Effect of statins type on incident prostate cancer risk: a meta-analysis and systematic review

Ping Tan, Chen Zhang, Shi-You Wei, Zhuang Tang, Liang Gao, Lu Yang, Qiang Wei

The aim of this study is to investigate the effect of statins type or even when grouping statins by hydrophilic or hydrophobic nature on prostate cancer risk. A literature search was performed without language restrictions using the databases of PubMed (1984.1–2015.3), MEDLINE (1984.1–2015.3), and EMBASE (1990.1–2015.3). Two independent reviewers appraised eligible studies and extracted data. Weighted averages were reported as relative risk (RR) with 95% confidence intervals (CI). Statistic heterogeneity scores were assessed with the standard Cochran's Q-test and I² statistic. Publication bias was detected using the Begg's and Egger's tests. All statistical analyses were conducted by STATA version 10. Finally, fourteen studies were included in the meta-analysis. Both hydrophilic and hydrophobic statins showed no association with incidence of prostate cancer (RR = 1.00, 95% CI: 0.82–1.17; RR = 0.90, 95% CI: 0.73–1.08, respectively). Meanwhile, the risk of prostate cancer was not reduced in simvastatin (RR = 0.89, 95% CI: 0.72–1.05), pravastatin (RR = 1.02, 95% CI: 0.94–1.11), atorvastatin (RR = 0.89, 95% CI: 0.76–1.02), fluvastatin (RR = 0.99, 95% CI: 0.97–1.01), or lovastatin users (RR = 0.94, 95% CI: 0.79–1.08). The funnel plot showed that there was no publication bias. The results showed that statins had a neutral effect on prostate cancer risk; hydrophilic and hydrophobic statins as well as any subtype of statins did not affect the risk of prostate cancer.

Asian Journal of Andrology (2017) 19, 666–671; doi: 10.4103/1008-682X.190327; published online: 2 December 2016

Keywords: meta-analysis; prostate cancer; statins type; systematic review

INTRODUCTION

Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitor, are widely used to lower the cholesterol levels. Prostate cancer (PCa) is the most common solid tumor in men from western countries and the second leading cause of death, while in China, it is the sixth common solid cancer and the tenth leading cause of death. Recently, a climbing amount of evidence on the anticancer effects of statins has become available. Although some studies found that statins had a neutral effect on PCa and PCa death risk, the other studies showed that statins lowered the risk of prostate cancer. In addition, some trials showed that the long-latency positive effects remained possible while some studies found a neutral effect of long-term statins use on PCa risk. All relevant meta-analyses found that statins could lower the risk of advanced prostate cancer. However, whether statins type also contributed to the inconformity of results and affected the statins’ effect on PCa risk remained unknown. Thus, it is necessary to conduct a systematic review and meta-analysis to comprehensively evaluate the association between commonly used types of statins and PCa risk.

METHODS

Study selection

We performed a literature search without language restrictions using the databases of PubMed (1984.1–2015.3), MEDLINE (1984.1–2015.3), EMBASE (1990.1–2015.3), the Cochrane Library, Web of Science, and ClinicalTrials.gov to identify clinical trials of statins use with a primary or secondary endpoint of PCa diagnosis or PCa death. A search strategy using the Medical Subject Heading and text keywords “statins”, “HMG-CoA reductase inhibitor”, “atorvastatin”, “cerivastatin”, “fluvastatin”, “lovastatin”, “mevastatin”, “pravastatin”, “rivastatin”, “rosuvastatin”, “simvastatin”, “cancer(s)”, “carcinoma(s)”, “neoplasm(s)”, “tumour(s)”, and “malignancy(ies)” was used. The search strategy was adjusted to adapt different databases. A manual search of abstracts published after 1990 at the American Heart Association, the American College of Cardiology, the American Society of Clinical Oncologists, the American Urological Association, and the American Society of Hematology was conducted. In addition, we conducted a manual search in published articles to identify the additional relevant studies. After removing duplicate publications, two reviewers (Ping Tan and Shi-You Wei) independently assessed all the remaining results by checking titles and abstracts. Studies investigating the association between statins and PCa were considered for further full-text assessment. We adapted a PRISMA flowchart to depict the study selection.

