancer
Khurana *et al*. (9)	2007	CCS	AM (US)	7,280/483,733	NR	18-100	8.3	Yes	0.55	0.52-0.59	Lung cancer
Friis *et al*. (39)	2005	CS	EU (Denmark)	3,339/334,754	Mean, 3.3	30-80	49.8	Yes	0.92	0.72-1.16	Any
Kaye *et al*. (40)	2004	CCS	EU (UK)	259/18,088	Mean, 6.4	50-89	49.6	Yes	0.90	0.60-1.30	Any
Graaf *et al*. (41)	2004	CCS	EU (Netherlands)	445/20,105	Mean, 7.2	NR	51.0	No	0.89	0.56-1.42	Any
Blais *et al*. (42)	2000	CCS	AM (Canada)	70/5,962	Mean, 2.7	>65	69.9	No	0.94	0.43-2.05	Any
RCT											
WOSCOPS (43)	2007	RCT	EU (Scotland)	211/6,577	Mean, 4.9	NR	NR		0.93	0.76-1.09	Lung cancer
4S (44)	2004	RCT	EU (Skandinavien)	56/4,444	Median, 10.4	Mean, 59	19.0		0.81	0.48-1.36	Any

Table 1 (*continued*)

Table 1 (continued)

Study	Year	Study design	Areas	Case/total	Follow-up (years)	Age (years)	Woman%	Adjust for smoking	RR	95% CI	Cancer outcomes measured
LIPS (45)	2002	RCT	EU, AM (Europe, Canada, Brazil)	8/1,677	Median, 3.9	Mean, 60	16.2		1.65	0.39-6.86	Lung cancer
ALLHAT (46)	2002	RCT	AM (US)	141/10,355	Mean, 4.8	Mean, 66	49.0		0.81	0.58-1.13	Lung cancer
HPS (47)	2002	RCT	EU (UK)	346/20,536	Mean, 5.0	Mean, 64	25.0		1.07	0.87-1.32	
LIPID (48)	2002	RCT	Australia	149/9,014	Mean, 8.0	Median, 62	17.0		0.75	0.54-1.04	Lung cancer
PROSPER (49)	2002	RCT	EU (Scotland, Ireland, Netherlands)	88/5,804	Mean, 3.2	Mean, 75	52.0		1.10	0.73-1.67	Lung cancer
AFCAPS (50)	1998	RCT	AM (US)	39/6,605	Mean, 5.2	Mean, 58	15.1		1.29	0.69-2.43	Any

CCS, case controlled study; CS, cohort study; RCT, randomized controlled trial; AS, Asia; AM, America; EU, Europe; NR, not report; RR, risk ratio; CI, confidence interval.

