Cancer risk in older people receiving statin therapy: a meta-analysis of randomized controlled trials

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Abstract

Background Although statins are well tolerated by most aged people, their potential carcinogenicity is considered as one of the biggest factors limiting the use of statins. The aim of the present study was to determine the risk of cancer in people aged over 60 years receiving statin therapy. Methods A comprehensive search for articles published up to December 2015 was performed, reviews of each randomized controlled trials (RCTs) that compared the effects of statin mono-therapy with placebo on the risk of cancer in people aged > 60 years were conducted and data abstracted. All the included studies were evaluated for publication bias and heterogeneity. Pooled odds ratios (OR) estimates and 95% confidence intervals (CIs) were calculated using the random effects model. Results A total of 12 RCTs, involving 62,927 patients (31,517 in statin therapy group and 31,410 in control group), with a follow-up duration of 1.9–5.4 years, contributed to the analysis. The statin therapy did not affect the overall incidence of cancer (OR = 1.03, 95% CI: 0.94–1.14, \( P = 0.52 \)); subgroup analyses showed that neither the variety nor the chemical properties of the statins accounted for the incidence of cancer in older people. Conclusions Our meta-analysis findings do not support a potential cancer risk of statin treatment in people over 60 years old. Further targeted researches with a longer follow-up duration are warranted to confirm this issue. J Geriatr Cardiol 2016; 13: 693–700. doi:10.11909/j.issn.1671-5411.2016.08.008

Keywords: Cancer; Meta-analysis; Older people; Statins

1 Introduction

Statin are inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyses the rate-limiting step in cholesterol formation. Accumulating studies have shown that statins can not only reduce serum total and low-density lipoprotein (LDL) cholesterol concentrations, but also effectively decrease ischemic cardiovascular disease related morbidity and mortality. A meta-analysis of data from nine randomized controlled trials (RCTs) including 19,569 elderly patients with coronary heart disease aged from 65 to 82 years confirmed that multiple clinical outcomes were better in statin-treated patients than in placebo controls. Many studies have demonstrated that statins are well tolerated by most elderly patients while they are less likely to receive statin treatment compared with the younger ones. In a retrospective study on Canadian residents aged > 65 years with a history of cardiovascular disease or diabetes, the likelihood of statin prescription decreased by 6.4% with each year of increasing age. Concerns about the increased risk of adverse events, especially cancer risk, might contribute to the under-prescription of statins in older patients.

For more than a decade, the scientific debate on the association of statin treatment with cancer risk has been unsettled. A considerable studies found that statin treatment has no relationship with cancer risk, or some even revealed that statin may prevent cancer. However, some studies yielded different results. For example, experimental studies suggested that statins may be carcinogenic. Clinical studies also showed a significant increased incidence of cancer in the patients with statin treatment, including older people. Whether statin use increases cancer risk is still in debate. Reports about the effect of the statin therapy on the incidence of cancer for the older adults are relatively few. The aim of this study was to systematically review and evaluate the evidence on the association between statin therapy and overall cancer risk in people aged > 60 years.

2 Methods

2.1 Search strategy

To obtain all of the original studies which compared...
statin therapy with placebo or usual care, including both primary and secondary prevention trials, we searched potentially eligible trials in the electronic databases PubMed and Cochrane Central Register of Controlled Trials up to September 2015. A combination of Medical Subject Headings (MeSH) terms or free text keywords was used without language restrictions: “hydroxymethylglutaryl coenzyme A reductase inhibitor(s)” or “HMG-CoA reductase inhibitor(s)” or “anticholesterolalamic agent(s)” or “statin(s)” or “pravastatin” or “fluvastatin” or “simvastatin” or “atorvastatin” or “rosuvastatin” or “lovastatin” AND “randomized controlled trials” AND “aged” or “elderly” or “over 60 years old” AND “neoplasm(s)” or “cancer(s)” or “Tumors” or “Neoplasm” or “malignancy(ies)”. Reference lists of the retrieved articles were also reviewed. We did not contact authors of the primary studies for additional information.

