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REVIEW

# Effect of statin therapy on cancer incidence

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**Abstract**

Statins, as lipid lowering agents have a well-established role in the primary and secondary prevention of cardiovascular (CV) events. They are one of the most prescribed medicines worldwide. Lipid-lowering drugs have been implicated in rodent carcinogenicity and concerns about the same effect in humans have been raised. Low plasma cholesterol levels has been associated with an increased risk of cancer and a possible reason for this observation could be related to the presence subclinical disease, where subclinical disease lowered cholesterol levels for years before cancer surfaced clinically. Many papers have discussed the possible mechanisms leading to the increased cancer incidence in statin users, but the results have been controversial and inconclusive. The aim of this paper is to present and evaluate the latest evidence regarding statin use on cancer incidence.

**Key words:** statin; simvastatin; therapy; cancer; incidence

## 1. Introduction

Statins have a well-established role in the primary and secondary prevention of cardiovascular (CV) events. As lipid lowering agents, statins act by competitively inhibiting hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, which is an important enzyme responsible for cholesterol synthesis in hepatocytes [1]. HMG-CoA reductase catalyses the conversion of HMG-CoA to mevalonate, which is further metabolized to precursors of sterol (i.e. cholesterol) and non-sterol (i.e. isoprenoid) products [2]. Inhibition of HMG-CoA enhances the expression of low-density lipoprotein receptors on hepatocyte membranes and consequently lowers low-density lipoprotein-cholesterol (LDL-C) concentration in the blood. There is vast of evidence that CV risk and all-cause mortality are positively correlated with LDL-C levels. The European Society of Cardiology (ESC) guidelines recommend the use of statins up to the highest recommended dose, or highest tolerable dose to reach the target level, for the pharmacological treatment of hypercholesterolemia [1]. Besides their LDL-C lowering effects, statins demonstrate pleiotropic effects by reducing inflammatory processes and modulating endothelial function. This additionally contributes to the prevention of macrovascular complications and reduction in mortality [3]. Since hypercholesterolemia is a common problem in the general population, these properties of statins make them a cornerstone of hypercholesterolemia treatment, and consequently one of the most prescribed drugs worldwide.

The incidence and severity of adverse reactions in statin users can vary from one subpopulation to another. Adverse reactions include some life threatening conditions, such as rhabdomyolysis, or a slightly higher incidence of diabetes mellitus (DM). Nevertheless, the benefit of their use substantially outweighs the risk [1,4].

Statin treatment might be associated with an increased incidence of cancer. Many studies have examined the relationship between cancer incidence and statin use; however, results have been controversial and inconclusive [5]. The possible beneficial effects of statins could be based on their inhibition of HMG-CoA reductase that is necessary for the synthesis of mevalonate. The mevalonate pathway and its downstream products, have an important role in the cellular function of neoplastic cells. Therefore, statins may lead to the inhibition of tumor initiation, growth and metastasis [6]. On the contrary, a hypothesis that statins influence and promote cancer growth exists. In vivo, statins induce the transcription regulator Foxp3 and result in an increased number of CD4 (+) CD (25+) regulatory T-cells (TREGS) [7]. TREGS can contribute to hampered antitumor immunity [8], and they are even considered as new targets for anticancer treatment [9]. Malenda and associates reported a neutral effect of statins in vitro. Although statins decreased the glucose uptake in Human Burkitt lymphoma, human follicular lymphoma and human colon adenocarcinoma cell lines, they did not significantly alter the cell cycle of Human Burkitt lymphoma cell lines. However, as statins decrease glucose uptake, they decreased the 18F-fluorodeoxyglucose (18F-FDG) uptake by tumor tissue in a patient with mantle cell lymphoma. Thus, statins can negatively affect PET/CT results and this could be of clinical significance in diagnostics [10]. Nevertheless, the effect of statins on cancer incidence, together with its possible mechanism, is still not truly elucidated and needs further research. The aim of this paper is to present and evaluate the latest evidence regarding statin use on cancer incidence.

## 2. Statins and their effect on cancer in observational trials

More than 30 years ago, Rose and Shipley found that low plasma cholesterol levels were associated with an increased risk of cancer [11]. A possible explanation for this observation could be related to presence of subclinical disease, which lowered cholesterol levels for up to 10 years before the cancer surfaced clinically [12].