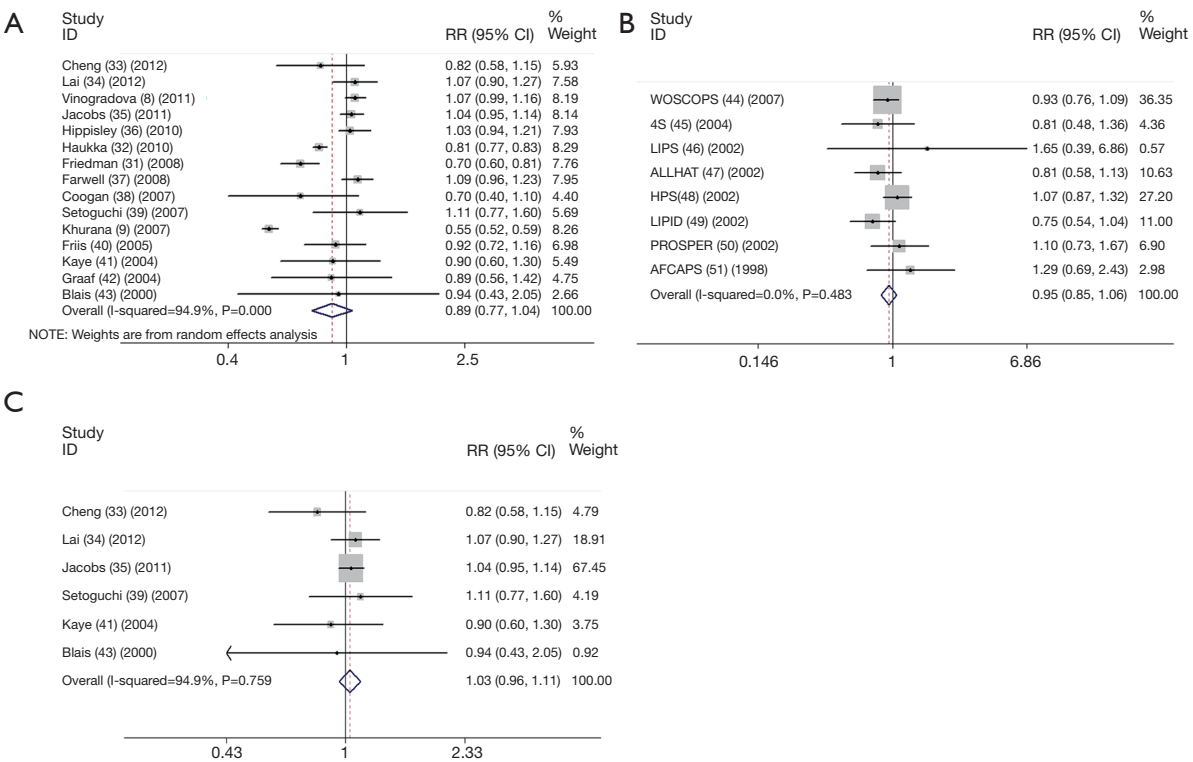

Figure 2 Forest plots of included studies. (A) Forest plots of 15 observational studies; (B) Forest plots of 8 RCTs; (C) Forest plots of 6 observational studies among elderly people. Squares indicate study-specific risk estimates (size of the square reflects the study-specific statistical weight); horizontal line indicates 95% CI; diamond indicates summary risk estimate with its corresponding 95% CI.

Table 2 Results of the meta-analysis

	No. of studies	RR (95% CI)		Heterogeneity			Publication bias	
		Fixed	Random	χ^2	I^2 (%)	P	Begg's P	Egger's P
All OSs	15	0.83 (0.80-0.85)	0.89 (0.77-1.04)	273.76	94.9	0	0.235	0.356
RCTs	8	0.95 (0.85-1.06)	0.95 (0.85-1.06)	6.50	0	0.483	0.536	0.743
OSs among elderly people	6	1.03 (0.96-1.11)	1.03 (0.96-1.11)	2.62	0	0.759	0.707	0.312

OS, observational study; RCT, randomized controlled trial; RR, relative risk; 95% CI, 95% confidence interval.