2.2 Selection criteria

Studies were included in this meta-analysis if they met the following criteria: (1) double-blinded, randomized comparison of statin versus inactive control (placebo or no statins); (2) average age of study participants > 60 years or presence of subgroup analyses limited to participants > 60 years of age; (3) duration of the randomized portion of the study at least one year, with at least 50% of the randomized participants completing one year of treatment; and (4) report of cancer incidence.

2.3 Data extraction

Two investigators (Liu HW and Bian SY) independently extracted the data. We reviewed article titles and abstracts from the initial search and excluded those that did not meet the inclusion criteria. Articles included in the study were completely reviewed. Any disagreement was resolved by discussion.

For each eligible study, the following details were extracted from the published manuscript: allocation, year of publication, duration of follow-up, sample size of each treatment, mean age of participants, type of statin and newly diagnosed cancer over the period of follow-up.

2.4 Statistical analysis

2.4.1 Risk of bias assessment of included studies

The probability of potential publication bias existing among the included studies was estimated by Begg’s funnel plots. The methodological quality of included studies was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews, using the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting bias (reporting bias) and other bias (sponsorship). Each domain was assessed, graded as high, low or unclear risk, then a risk of bias graph was generated. In the graph of bias risk assessment, “blank space” meant “not clear”, “red” meant “no”, and “green” meant “yes”, respectively. The more “green” the graph showed, the low bias risk and higher quality the trials had.

2.4.2 Data synthesis

We evaluated the statistical heterogeneity between trials with the $I^2$ value [with 95% confidence intervals (CIs)], which is derived from RevMan 5.3 software (Cochrane). Random-effect meta-analysis was performed instead of the fixed-effect model because the former approach provides a more conservative assessment of the average effect size. Odds ratios (ORs) and 95% CIs were calculated using binary data. We conducted meta-analyses that included all trials, different types of statins (pravastatin, simvastatin, atorvastatin, fluvastatin, lovastatin and rosuvastatin), and different chemical properties of the statins [hydrophilic (pravastatin and rosuvastatin), or lipophilic (simvastatin, atorvastatin, fluvastatin and lovastatin)].

3 Results

3.1 Study characteristics and quality assessment

A flow chart of study selection for this meta-analysis is shown in Figure 1. Briefly, of the 464 initial hits, 33 studies...
Table 1. Characteristics of the twelve randomized controlled statins trials included in the meta-analysis.

| Study          | Countries                      | Year of publication | Agent       | No. of subjects (statin/control) | Mean age, yrs | Mean follow-up, yrs | Primary endpoint                                      | Incident cancer (statin/control), n (%) |
|----------------|--------------------------------|---------------------|-------------|----------------------------------|---------------|---------------------|------------------------------------------------------|----------------------------------------|
| 4S[13, 43]     | Nordic countries               | 1997, 1996          | Simvastatin | 1021 (518/503)                  | 67            | 5.4                 | All-cause and CHD mortality                         | 24 (4.6%)/30 (6.0%)                    |
| AFCAPS/ TexCAPS[14] | USA                          | 1998               | Lovastatin  | 997 (499/498)                   | 63            | 5.2                 | First acute major coronary events                   | 32 (6.4%)/28 (5.6%)                     |
| SCAT[15]       | Canada                         | 2000               | Simvastatin | 460 (230/230)                   | 61            | 4                   | QCA measures                                        | 23 (10%)/13 (0.4%)                     |
| GISSI[16]      | Italy                          | 2000               | Pravastatin | 4271 (2138/2133)                | 60            | 2                   | Death, non-fatal myocardial infarction, and non-fatal stroke | 15 (0.7%)/24 (1.1%)                     |
| LIPID[17]      | Australia, New Zealand         | 2001               | Pravastatin | 3514 (1741/1773)                | 68.8          | 6                   | CHD mortality                                       | 367 (8.4%)/324 (8.9%)                   |
| ALLHAT-LLT[18] | US, Puerto Rico, US Virgin, Islands and Canada | 2002 | Pravastatin | 10355 (5170/5185)              | 66            | 4.8                 | All-cause mortality                                 | 378 (7.3%)/369 (7.1%)                   |
| HPS[19]        | United Kingdom                 | 2002               | Simvastatin | 20536 (10269/10267)             | 64            | 5                   | All-cause mortality                                 | 814 (7.9%)/803 (7.8%)                   |
| LIPS[20]       | Europe, Canada, Brazil         | 2002               | Fluvastatin | 1677 (844/833)                  | 60            | 3.9                 | MACE                                                 | 46 (5.5%)/49 (5.9%)                     |
| PROSPER[11]    | Scotland, Ireland, The Netherlands | 2002 | Pravastatin | 5804 (2891/2913)                | 75            | 3.2                 | A composite of coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke | 245 (8.5%)/199 (6.8%)                   |
| ASCOT-LLA[21]  | Nordic countries, UK, Ireland  | 2011               | Atorvastatin | 10305 (5168/5137)              | 63            | 3.3                 | A composite of nonfatal myocardial infarction and fatal CHD | 81 (1.6%)/87 (1.7%)                     |
| CARDs[22]      | United Kingdom, Ireland        | 2006               | Atorvastatin | 2838 (1428/1410)                | 62            | 3.9                 | Acute coronary heart disease events, coronary revascularizations, or stroke | 20 (1.4%)/30 (2.1%)                     |
| JUPITER[23]    | North America, South America, Europe and Africa | 2010 | Rosuvastatin | 5695 (2878/2817)                | 74            | 1.9                 | Cardiovascular event                                 | 144 (2.3%)/155 (2.5%)                   |