Lipid-lowering drugs have also been implicated in rodent carcinogenicity, and they raised concerns about the same effect in humans [13].

A large population-based case-control study revealed a 1.83-fold increased risk of invasive ductal carcinoma (IDC) [95% confidence interval (CI): 1.1-2.93] and a 1.97-fold increased risk of invasive lobular carcinoma (ILC) (95% CI: 1.25-3.12) in women (55 to 74 years) using statins for 10 years or longer, compared to no users. This risk was not observed in women using statins for periods shorter than 10 years. The vast majority (88%) of this population used lipophilic statins. In women with hypercholesterolemia, statins use for at least 6 months and less than 5 years resulted in a 1.55-fold increased risk of ILC (95% CI: 1.01 - 2.37). In the same subpopulation, the use of statins for 10 years or longer, increased the risk

of IDC and ILC by 2.04-fold (95% CI: 1.17 - 3.57) and 2.43-fold (95% CI: 1.40 - 4.21), respectively. The study found that statins increased the risk of estrogen receptor (ER) positive cancer [14].

On the other hand, a meta-analysis of observational studies and randomized clinical trials (RCTs) [15,16], as well as a large number of observational case-control studies [17-21] and prospective cohort trials [22],

**Table 1. Effect of statins on cancer incidence in observational trials**

| Trial | Design of a trial | Number of patients | Primary endpoint of a trial | Type of cancer | Effect on cancer incidence |
|---|---|---|---|---|---|
| Mcdougall et al. (2013)14 | Case-control | 2,886 | Relationship between long-term statin use and BC risk | BC | ↑ |
| Woditschka et al. (2010)17 | Case-control | 247,348 | To determine whether chronic use of lipophilic statins is associated with decreased risk of HR-negative BC or other BC subtypes | BC | ↕ |
| Baandrup et al. (2015)18 | Case-control | 62,809 | Association between ever use of statins and epithelial ovarian cancer risk | Epithelial ovarian cancer | ↕ |
| Mcglynn et al. (2015)19 | Case-control | 5,835 | Statins-liver cancer relationship | Liver cancer | ↓ |
| Mamtani et al. (2016)20 | Case-control | 108,701 | Association of colorectal cancer risk with statin use | Colorectal cancer | ↓ |
| Lavie et al. (2013)21 | Case-control | 765 | Effects of statins on gynecological cancers | Endometrial cancer | ↓ |
| Khurana et al. (2007)23 | Case-control | 483,733 | Association of lung cancer and the use of statins | Lung cancer | ↓ |
| Cauley et al. (2006)22 | Cohort, prospective | 156,351 | Associations between potency, duration of use, and type of statin used and risk of invasive BC | BC | ↕ |
| Wang et al. (2013)15 | Meta-analyses of observational trials and RCTs | 4,980,009 | Association between statin use and risk of lung cancer | Lung cancer | ↕ |
| Shi et al. (2014)16 | Meta-analyses of observational trials and RCTs | 5,640,313 | Association between statin use and risk of liver cancer | Liver cancer | ↓ |

* Breast cancer = BC, Randomized clinical trials (RCTs), Statin increase cancer incidence = ↑, Statin have no effect on cancer incidence = ↕, Statin decrease cancer incidence = ↓

reported no effect or a beneficial effect of statins on different cancer incidences. Statin use had no effect on the incidence of lung cancer [15], breast cancer (BC)[17,22] or epithelial ovarian cancer [18], but reduced the risk for liver cancer [16,19], colorectal cancer [20] and endometrial cancer [21]. In a nested case-control study of 483 733 patients, statins appeared to be protective for the development of lung cancer. Statin use for ≥ 6 months demonstrated a cancer risk reduction by 55% (odds ratio [OR] 0.45, 95% CI, 0.42 to 0.48, $p < 0.01$). This protective effect of statins was further increased with the duration of statin therapy [23]. Although there was an enormous reduction of lung cancer incidence (55%), these results cannot be considered confirmatory regarding beneficial effect of statins on cancer incidence due to study's design (case-control), which is prone to bias.