Inclusion and exclusion criteria

Included studies focused on men of all ages without PCa before using statins. The inclusion criteria including (1) clearly defined exposure.
to statins; (2) statins' types were available; (3) incidence of PCa as the one interested outcome; (4) hazard ratio (HR), relative risk (RR), or odds ratio (OR) with 95% confidence intervals (CIs) or primary data for their calculation were available. All randomized controlled trials (RCTs), cohort studies, and case–control studies with both full-text articles and abstracts associated with the topic were considered to be eligible. Letters to the editor, comments, editorials, case reports, and animal studies were excluded. When studies reported outcomes from similar or overlapping databases or cohorts, only data from the most recent publication were included. Studies that were not published in the English language were also excluded. The primary outcome is to evaluate the effect of different statins types on PCa risk.

Quality assessment
Two reviewers (Ping Tan and Shi-You Wei) independently used the Newcastle–Ottawa Scale (NOS) to assess the quality of the observational studies included (cohort and case–control studies). NOS comprises three parts (selection, comparability, and exposure for case–control studies or outcome for cohort studies) and scores of 4, 2, and 3 are assigned for these three parts, respectively. Studies with scores of 0–3, 4–6, and 7–9 were considered as low, moderate, and high quality, respectively. The quality assessment of RCTs was conducted using the modified Jadad scale, which gave the following scores: generation of the allocation sequence (2), concealment of allocation (2), blinding (2), and incomplete outcome data (1). Scores of 1–3 indicate low quality and 4–7 indicate high quality.

Data extraction and analysis
Data from each study were independently extracted by the two reviewers. Hydrophilic statins included pravastatin, rosuvastatin, atorvastatin, and fluvastatin; hydrophobic statins included lovastatin and simvastatin. RR effect estimates with their 95% CIs were used to assess potential association between statins type and PCa risk, as HR and OR were broadly equivalent to RR when disease incidence was low. Statistic heterogeneity scores were assessed with the standard Cochrane’s Q-test with a significance level of $\alpha = 0.10$. $I^2$ statistic was also used to quantify inconsistency across studies to assess the impact of meta-analysis heterogeneity. $I^2 > 50\%$ indicates a considerable level of heterogeneity. When a significant heterogeneity was observed, random-effect model was used, otherwise the fixed-effect model was accepted. Publication bias was detected using the Begg’s and Egger’s tests. Statistical significance was determined using the two-tailed test where $P < 0.05$ was considered statistically significant. All statistical analyses were conducted by STATA version 10 (Stata Corporation, College Station, TX, USA).

RESULTS
Our initial search yielded 8633 citations. After employing exclusion criteria, 19 studies were remained in the meta-analysis (Figure 1). PCa patients were confirmed by positive prostate biopsy during the follow-up. A total of 104,707 PCa patients were included in the analysis as well as more than 1.6 million subjects. Table 1 and 2 show the characteristics of the studies included. Three studies revealed an inverse association between hydrophilic statins and PCa risk while only one found a lowered risk of PCa among hydrophilic users. Different effect on incident PCa risk between hydrophilic and hydrophobic statins was observed by five trials. Different effect on incident PCa risk between hydrophilic and hydrophobic statins was observed in five trials. The effect of simvastatin, lovastatin, atorvastatin, fluvastatin, and pravastatin on PCa risk was available for meta-analysis. The definitions of statins users and duration of statins use were various among studies (Table 1 and 2).

In this meta-analysis, we found that there was no obvious evidence supporting that hydrophilic or hydrophobic statins could reduce the incidence risk of PCa (RR $= 1.00$, 95% CI: 0.82–1.17; RR $= 0.90$, 95% CI: 0.73–1.08, respectively) (Figure 2 and 3). High heterogeneities existed among studies evaluating hydrophilic and hydrophobic statins ($I^2 = 68.8\%$, $P = 0.001$, and $I^2 = 94.9\%$, $P < 0.001$, respectively). Then, subgroup analyses were performed on the basis of the study design. The pooled results of four cohort studies and three RCTs both showed that hydrophilic statins had a neutral effect on PCa risk. However, a positive impact on PCa risk was observed in the result of three case–control studies (HR $= 0.95$, 95% CI: 0.92–0.99). In terms of hydrophilic statins, results of both cohort studies and case–control studies as well as RCTs showed a neutral effect on PCa incidence. However, high heterogeneities still existed among cohort studies. The details are shown in Table 3.