CHD: coronary heart disease; MACE: major adverse cardiovascular events, including cardiac death, nonfatal myocardial infarction and target vessel revascularization; QCA: quantitative coronary angiography.

Basic characteristics of the included trials are outlined in Table 1. The absence of asymmetry of the Begg’s funnel plots indicates that there was no potential publication bias (Figure 2).

Quality assessments of these RCTs are shown in Figure 3. Most of the bias risk graphs display green, meaning that all the trials are of high quality.

3.2 Effects of statin therapy on the incidence of cancer

The statin therapy did not affect the overall incidence of cancer in people over 60 years old (OR = 1.03, 95% CI: 0.94–1.14, P = 0.52; Figure 4). The subgroup analyses of the individual statin revealed no significant effect on the incidence of cancer in aged people (Figure 5): pravastatin therapy (OR = 1.11, 95% CI: 0.96–1.30, P = 0.17), simvastatin therapy (OR = 1.05, 95% CI: 0.75–1.47, P = 0.77), atorvastatin therapy (OR = 0.85, 95% CI: 0.63–1.14, P = 0.27), fluvastatin therapy (OR = 0.92, 95% CI: 0.61–1.40, P = 0.70), lovastatin therapy (OR = 1.15, 95% CI: 0.68–1.94,
P = 0.60) and rosuvastatin therapy (OR = 0.90, 95% CI: 0.72–1.14, P = 0.40). In another analysis grouped statins by different chemical properties showed that neither the hydrophilic (OR = 1.07, 95% CI: 0.92–1.24, P = 0.38) nor lipophilic statins (OR = 0.99, 95% CI: 0.87–1.11, P = 0.81) affected the incidence of cancer in the elderly patients (Figure 6).

4 Discussion

The present meta-analysis showed that statins therapy did not increase the overall incidence of cancer in people aged over 60 years. In China, 60+ years are usually denoted as old age, while most developed western countries set the age of 60 to 65 for retirement and old-age social programs eligibility. Then, in order to provide more evidence for Chinese doctors, we only included RCTs when their study participants’ average age > 60 years or presents subgroup analyses limited to participants > 60 years of age.

Although RCTs are considered as the “gold standard” and provide the highest evidence for internal validity, controlling for potential confounders and effect modifiers, they are also most unlikely to miss events owing to close follow-up. Moreover, they have the disadvantage of relatively small size, so might not be adequately powered to detect a true effect, especially when events are rare, such as cancer.[24] Meta-analyses are considered as a valuable tool for studying this kind of rare and unintended effects of treatment. The results of this 12 RCTs meta-analysis were relatively stable according to sensitivity analysis. Begg’s funnel plot showed no underlying publication bias and the bias risk graph indicated that all the included trials are highly qualified, so that bias due to differential attrition was unlikely to be an issue.