## 3. Statins and their effect on cancer in RCTs

Several placebo-controlled RCTs have also documented hazardous effects of statins on cancer incidence [24-26]. In the PROSPER trial, pravastatin increased cancer incidence [hazard ratio (HR) 1.25, 95% CI 1.04–1.51, P=0.020] in elderly individuals (aged 70-82) during a mean follow-up of 3.2 years (range 2.8–4.0). Gastrointestinal (GIT) cancer incidence was of near borderline significance (HR 1.46, 95% CI 1.00–2.13, P=0.053). Pravastatin was implicated in more cases of cancer death, although not statistically significant (HR 1.28, 95% CI 0.97–1.68, P=0.082). During the four years of follow-up, more cases of cancer were reported in the pravastatin group [25].

In the CARE trial, pravastatin was not associated with an increased cancer incidence during a median duration of follow-up of 5.0 years (range, 4.0 to 6.2), but it was implicated in a higher incidence of BC (12 vs. 1 case of BC, P=0.002). It needs to be stated that only a small number of BC cases were reported [24].

Interestingly, the meta-analysis of pravastatin and all statin RCT trials has not confirmed any association of pravastatin with excess cancer incidence [25]. Even the post-trial follow-ups of RCTs involving pravastatin (subsequent 10 years and 5 more years in the WOSCOPS and 2 years in the LIPID trial) did not demonstrate a higher incidence of cancer [27-29].

The combination of simvastatin and ezetimibe in the randomized controlled SEAS trial showed an increased cancer incidence (105 cases versus 70 in the placebo group, P=0.01) during a median follow-up of 52.2 months. The difference in any specific type of cancer did not reach statistical significance, although more cases of skin cancer (8 vs. 18) and prostate cancer (13 vs. 21) were seen [26]. However, large RCTs have not confirmed assumptions that ezetimibe, simvastatin, or their combination is carcinogenic [30-33]. The same finding was reported in a post-trial follow-up of RCTs with simvastatin, for any specific type of cancer and overall cancers [34,35]. However, there was one exception; the HPS and 4S trial with simvastatin documented a numerically higher incidence of non-melanoma skin cancer (NMSC) [32,33].

The difference is statistically significant if the results from both studies are combined (in simvastatin groups, 256 of the 12,490 participants; and in control groups, 208 of the 12,490 participants; $p = 0.028$) [36]. However, both post-trial follow-ups have not documented any increase in NMSC incidence [34,35].

A large CTT meta-analysis from 27 randomized trials (22 statin vs. control trials and 5 intensive vs. less intensive statin therapy trials) evaluated the effect of lowering LDL-C with statins on cancer incidence. It included only trials that recruited at least 1000 participants, with scheduled treatment duration of at least 2 years. Patient records that included 10 000 cancer cases among 175 000 participants, showed no evidence of increased cancer incidence when reducing LDL-C with a statin for about 5 years. Results were the same when statin vs. control trials were examined [rate ratio (RR) 1.00 (95% CI 0.96-1.05)] or more vs. less intensive statin therapy trails were examined [RR 1.00 (95% CI 0.93–1.07)]. The same results were found for shorter or longer periods of use, for any individual statin or statin type, for any specific type of cancer, or in any given subgroup. Even in patients with a low baseline LDL-C (<2 mmol/L) further lowering LDL-C with statin had no effect on cancer incidence (RR 0.92 [99% CI 0.76–1.10]) [37]. An overall risk of cancer with statin use was also examined in a meta-analysis of 35 RCTs of statins for CV outcomes, and gave the same results. Statin use was not associated with a decreased or increased risk of cancer (RR, 0.99; 95% CI: 0.94-1.04) [38].

**Table 2. Effect of statins on cancer incidence in RTCs**

| Trial | Design of a trial | Median follow-up | Number of patients | Type of cancer | Effect on cancer incidence |
|---|---|---|---|---|---|
| Shepherd et al. (PROSPER) (2002)25 | Multicentric, double-blind, placebo-controlled RCT | 3.3 years | 5,804 | All cancers | ↑ |
| Sacks et al. (CARE) (1996)[24] | Multicentric, double-blind, placebo-controlled RCT | 5.0 years | 4,159 | BC | ↑ |
| Rossebø et al. (SEAS) (2008)[26] | Multicentric, double-blind, placebo-controlled RCT | 52.2 months | 1,873 | All cancers | ↑ |
| Baigent et al. (SHARP) (2011)[30] | Multicentric, double-blind, placebo-controlled RCT | 4.9 years | 9.270 | All cancers | ↕ |
| Mascitelli et al. (2010)[36] | 2 Multicentric, double-blind, placebo-controlled RCTs | 5.4 years (HPS) [33] and 5.4 years (4S) [32] | 20,536 (HPS) and 4444 (4S) | NMSC | ↑ |
| Shepherd et al. meta-analyses of RCTs with pravastatin(2002)[25] | 4 randomised double-blind placebocontrolled clinical trials | more than 3 years | 25,572 | All cancers | ↕ |
| Bonovas et al. meta-analysis of 35 RCTs (2006)[38] | 35 RCTs of statins for cardiovascular outcomes | 4.5 years on average | 109,143 | All cancers | ↕ |
| Cholesterol Treatment Trialists (CTT) | 22 randomised trials of statin versus control and 5 trials of more intensive versus less intensive statin therapy | 5 years | 175,000 | All cancers | ↕ |