Five commonly used statins’ brands were evaluated in subgroups; however, no statistically significant effect was seen in simvastatin (RR $= 0.89$, 95% CI: 0.72–1.05) (Figure 4), pravastatin (RR $= 1.02$, 95% CI: 0.94–1.11) (Figure 5), atorvastatin (RR $= 0.89$, 95% CI: 0.76–1.02), fluvastatin (RR $= 0.99$, 95% CI: 0.97–1.01), or lovastatin users (RR $= 0.94$, 95% CI: 0.79–1.08) (Table 3). As results shown in Table 3, simvastatin and atorvastatin as well as fluvastatin had a neutral effect on PCa incidence risk in all subgroups. A benefit impact of lovastatin on PCa risk was observed in result of two cohort studies while a neutral effect was found in pooled outcome of two case–control studies. In terms of pravastatin, it did not affect PCa risk in pooled result of three cohort studies or the two RCTs while a negative effect of pravastatin was observed in the result of two case–control studies.

Studies of low quality, such as Coogan et al. have been further excluded in subgroup analyses to confirm their effect on results. However, the results remained stable and presented the same trend as before (data was not shown).

Funnel plot showed that there were no publication bias among studies exploring the effect of hydrophilic or hydrophobic statins on PCa risk (Begg’s $P = 1.0$, Egger’s $P = 0.98$; and Begg’s $P = 0.59$, Egger’s $P = 0.53$, respectively; Figure 6). Sensitivity analysis results remained stable and no significant variability was found (data not shown).
DISCUSSION

To our knowledge, this is the first meta-analysis analyzing the effect of statins' types and brands on PCa incidence. In the past decade, the role of statins in the development of PCa has been increasingly discussed; however, their effect is controversial.4–7,32 In this meta-analysis, hydrophilic and hydrophobic statins as well as any subtype of statin did not affect the risk of PCa. Although a small benefit of lovastatin to PCa was found in synthesis of two cohort studies, this effect was untrusted because of few studies and the reverse result in case–control studies. Similarly, pravastatin's adverse effect on PCa risk could not be confirmed either.

Table 2: Characteristics of case–control studies included in the meta-analysis

| Sources                  | Country | Participants (n) | Statin users (n) | Statin users (n)/cases (n)* | Statin users (n)/controls (n) | Statin type | Mean follow-up time (year) | Duration of follow-up (year) | Quality score |
|--------------------------|---------|-----------------|-----------------|----------------------------|----------------------------|-------------|--------------------------|-----------------------------|---------------|
| Jespersen et al.         | Denmark | 254 880         | 47 299          | 7125/41 690                 | 35 485/208 501              | a, b        | NR                       | 13 (1997–2010)               | 7              |
| Vinogradova et al.       | UK      | 76 617          | 13 858          | 2774/14 764                 | 15 473/53 557              | c, d, g     | 10 (1998.1–2008.7)        | 7              |
| Coogan et al.            | USA     | 3374            | 526             | 250/1367                    | 178/2007                   | a, b        | NR                       | 16 (1992–2008)               | 3              |
| Agalliu et al.           | USA     | 1943            | 554             | 272/1007                    | 244/942                    | a, b        | NR                       | 4 (2001.2–2005.12)           | 5              |
| Murtola et al.           | Finland | 49 446          | 5061            | 2622/24 723                 | 2439/24 723                | c, d, e, f, g | NR                       | 7 (1995–2002)               | 6              |
| Shannon et al.           | USA     | 302             | 133             | 34/100                      | 99/202                     | c, f        | NR                       | 7 (1997–2004)               | 4              |

*Prostate cancer cases. a: hydrophilic; b: hydrophobic; c: simvastatin; d: atorvastatin; e: fluvastatin; f: lovastatin; g: pravastatin; RCT: randomized controlled trial; PCa: prostate cancer; NR: not reported

Figure 2: The effect of hydrophilic statins on incident prostate cancer risk. RR: relative risk; CI: confidence interval; RCT: randomized controlled trial.

| Study ID | RR (95%CI) | % Weight |
|----------|------------|----------|
| Cohort   |            |          |
| Boudreau et al. | 0.67 (0.33, 1.34) | 7.69     |
| Murtola et al. | 0.70 (0.56, 0.97) | 17.75    |
| Lustman et al. | 0.63 (0.36, 1.09) | 4.05     |
| Nordstrom et al. | 1.38 (1.16, 1.64) | 14.88    |
| Subtotal (I² = 88.7%, P=0.000) | 0.92 (0.48, 1.86) | 44.24    |
| Case-control |            |          |
| Agalliu et al. | 0.91 (0.38, 2.18) | 19.44    |
| Coogan et al. | 1.23 (0.99, 2.00) | 3.88     |
| Jespersen et al. | 0.95 (0.86, 1.04) | 32.51    |
| Subtotal (I² = 0.0%, P=0.919) |          |          |
| RCT      |            |          |
| The LIPID Study Group | 1.02 (0.81, 1.27) | 15.20    |
| Serruya et al. | 0.69 (0.38, 1.10) | 23.52    |
| Ford et al. | 1.56 (0.94, 2.68) | 7.73     |
| Subtotal (I² = 32.6%, P=0.226) | 1.18 (0.59, 2.48) | 23.25    |
| Overall (I² = 58.8%, P=0.001) | 1.00 (0.82, 1.17) | 100.00    |