Our findings were in line with the previous meta-analysis of statin use and overall cancer risk in the elderly patients.[2] The subgroup analyses of the individual statin also found no substantial evidence for increasing cancer risk among statin
users as compared with non-users. Among the studies selected for our meta-analysis, only two RCTs have reported an increased risk of cancer in the statin group compared to the placebo group. The PROSPER study,\textsuperscript{[11]} which is the only randomized placebo controlled study to evaluate pravastatin in a unique population of elderly patients, found a 1.25 increased risk for cancer incidence for the pravastatin-treated patients compared to the placebo group. However, when the PROSPER trial extended follow-up period to 14 years, no relationship was found between statin use and cancer risks.\textsuperscript{[25]} The LIPID trial also indicated an increased cancer risk in the elderly patients assigned to pravastatin.

**Figure 5. Association of different statins use with incident cancer.**

| Study or Subgroup | Weight | Odds Ratio M-H, Random, 95% CI |
|-------------------|--------|--------------------------------|
| 1.1.1 Pravastatin  |        |                                |
| ALLHAT-LLT\textsuperscript{[11]} | 16.5%  | 1.03 [0.89, 1.19]               |
| GISS\textsuperscript{[15]} | 2.1%   | 0.62 [0.33, 1.19]               |
| LIPID\textsuperscript{[17]} | 15.0%  | 1.19 [1.01, 1.41]               |
| PROSPER\textsuperscript{[1]} | 12.9%  | 1.26 [1.04, 1.53]               |
| Subtotal           | 46.5%  | 1.11 [0.96, 1.30]               |

Total events
Heterogeneity: Tau\textsuperscript{2} = 0.01; Chi\textsuperscript{2} = 6.42, df = 3 (P = 0.09); I\textsuperscript{2} = 53%
Test for overall effect: Z = 1.38 (P = 0.17)

1.1.2 Simvastatin

| Study or Subgroup | Weight | Odds Ratio M-H, Random, 95% CI |
|-------------------|--------|--------------------------------|
| 4S\textsuperscript{[12,42]} | 2.8%   | 0.77 [0.44, 1.33]               |
| HPS\textsuperscript{[22]} | 20.9%  | 1.01 [0.92, 1.12]               |
| SCAT\textsuperscript{[10]} | 1.8%   | 1.85 [0.92, 3.76]               |
| Subtotal           | 25.4%  | 1.05 [0.75, 1.47]               |

Total events
Heterogeneity: Tau\textsuperscript{2} = 0.05; Chi\textsuperscript{2} = 3.80, df = 2 (P = 0.15); I\textsuperscript{2} = 47%
Test for overall effect: Z = 0.29 (P = 0.77)

1.1.3 Atorvastatin

| Study or Subgroup | Weight | Odds Ratio M-H, Random, 95% CI |
|-------------------|--------|--------------------------------|
| ASCOT-LLA\textsuperscript{[21]} | 7.3%   | 0.92 [0.68, 1.25]               |
| CARD\textsuperscript{[3]} | 2.6%   | 0.65 [0.37, 1.16]               |
| Subtotal           | 9.9%   | 0.85 [0.63, 1.14]               |

Total events
Heterogeneity: Tau\textsuperscript{2} = 0.01; Chi\textsuperscript{2} = 1.10, df = 1 (P = 0.29); I\textsuperscript{2} = 9%
Test for overall effect: Z = 1.10 (P = 0.27)

1.1.4 Fluvastatin

| Study or Subgroup | Weight | Odds Ratio M-H, Random, 95% CI |
|-------------------|--------|--------------------------------|
| LIP\textsuperscript{[21]} | 4.5%   | 0.92 [0.61, 1.40]               |
| Subtotal           | 4.5%   | 0.92 [0.61, 1.40]               |

Total events
Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.70)

1.1.5 Lovastatin

| Study or Subgroup | Weight | Odds Ratio M-H, Random, 95% CI |
|-------------------|--------|--------------------------------|
| AFCAPS/TexCAPS\textsuperscript{[14]} | 3.0%   | 1.15 [0.68, 1.94]               |
| Subtotal           | 3.0%   | 1.15 [0.68, 1.94]               |

Total events
Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)