* Breast cancer = BC, Randomized clinical trials (RCTs), Non-melanoma skin cancer (NMSC), Statin increase cancer incidence = ↑, Statin have no effect on cancer incidence = ↕, Statin decrease cancer incidence = ↓

## 4. Discussion

Many inconclusive evidence-based results regarding this topic make it difficult to answer whether statins have a positive, negative, or no effect on cancer incidence.

A large population-based case-control trial found a connection between long-term (>10 years) statin use and the risk of BC in women (55 to 74 years). The same connection was observed among women with hypercholesterolemia, using statins for at least 6 months and less than 5 years [14]. On the other hand, a larger case-control trial [17] and prospective cohort trial [22] with similar populations, found no association between BC incidence and statin use, including women using statins for more than 5 and 3 years, respectively. Unfortunately, these results cannot be considered confirmatory, due to

the design of the trials and relatively modest increases in cancer risk. Considering RCTs, although in the CARE trial pravastatin was implicated in more BC cases (12 vs. 1) [24], this was not the case in the HPS trial [33] and the CTT meta-analysis of RCTs [37]. Even the HPS trial follow-up (mean total duration of follow-up was 11.0 years) did not document any significant differences in specific cancer incidence in statin uses, nor a trend towards a higher incidence of total cancer incidence at 10 or more years of follow-up [35]. Follow-up of the 4S RCT (median trial follow-up 5.4 years and median total follow-up period of 10.4 years) also did not document any significant differences in any type of cancer incidence (including BC) with statin treatment. There was no difference in cancer incidence during the entire follow-up and no trend towards a higher risk of total cancer incidence in the later years of follow-up [34].

Although the meta-analyses of observational studies and RCTs [16] and several observational case-control trials [19-21,23] suggested lower incidences of several types of cancer, this was not confirmed in the large CTT meta-analysis of RCTs [37]. Results from observational trials cannot be considered confirmatory regarding the beneficial effect of statins on cancer incidence due to the design of the trials, which is prone to bias. Neither of the observational trials and meta-analyses of observational studies and RCTs reported the long-term effect of statin treatment. Therefore, the CTT meta-analysis of RCTs that reported the effect of statins within 5 years of treatment initiation is stronger evidence compared to the previous meta-analysis. In a series of nested case-control studies within a cohort of patients registered in the UK that evaluated long-term (≥6 years) statin use, no association between statin treatment and increased lung cancer incidence was found [39]. Still, it is interesting that in the case-control trial statin treatment for <5 years reduced the risk of mucinous ovarian cancer, but the same effect was not observed for statin treatment ≥5 years. Overall, statin treatment for ≥5 years had no effect on the incidence of epithelial ovarian cancer [18].

The PROSPER RCT raised concerns for a higher cancer incidence among elderly patients on statin treatment [25], but the CTT meta-analysis did not find an increased risk in this subpopulation [37]. The WOSCOPS trial follow-up of 15 years (5-year trial and 10 year post-trial follow-up) documented a higher incidence of prostate cancer in statin users [27]. However, the WOSCOPS 20 year follow-up did not confirm an increase in any type of cancer incidence [29]. There are several limitations of follow-ups that could limit the interpretation of data. Although significantly more participants in the original pravastatin group were taking statins than in the original placebo group (P<0.001 for all comparisons), after 5 years approximately 37% of patients from each group were taking statins. Unfortunately, data on statin used is not known for the entire 10-year period, but only for 5 years of the post-trial follow-up [27]. Thus, out of the total 20-year follow-up, data pertaining to the use of lipid-lowering therapy is not know in the last 10 years of follow-up. These flaws could have an impact on the study results.