| Study ID | RR (95%CI) | % Weight |
|----------|------------|----------|
| Cohort   |            |          |
| Boudreau et al. | 0.79 (0.69, 0.94) | 10.79    |
| Murtola et al. | 0.85 (0.68, 1.06) | 10.28    |
| Lustman et al. | 0.42 (0.35, 0.50) | 11.34    |
| Nordstrom et al. | 1.07 (0.85, 1.32) | 10.94    |
| Subtotal (I² = 95.9%, P=0.000) | 0.78 (0.45, 1.11) | 43.33    |
| Case-control |            |          |
| Agalliu et al. | 1.02 (0.63, 1.27) | 9.80     |
| Coogan et al. | 1.10 (0.60, 1.85) | 8.65     |
| Jespersen et al. | 0.95 (0.62, 0.99) | 11.53    |
| Subtotal (I² = 0.0%, P=0.921) | 0.85 (0.92, 0.99) | 29.88    |
| RCT      |            |          |
| Downs et al. | 1.01 (0.78, 1.31) | 9.18     |
| Strandberg et al. | 0.92 (0.82, 1.14) | 7.88     |
| HPSC Group | 1.00 (0.80, 1.26) | 9.05     |
| Subtotal (I² = 0.0%, P=9.15) | 0.89 (0.63, 1.44) | 26.68    |
| Overall (I² = 94.9%, P=0.000) | 0.90 (0.73, 1.08) | 100.00   |

Figure 3: The effect of hydrophilic statins on incident prostate cancer risk. RR: relative risk; CI: confidence interval; RCT: randomized controlled trial.

High heterogeneities were observed in the overall analyses. Then, subgroup analyses were conducted on the basis of the study design. The heterogeneities were lowered in some subgroups, which suggested that the study design and statins type might contribute to them. In addition, duration of statins use and various definition of statin users might also affect the heterogeneities.
Effect of statins type on incident prostate cancer risk
P Tan et al

Previous research demonstrated that statins had ability to kill PCa cells through inhibiting HMG-CoA reductase, causing a pronounced reduction in serum cholesterol and may lead to a decreased formation of lipid rafts and promote cancer cell apoptosis.\(^{33}\) Meanwhile, statins, via inhibiting lipid raft signaling, inflammation, inducing cell cycle arrest and apoptosis, and anti-angiogenesis, performed an effect on prostate tumorigenesis.\(^{34–36}\) Moreover, simvastatin, lovastatin, and fluvastatin had shown to inhibit PCa cell proliferation,\(^{37}\) through downregulating the insulin-like growth factor 1 receptor.\(^{38}\) One previous study has suggested that lipophilic statins have greater lipid solubility and more readily permeate cell membranes to exert potential anticancer effects,\(^{39–41}\) but this was not evident in our study. Meanwhile, as lipophilic agents were limited in available trials, the pooled estimates of previous meta-analyses may have been diluted. In addition, another trial thought that hydrophilic statins, with their impaired ability to penetrate biological membranes, might perform better than lipophilic statins which readily entered cells. But this difference was not observed in our study.\(^{42}\)