1.1.6 Rosuvastatin

| Study or Subgroup | Weight | Odds Ratio M-H, Random, 95% CI |
|-------------------|--------|--------------------------------|
| JUPITER\textsuperscript{[22]} | 10.5%  | 0.90 [0.72, 1.14]               |
| Subtotal           | 10.5%  | 0.90 [0.72, 1.14]               |

Total events
Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)

Total
100.0% 1.03 [0.94, 1.14]

Total events
Heterogeneity: Tau\textsuperscript{2} = 0.01; Chi\textsuperscript{2} = 17.85, df = 11 (P = 0.09); I\textsuperscript{2} = 36%
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Chi\textsuperscript{2} = 4.26, df = 5 (P = 0.51), I\textsuperscript{2} = 0%
Figure 6. Lipophilic or hydrophilic statins and incident cancer.

| Study or Subgroup | Weight | M-H Ratio | M-H Random | 95% CI |
|-------------------|--------|-----------|------------|--------|
| **1.1.1 Hydrophilic** |        |           |            |        |
| ALLHAT-LIT [16]    | 16.5%  | 1.03 [0.89, 1.19] |            |        |
| GISSI [16]         | 2.1%   | 0.62 [0.33, 1.19] |            |        |
| JUPISTER [23]      | 10.5%  | 0.90 [0.72, 1.14] |            |        |
| LIPID [16]         | 15.0%  | 1.19 [1.01, 1.41] |            |        |
| PROSPER [11]       | 12.9%  | 1.26 [1.04, 1.53] |            |        |
| **Subtotal**       | 57.1%  | 1.07 [0.92, 1.24] |            |        |
| Total events       |        |           |            |        |
| Heterogeneity: Tau² = 0.01; Chi² = 9.26, df = 4 (p = 0.06); I² = 57% | | |
| Test for overall effect: Z = 0.89 (p = 0.38) | | |

| **1.1.2 Lipophilic** |        |           |            |        |
|---------------------|--------|-----------|------------|--------|
| 4S [13, 43]         | 2.8%   | 0.77 [0.44, 1.33] |            |        |
| AFCAPS/TexCAPS [14] | 3.0%   | 1.15 [0.68, 1.94] |            |        |
| ASCOT-LLA [25]      | 7.3%   | 0.92 [0.68, 1.25] |            |        |
| CARDS [13]          | 2.6%   | 0.65 [0.37, 1.16] |            |        |
| HPS [10]            | 20.9%  | 1.01 [0.92, 1.12] |            |        |
| LIPS [20]           | 4.5%   | 0.92 [0.61, 1.40] |            |        |
| SCAT [13]           | 1.8%   | 1.85 [0.92, 3.76] |            |        |
| **Subtotal**        | 42.9%  | 0.99 [0.87, 1.11] |            |        |

Duncan, et al. [32] suggested that pravastatin may promote the development of cancer by inducing mevalonate synthesis in extrahepatic tissues. The post hoc analysis in the JUPITER found that high-intensity rosuvastatin (another hydrophilic statin) therapy achieved LDL-C levels < 30 mg/dL but not associated with increased cancer risk. [33] Whether hydrophilic or lipophilic properties of statin have relationship to incident cancer required further discussion.

The present meta-analysis also failed to find favor results for statins as antitumor agents. Lipid metabolism is involved in the regulation of key cellular processes such as proliferation, differentiation and apoptosis. Statins may inhibit HMG-CoA reductase to lower the concentration of mevalonate, thereby decreasing the amount of isoprenylated intermediates that are known to affect signaling pathways from cancer formation to progression. [34, 35] In vitro/in vivo evidences have shown promising results for the use of statins in the treatment of various human malignancies. [36–39]

However, the epidemiological data and several meta-analyses failed to find conclusive results, for example, results of statin on colorectal cancer ranging from very protective, [40] to moderately harmful. [41] As we known, cancer is not a

treatment compared to placebo group. [17] Consist with these results, a meta-analysis of 12 RCTs showed that pravastatin therapy presented an increasing risk of cancer incidence with advancing patient age. [26] Our meta-analysis only included four RCTs of pravastatin, the different inclusion criteria might explain in part the contrary results. Cancer is an endpoint that needs to be followed-up for at least 10 years. Given to the relatively shorter follow-up period, it is too early to say whether some statins might have a carcinogenic effect for some cancer types. Nevertheless, the findings on pravastatin require cautious interpretation and need to be confirmed by further studies.