A higher incidence of NMSC was reported in the HPS and 4S RCTs with simvastatin [32,33], but not in the RCT with lovastatin [40] and post-trial follow-ups of HPS and 4S RCTs. The WHI prospective cohort trial, with a mean follow-up of 10.5 years, demonstrated an association between lovastatin (OR 1.52; 95% CI: 1.08–2.16) and simvastatin (OR 1.38; 95% CI: 1.12–1.69) and a higher risk of NMSC in non-Hispanic white postmenopausal women. A higher risk was documented for treatment <3 years but not >3 years [41]. Interestingly, NMSC is excluded in reports from all statin trials [42-44] and in the CTT meta-analysis of RCTs [37]. In the HPS and 4S RCT post-trial follow-ups, a similar number of trial participants (from the active and comparator groups) where using statins. Simvastatin seems to be implicated in a higher risk for NMSC. For other lipophilic statins, further research is needed.

A significant limitation of all observational trials is the probable poor adherence of patients, along with other biases that are accompanied with an observational design [45-47]. Therefore, the results from observational trials presented in this article should be interpreted with caution and cannot be considered confirmatory, or invalidate the connection between statins and cancer incidence. It is important to highlight that the risk ratios documented in these trials were relatively modest. Limitations of the RCTs and the corresponding post-trial follow-ups of statin use is that the RCTs were not designed to determine cancer incidence. Most of the RCTs were designed to evaluate CV events and all-cause mortality with statin treatment. Thus, because these RCTs were designed for the evaluation of other clinical endpoints, significant bias is present, and the results regarding cancer incidence need to be interpreted with caution. Another potential problem regarding data from RCTs and clinical practice is that trial

participants can differ from patients in clinical practice in terms of demography, concomitant drug use, co-morbidities [48] and adherence [45,49]. Therefore, these factors can have possible consequences on the effectiveness and safety of treatment [48]. Nevertheless, the CTT meta-analysis of RCTs provides the strongest evidence on this topic, and it did not show any association between statin use and cancer incidence.

In a conclusion, current evidence does not suggest that here is any connection between increased or decreased incidence of cancer and statin use. However, simvastatin might be associated with a higher risk of NMSC. Unfortunately, many statin trials do not report on NMSC incidence. Further long-term (>10 years) epidemiologic trials are needed to establish if there is an association between statin treatment and the incidence of various types of cancer.

## Author contributions

MS gave the idea for the article, critically revised the manuscript and gave the final approval. MS and EJ performed the literature review, wrote the article, evaluated the evidence included in the article and participated in drafting the article. LJP and MM performed a literature review and participated in drafting the article. VP and RŠ gave suggestions regarding data presentation and gave their final approval.

## References

1. Reiner Ž, Catapano AL, De backer G, Graham I, Taskinen MR, Wiklund O, et al. [ESC/EAS Guidelines for the management of dyslipidaemias]. Rev Esp Cardiol 2011;64:1168.e1-1168.e60. https://doi.org/10.1016/j.recesp.2011.09.014

2. Yeganeh B, Wiechec E, Ande SR, Sharma P, Moghadam AR, Post M, et al. Targeting the mevalonate cascade as a new therapeutic approach in heart disease, cancer and pulmonary disease. Pharmacol Ther 2014;143:87-110. https://doi.org/10.1016/j.pharmthera.2014.02.007

3. Blum A, Shamburek R. The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. Atherosclerosis. 2009;203:325-30. https://doi.org/10.1016/j.atherosclerosis.2008.08.022

4. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016. Sep 8. pii: S0140-6736(16)31357-5. doi: 10.1016/S0140-6736(16)31357-5. https://doi.org/10.1016/S0140-6736(16)31357-5

5. Boudreau DM, Yu O, Johnson J. Statin use and cancer risk: a comprehensive review. Expert Opin Drug Saf 2010;9:603-21. https://doi.org/10.1517/14740331003662620

6. Chan KK, OzaAM, Siu LL. The statins as anticancer agents. Clin Cancer Res 2003;9:10-9.

7. Mausner-Fainberg K, Luboshits G, Mor A, Maysel-Auslender S, Rubinstein A, Keren G, et al. The effect of HMG-CoA reductase inhibitors on naturally occurring CD4+CD25+ T cells. Atherosclerosis 2008;197:82. https://doi.org/10.1016/j.atherosclerosis.2007.07.031