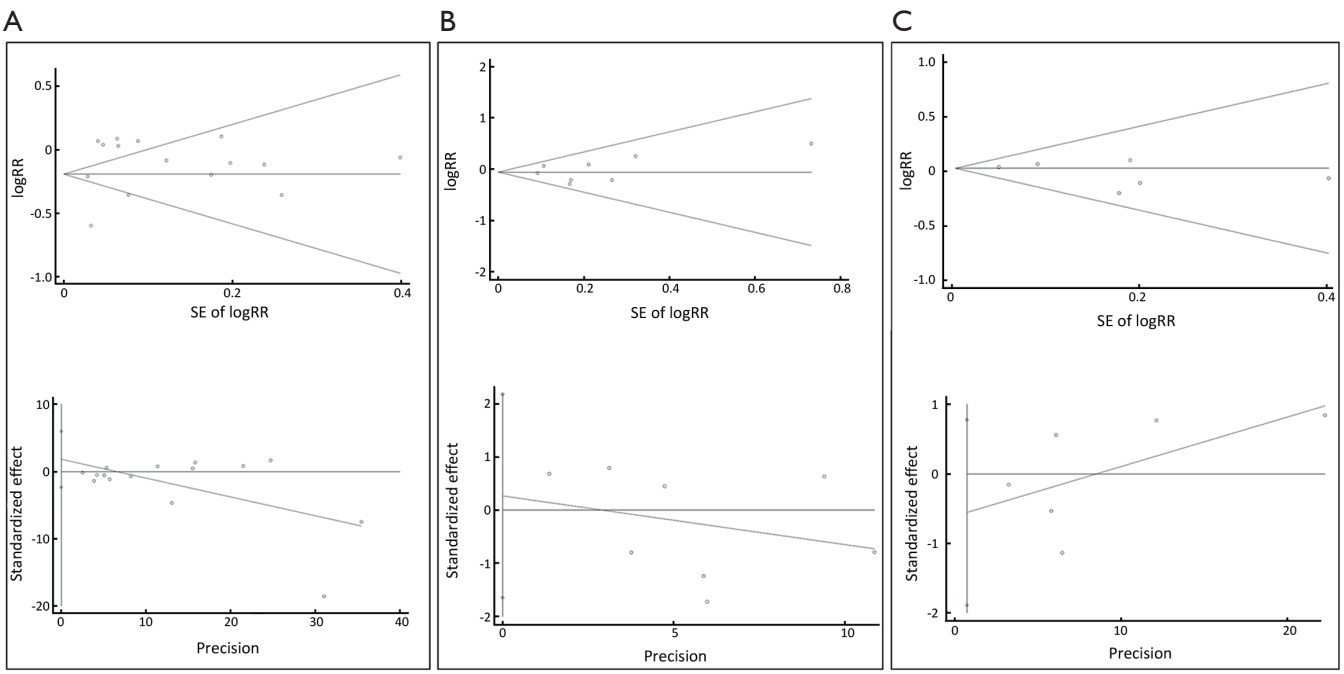

Figure 3 Begg's funnel plots and Egger's publication bias plots for lung cancer risk. (A) Begg's funnel plots and Egger's publication bias plots for all 15 observational studies; (B) Begg's funnel plots and Egger's publication bias plots for 8 RCTs; (C) Begg's funnel plots and Egger's publication bias plots for 6 observational studies on elderly people. SE, standard error.

Table 3 Assessment of methodological quality of RCTs by using Jadad scoring system

Study	Randomization	Allocation concealment	Blinding (observer)	Blinding (patient)	Adequate follow-up	Jadad score
WOSCOPS (44)	*		*	*	*	4
4S (45)	*		*	*	*	4
LIPS (46)	*	*	*	*	*	5
ALLHAT (47)	*	*			*	3
HPS (48)	*	*	*	*	*	5
LIPID (49)	*	*	*	*	*	5
PROSPER (50)	*	*	*	*	*	5
AFCAPS (51)	*	*	*	*	*	5

Each asterisk "*" means one point of the Jadad scoring system.

Table 4 Subgroup analysis of observational studies

Outcome measures	No. of studies	RR (95% CI)		Heterogeneity		
		Fixed	Random	χ^2	I^2%	P
Study design						
CCS	8	0.74 (0.71-0.78)	0.85 (0.62-1.16)	187.99	96.3	0
CS	7	0.89 (0.86-0.93)	0.94 (0.82-1.07)	49.09	87.8	0
Region						
Asia	2	1.01 (0.87-1.18)	0.98 (0.76-1.25)	1.85	46.0	0.173
America	7	0.73 (0.70-0.76)	0.84 (0.62-1.14)	181.00	96.7	0
Europe	6	0.90 (0.87-0.94)	0.94 (0.81-1.10)	36.67	86.4	0
Woman%						
≥50%	8	1.03 (0.96-1.09)	1.03 (0.96-1.09)	4.74	0	0.691
<50%	5	0.72 (0.69-0.75)	0.80 (0.56-1.14)	171.39	97.7	0
Mean follow-up						
<5 years	4	0.93 (0.79-1.10)	0.93 (0.79-1.10)	1.43	0	0.699
≥5 years	4	0.83 (0.79-0.88)	0.91 (0.76-1.09)	9.34	67.9	0.025
Adjustment for smoking						
Yes	8	0.80 (0.77-0.83)	0.85 (0.66-1.09)	239.12	97.1	0
No	7	0.87 (0.83-0.91)	0.96 (0.82-1.13)	26.55	77.4	0

CCS, case-control study; CS, cohort study; RR, relative risk; 95% CI, 95% confidence interval.

people.

Subgroup analysis of statin use and lung cancer risk

We performed a subgroup analysis according to study design, investigation regions, mean follow-up, gender and adjustment for smoking. *Table 4* summarizes the results of the subgroup analysis on 15 observational studies.

In the subgroup of study design, both case-control studies and cohort studies showed that statins had no association with the risk of lung cancer (*Table 4*).

In the subgroup of investigation regions, studies in Asia, Europe and America all showed no protective effect of statin use on lung cancer risk (*Table 4*). The results pointed out that the effect of statins has no association with areas.