The other subgroup analysis of statins with different chemical properties showed that neither the hydrophilic nor lipophilic affected the incidence of cancer in people aged > 60 years, which are also in accord with previous reports. [27, 28] With respect to statin type, it has been hypothesized that only lipophilic statins can potentially be capable of inhibiting tumor development; in contrast, hydrophilic statins could be expected to promote tumor development. [29] However, clinical studies yielded conflicting results. Several RCTs of lipophilic statin therapy have not reported an increased risk of cancer. [14, 19, 30] In a recently published study, lipophilic statin was reported to play a therapeutic role in cancer treatment. [31] Different from lipophilic statins, results from hydrophilic statins are inconsistent. Duncan, et al. [32] suggested that pravastatin may promote the development of cancer by inducing mevalonate synthesis in extrahepatic tissues. The post hoc analysis in the JUPITER found that high-intensity rosuvastatin (another hydrophilic statin) therapy achieved LDL-C levels < 30 mg/dL but not associated with increased cancer risk. [33] Whether hydrophilic or lipophilic properties of statin have relationship to incident cancer required further discussion.
homogenous disease entity, and overall cancer risk is not a very sensitive outcome. Therefore, the effects of statins might significantly differ according to anatomical site and molecular type. More investigations are needed to assess the effects of statins for the treatment of particular cancer type.

Several limitations of our study should be noted. First, the number of studies included in our meta-analysis is limited, especially for some individual statin. Second, analysis from subgroups should be interpreted with caution. The results from several included studies were obtained from subgroup data and not all studies population. Power is also likely to be limited in a subgroup analysis and the risks of obtaining spurious results are higher due to the inability of subgroups to account for multiple hypotheses assumed in the overall trial.\cite{42} Third, studies included in this study had a relatively shorter follow-up duration (1.9–5.4 years). Given that many individuals are treated with statins for decades, this duration of time may not be adequate to fully assess cancer risk.

In summary, meta-analyses of 12 large RCTs of statins showed that the statin therapy did not affect the overall incidence of cancer, subgroup analyses showed that neither the variety nor the chemical properties of statins affected the incidence of cancer in people aged > 60 years. These findings are limited by the relatively short follow-up duration of the included studies. More uniform reporting of cancer outcomes and longer follow-up periods are needed to firmly establish the role of statins in cancer development, particularly in people aged over 60 years.

References

1. Delahoy PJ, Magliano DJ, Webb K, et al. The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. Clin Ther 2009; 31: 236–244.
2. Afilalo J, Duque G, Steele R, et al. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. J Am Coll Cardiol 2008; 51: 37–45.
3. Alexander KP, Blazing MA, Rosenson RS, et al. Management of hyperlipidemia in older adults. J Cardiovasc Pharmacol Ther 2009; 14: 49–58.
4. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. JAMA 2004; 291: 1864–1870.
5. Kumar AS, Benz CC, Shim V, et al. Estrogen receptor-negative breast cancer is less likely to arise among lipophilic statin users. Cancer Epidemiol Biomarkers Prev 2008; 17: 1028–1033.
6. Tan M, Song X, Zhang G, et al. Statins and the risk of lung cancer: a meta-analysis. PLoS One 2013; 8: e57349.
7. Kuoppala J, Lamminpaa A, Pukkala E. Statins and cancer: A systematic review and meta-analysis. Eur J Cancer 2008; 44: 2122–2132.
8. Bansal D, Undela K, D'Cruz S, et al. Statin use and risk of prostate cancer: a meta-analysis of observational studies. PLoS One 2012; 7: e46691.
9. Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. JAMA 1996; 275: 55–60.
10. Friedman GD, Flick ED, Udaltsova N, et al. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. Pharmacoepidemiol Drug Saf 2008; 17: 27–36.
11. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360: 1623–1630.
12. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629–634.
13. Miettinen TA, Pyorala K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction and angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). Circulation 1997; 96: 4211–4218.
14. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998; 279: 1615–1622.
15. Teo KK, Burton JR, Buller CE, et al. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: The Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). Circulation 2000; 102: 1748–1754.
16. Results of the low-dose (20 mg) pravastatin GISSI Prevention trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico). Ital Heart J 2000; 1: 810–820.
17. Hunt D, Young P, Simes J, et al. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: Results from the LIPID trial. Ann Intern Med 2001; 134: 931–940.
18. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002; 288: 2998–3007.
19. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7–22.
20. Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA 2002; 287: 3215–3222.