8. Tiemessen MM, Jagger AL, Evans HG, Van Herwijnen MJ, John S, Taams LS. CD4+CD25+Foxp3+ regulatory T cells induce alternative activation of human monocytes/macrophages. Proc Natl Acad Sci USA 2007;104:19446-51. https://doi.org/10.1073/pnas.0706832104

9. Curiel TJ. Tregs and rethinking cancer immunotherapy. J Clin Invest 2007;117:1167-74. https://doi.org/10.1172/JCI31202

10. Malenda A, Skrobanska A, Issat T, et al. Statins impair glucose uptake in tumor cells. Neoplasia 2012;14:311-23. https://doi.org/10.1593/neo.12444

11. Rose G, Shipley MJ. Plasma lipids and mortality: a source of error. Lancet 1980;1:523-6. https://doi.org/10.1016/S0140-6736(80)92775-0

12. Törnberg SA, Holm LE, Carstensen JM, Eklund GA. Cancer incidence and cancer mortality in relation to serum cholesterol. J Natl Cancer Inst 1989;81:1917-21. https://doi.org/10.1093/jnci/81.24.1917

13. Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. JAMA 1996;275:55-60. https://doi.org/10.1001/jama.1996.03530250059028

14. Mcdougall JA, Malone KE, Daling JR, Cushing-Haugen KL, Porter PL, Li CI. Long-term statin use and risk of ductal and lobular breast cancer among women 55 to 74 years of age. Cancer Epidemiol Biomarkers Prev 2013;22:1529-37. https://doi.org/10.1158/1055-9965.EPI-13-0414

15. Wang J, Li C, Tao H, Cheng Y, Han L, Li X et al. Statin use and risk of lung cancer: a meta-analysis of observational studies and randomized controlled trials. PLoS ONE 2013;8:e77950. https://doi.org/10.1371/journal.pone.0077950

16. Shi M, Zheng H, Nie B, Gong W, Cui X. Statin use and risk of liver cancer: an update meta-analysis. BMJ Open 2014;4:e005399. https://doi.org/10.1136/bmjopen-2014-005399

17. Woditschka S, Habel LA, Udaltsova N, Friedman GD, Sieh W. Lipophilic statin use and risk of breast cancer subtypes. Cancer Epidemiol Biomarkers Prev 2010;19:2479-87. https://doi.org/10.1158/1055-9965.EPI-10-0524

18. Baandrup L, Dehlendorff C, Friis S, Olsen JH, Kjær SK. Statin use and risk for ovarian cancer: a Danish nationwide case-control study. Br J Cancer 2015;112:157-61. https://doi.org/10.1038/bjc.2014.574

19. Mcglynn KA, Hagberg K, Chen J, Graubard BI, London WT, Jick S, et al. Statin use and risk of primary liver cancer in the Clinical Practice Research Datalink. J Natl Cancer Inst 2015;107(4). pii: djv009. doi: 10.1093/jnci/djv009. https://doi.org/10.1093/jnci/djv009

20. Mamtani R, Lewis JD, Scott FI, Ahmad T, Goldberg DS, Datta J, et al. Disentangling the Association between Statins, Cholesterol, and Colorectal Cancer: A Nested Case-Control Study. PLoS Med 2016;13:e1002007. https://doi.org/10.1371/journal.pmed.1002007

21. Lavie O, Pinchev M, Rennert HS, Segev Y, Rennert G. The effect of statins on risk and survival of gynecological malignancies. GynecolOncol 2013;130:615-9. https://doi.org/10.1016/j.ygyno.2013.05.025

22. Cauley JA, McTiernan A, Rodabough RJ, LaCroix A, Bauer DC, Margolis KL, et al. Statin use and breast cancer: prospective results from the Women's

Health Initiative. J Natl Cancer Inst 2006;98:700-7.
https://doi.org/10.1093/jnci/djj188

23. Khurana V, Bejjanki HR, Caldito G, Owens MW. Statins reduce the risk of lung cancer in humans: a large case-control study of US veterans. Chest 2007;131:1282-8.
https://doi.org/10.1378/chest.06-0931

24. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996;335:1001-9.
https://doi.org/10.1056/NEJM199610033351401

25. Shepherd J, Blauw GJ, Murphy MB,Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623-30.
https://doi.org/10.1016/S0140-6736(02)11600-X

26. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008;359:1343-56.
https://doi.org/10.1056/NEJMoa0804602

27. Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM. Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med 2007;357:1477-86.
https://doi.org/10.1056/NEJMoa065994

28. Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. Lancet 2002;359:1379-87.
https://doi.org/10.1016/S0140-6736(02)08351-4

29. Ford I, Murray H, Mccowan C, Packard CJ. Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy: 20-Year Follow-Up of West of Scotland Coronary Prevention Study. Circulation 2016;133:1073-80.
https://doi.org/10.1161/CIRCULATIONAHA.115.019014

30. Baigent C, Landray M J, Reith C, Emberson J, Wheeler DC, Tomson C, et al. 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;377:2181-92.
https://doi.org/10.1016/S0140-6736(11)60739-3

31. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015;372:2387-97.
https://doi.org/10.1056/NEJMoa1410489

32. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). Lancet 1994;344:1383–1389.

33. 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.
https://doi.org/10.1016/S0140-6736(02)09327-3

34. Strandberg TE, Pyorala PK, Cook TJ, Wilhelmsen L, Faergeman O, Thorgeirsson G, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). Lancet 2004;364:771-777.
https://doi.org/10.1016/S0140-6736(04)16936-5

35. Bulbulia R, Bowman L, Wallendszus K, Parish S, Armitage J, Peto R, et al. 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.
https://doi.org/10.1016/S0140-6736(11)61125-2

36. Mascitelli L, Pezzetta F, Goldstein MR. The epidemic of nonmelanoma skin cancer and the widespread use of statins: Is there a connection? Dermato Endocrinol 2010;2:37-8.
https://doi.org/10.4161/derm.2.1.12128

37. Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, Bhala N, et al. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. PLoS ONE 2012;7:e29849.
https://doi.org/10.1371/journal.pone.0029849

38. Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Statins and cancer risk: a literature-based meta-analysis and meta-regression analysis of 35 randomized controlled trials. J Clin Oncol 2006;24:4808-17.
https://doi.org/10.1200/JCO.2006.06.3560

39. 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.
https://doi.org/10.1186/1471-2407-11-409

40. 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;279:1615-22.
https://doi.org/10.1001/jama.279.20.1615

41. Wang A, Stefanick ML, Kapphahn K, Whitney E, Shapiro DR, Beere PA, et al. Relation of statin use with non-melanoma skin cancer: prospective results from the Women's Health Initiative. Br J Cancer 2016;114:314-20.
https://doi.org/10.1038/bjc.2015.376

42. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301-7.
https://doi.org/10.1056/NEJM199511163332001

43. Domanski M, Tian X, Fleg J, Coady S, Gosen C, Kirby R, et al. Pleiotropic effect of lovastatin, with and without cholestyramine, in the post coronary artery bypass graft (Post CABG) trial. Am J Cardiol 2008;102:1023-7.
https://doi.org/10.1016/j.amjcard.2008.05.053

44. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395-407.
https://doi.org/10.1056/NEJMoa0810177

45. Parris ES, Lawrence DB, Mohn LA, Long LB. Adherence to statin therapy and LDL cholesterol goal attainment by patients with diabetes and dyslipidemia. Diabetes Care 2005;28:595-9.
https://doi.org/10.2337/diacare.28.3.595

46. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002;288:462-7.
https://doi.org/10.1001/jama.288.4.462

47. Bijlsma MJ, Vansteelandt S, Janssen F, Hak E. The effect of adherence to statin therapy on cardiovascular mortality: quantification of unmeasured bias using falsification end-points. BMC Public Health 2016;16:303.
https://doi.org/10.1186/s12889-016-2986-0

48. Martin K, Bégaud B, Latry P, Miremont-Salamé G, Fourrier A, Moore N. Differences between clinical trials and postmarketing use. Br J ClinPharmacol 2004;57:86-92.
https://doi.org/10.1046/j.1365-2125.2003.01953.x

49. Zhang Z, Peluso MJ, Gross CP, Viscoli CM, Kernan WN. Adherence reporting in randomized controlled trials. Clin Trials 2014;11:195-204.
https://doi.org/10.1177/1740774513512565