We also took into account the effect of gender on the results. In the subgroup of the percentage of women, the studies that the number of women was more than 50% and less than 50% both showed there was no association between statins and lung cancer risk (*Table 4*). So gender was not an influence factor of the statin effect.

In the subgroup of the mean follow-up years, the group <5 years and the group ≥5 years showed no protective association between statins and cancer risk (*Table 4*). It hinted that long-term statin use also had no protective effect on lung cancer risk.

Because the risk lung cancer was strongly associated with smoking, the adjustment for smoking might affect the results of the researches. But in our subgroup analysis, the group with adjustment for smoking and the group without adjustment for smoking both showed no association between statin use and lung cancer risk (*Table 4*).

Discussion

Although our meta-analysis showed that statins had inconsistent effect on the overall lung cancer risk and elderly people's lung cancer risk, it could be affected by many factors. Many factors were not considered in our meta-analysis and the previous meta-analysis, such as doses, races, body mass index (BMI), and other lung diseases like chronic obstructive pulmonary disease (COPD).

Four meta-analyses of Bonovas *et al.* (11), Dale *et al.* (14), Kuoppala *et al.* (13) and Browning *et al.* (12) had investigated the association between statin therapy and cancer risk, and all showed that there was no evidence to prove the association between statin therapy and cancer risk. But they all focused on the overall cancer risk. Our study emphasized

the statin effects on the risk of lung cancer, especially among elderly people. Although our results also pointed out there is no evidence to prove the association between statin use and lung cancer risk, it was further showed that statin use had no protective effect on lung cancer among elderly people. This result was different from the studies of Khurana *et al*. (9) and Farwell *et al*. (36). Khurana *et al*. showed statin use could reduce lung cancer risk (RR: 0.55, 95% CI: 0.52-0.59) and Farwell *et al*. showed the reduction of lung cancer risk (RR: 0.70, 95% CI: 0.60 to 0.81) on veterans. But few RCTs focused on the effect of statins on lung cancer risk among elderly people. All these results will raise the attention to the prevention of lung cancer by using statins among elderly people.

On the other hand, our study pointed out long-term effect of statins (≥5 years) has no protective effect on lung cancer risk, but the long-term effects of statins are always contentious. Study by Setoguchi *et al*. (38) showed long-term users of statins had no protective effect of lung cancer risk (RR: 1.11, 95% CI: 0.77-1.60), which was similar to the study by Gary D. Friedman *et al*. (30) showing long-term statin use did not reduce the risk of lung cancer (RR: 1.09, 95% CI: 0.96-1.23). And Vinogradova *et al*. (8) even showed that long-term use of statins would increase the risk of lung cancer (RR: 1.18, 95% CI: 1.05-1.34). Although statins have few side effects, the safety of long-term effect of statins should be paid attention.

Our study has several strengths. Firstly, our study included observational studies (cohort studies and case-control studies) and RCTs. This has allowed us to perform the analysis separately by difference study designs and make the results more convincing. Secondly, we selected six observational studies which focused on elderly people to show the effect of statins. Thirdly, all pooled RR estimates were calculated by the fixed-effects model and the random-effects model. The publication bias was calculated by the Begg's test and the Egger's test to make sure any bias from misclassification is likely to be small. Fourthly, subgroup analysis was performed to analyze the influencing factors of statin therapy on lung cancer risk.

But our study also has some limitations. Firstly, information on risk factors for lung cancer, such as level of physical activity, obesity, alcohol use, smoking status and diets, were not included in the study. Secondly, the information on statin therapy on patients was also not classified by the types of statins, and the dose of daily use. Thirdly, the meta-analysis among elderly people is based on observational studies, which needs more RCTs and further studies on it. Fourthly, we used the adjusted RR to contribute to our meta-analysis, but every study adjusted their results by difference factors.

To date, no effective chemopreventive agent is identified for lung cancer. A study by Nowak *et al*. (51) suggested that high levels of beta-carotene in the diet or in the blood were associated with low risk of lung cancer, while a study by Boone *et al*. (52) and a study by Woodson *et al*. (53) suggested that low levels of vitamins A and E in blood were associate with the development of lung cancer. And then, the study by Newman *et al*. (18) on animal models showed that statins might cause cancer in rodents. More and more studies on statin use against lung cancer are in progress, and we look forward to further studies on statin use against lung cancer.

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