http://www.jgc301.com; jgc@mail.sciencep.com | Journal of Geriatric Cardiology
21 Collier DJ, Poulter NR, Dahlöf B, et al. Impact of atorvastatin among older and younger patients in the Anglo-Scandinavian cardiac outcomes trial lipid-lowering arm. J Hypertens 2011; 29: 592–599.

22 Neil HA, DeMicco DA, Luo D, et al. Analysis of efficacy and safety in patients aged 65–75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). Diabetes Care 2006; 29: 2378–2384.

23 Glynn RJ, Koenig W, Nordestgaard BG, et al. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med 2010; 152: 488–496, W174.

24 Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006; 97: 52C–60C.

25 Jukema JW, Cannon CP, de Craen AJ, et al. The controversies of statin therapy: weighing the evidence. J Am Coll Cardiol 2012; 60: 875–881.

26 Bonovas S, Sitaras NM. Does pravastatin promote cancer in elderly patients? A meta-analysis. CMAJ 2007; 176: 649–654.

27 Sun H, Yuan Y, Wang P, et al. Intensified low-density lipoprotein-cholesterol target of statin therapy and cancer risk: a meta-analysis. Lipids Health Dis 2015; 14: 140.

28 Dale KM, Coleman CI, Henyan NN, et al. Statins and cancer risk: a meta-analysis. JAMA 2006; 295: 74–80.

29 Hawk E, Viner JL. Statins and cancer—beyond the “one drug, one disease” model. N Engl J Med 2005; 352: 2238–2239.

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

31 Cuello FM, Kato CS, Diaz SD, et al. Effects of statins in cancer. Rev Med Chil 2013; 141: 227–236.

32 Duncan RE, El-Sohemy A, Archer MC. Statins and cancer development. Cancer Epidemiol Biomarkers Prev 2005; 14: 1897–1898.

33 Everett BM, Mora S, Glynn RJ, et al. Safety profile of subjects treated to very low low-density lipoprotein cholesterol levels (< 30 mg/dL) with rosuvastatin 20 mg daily (from JUPITER). Am J Cardiol 2014; 114: 1682–1689.

34 Demierre MF, Higgins PD, Gruber SB, et al. Statins and cancer prevention. Nat Rev Cancer 2005; 5: 930–942.

35 Chan KK, Oza AM, Siu LL. The statins as anticancer agents. Clin Cancer Res 2003; 9: 10–19.

36 Katz MS. Therapy insight: Potential of statins for cancer chemoprevention and therapy. Nat Clin Pract Oncol 2005; 2: 82–89.

37 Apostolova S, Toshkova R, Momchilova A, et al. Statins and alkylphospholipids as new anticancer agents targeting lipid metabolism. Anticancer Agents Med Chem 2016. Published Online First: Jun 23, 2016. DOI: 10.2174/1871520616666160624093955

38 Pikoulis E, Margonis GA, Angelou A, et al. Statins in the chemoprevention of colorectal cancer in established animal models of sporadic and colitis-associated cancer. Eur J Cancer Prev 2016; 25: 102–108.

39 Santa-Maria CA, Stearns V. Statins and breast cancer: future directions in chemoprevention. Curr Breast Cancer Rep 2013; 5: 161–169.

40 Poynter JN, Gruber SB, Higgins PD, et al. Statins and the risk of colorectal cancer. N Engl J Med 2005; 352: 2184–2192.

41 Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to statins and risk of common cancers: a series of nested case-control studies. BMC Cancer 2011; 11: 409.

42 Nagara O, Raymond J, Guilbert F, et al. The problem of subgroup analyses: an example from a trial on ruptured intracranial aneurysms. AJNR Am J Neuroradiol 2011; 32: 633–636.

43 Pedersen TR, Berg K, Cook TJ, et al. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. Arch Intern Med 1996; 156: 2085–2092.