Table 3: The pooled estimates of meta-analysis in subgroups

| Outcomes       | Studies (n) | Pooled estimates | I\(^2\) statistic (P) | RR   | 95% CI     |
|----------------|-------------|------------------|-----------------------|------|------------|
| Hydrophobic    |             |                  |                       |      |            |
| Total          | 10          | 0.90             | 0.73–1.08             | <0.001 |            |
| Cohort studies | 4           | 0.78             | 0.45–1.11             | <0.001 |            |
| Case-control studies | 3     | 0.95             | 0.92–0.99             | 0.521 |            |
| RCT            | 3           | 0.99             | 0.83–1.14             | 0.915 |            |
| Hydrophilic    |             |                  |                       |      |            |
| Total          | 10          | 1.00             | 0.82–1.17             | 0.001 |            |
| Cohort studies | 4           | 0.92             | 0.48–1.36             | <0.001 |            |
| Case-control studies | 3     | 0.95             | 0.86–1.04             | 0.919 |            |
| RCT            | 3           | 1.18             | 0.82–1.54             | 0.226 |            |
| Atorvastatin   |             |                  |                       |      |            |
| Total          | 7           | 0.89             | 0.76–1.02             | <0.001 |            |
| Cohort studies | 5           | 0.82             | 0.60–1.04             | <0.001 |            |
| Case-control studies | 2     | 1.03             | 0.93–1.13             | 0.181 |            |
| Fluvastatin    |             |                  |                       |      |            |
| Total          | 6           | 0.99             | 0.97–1.01             | 0.953 |            |
| Cohort studies | 4           | 0.99             | 0.97–1.01             | 0.775 |            |
| Lovastatin     |             |                  |                       |      |            |
| Total          | 5           | 0.94             | 0.79–1.08             | 0.008 |            |
| Cohort studies | 2           | 0.94             | 0.93–0.96             | 0.362 |            |
| Case-control studies | 2     | 0.73             | 0.05–1.42             | 0.001 |            |
| Pravastatin    |             |                  |                       |      |            |
| Total          | 7           | 1.02             | 0.94–1.11             | 0.086 |            |
| Cohort studies | 3           | 0.96             | 0.87–1.05             | 0.220 |            |
| Case-control studies | 2     | 1.14             | 1.01–1.26             | 0.774 |            |
| RCT            | 2           | 1.19             | 0.77–1.60             | 0.108 |            |
| Simvastatin    |             |                  |                       |      |            |
| Total          | 10          | 0.89             | 0.72–1.05             | <0.001 |            |
| Cohort studies | 5           | 0.86             | 0.58–1.14             | <0.001 |            |
| Case-control studies | 3     | 0.96             | 0.80–1.11             | 0.005 |            |
| RCT            | 2           | 0.98             | 0.78–1.17             | 0.711 |            |

RR: relative risk; CI: confidence interval; RCT: randomized controlled trial.

Statins use could lower the risk of PCa compared with nonusers in some previous studies.\(^{6,10,11,43,44}\) However, some other studies found that there was no association between statins and PCa risk.\(^{5,7,20,43–49}\) Previous studies reported that this inconsistence might be attributed to prostate-specific antigen (PSA) testing, causing the detection bias, and statins dosage.\(^{12,30}\) Comparing with duration of statins use, statins dosage or cumulative amount of statins use might perform a stronger relation to PCa risk, as the drug usage was irregular with months of nonuse between periods of use.\(^{5,12}\) In addition, statins dosage of \textit{in vitro} studies reporting growth inhibition in prostate-derived cell lines, was much higher than standard therapeutic use. Our results showed that...
Effect of statins type on incident prostate cancer risk
P Tan et al

no subtype of statin affected the risk of PCa; thus, we could believe that subtype of statin did not affect the statins’ effect on the incidence of PCa risk.

Our meta-analysis had some limitations. First, this study was limited by the small number of studies and patients that were available for analysis. Second, the study design, definition of drug exposure, and usage of statins type among included studies were diverse, which might contribute to significant heterogeneities observed in subgroups.

To minimize the confounding biases in this meta-analysis, we chose multivariable adjusted-effect estimates to pool the effects, and subgroup analyses were conducted on the basis of the study design. Furthermore, the effect of various statins type on advanced PCa was not available at the moment, thus whether statins type affected the risk of advanced PCa remained to be seen. In addition, duration of follow-up was limited in all included studies; only 2 trials were followed up over 5 years and most studies did not report mean follow-up time. Thus, whether long-term statins use could affect PCa risk was unavailable for meta-analysis. Finally, only one randomized controlled trials reporting the effect of pravastatin on PCa risk was available at present,23 lowering the precision of our results. Thus, more future studies should be randomized designed.

CONCLUSIONS
We conclude that statins had a neutral effect on the incident PCa risk, both hydrophilic and hydrophobic, and no subtype of statins affect the risk of PCa (simvastatin, atorvastatin, fluvastatin, pravastatin, and lovastatin). As most studies had relatively short follow-up, it will be important for future studies to explore long-latency effects of statins on PCa and to rule out their effects on incident advanced PCa risk.

AUTHOR CONTRIBUTIONS
QW, LY, and PT conceived this review. PT, CZ, and SYW identified reports of trials and extracted data. LG provided statistical advice and CZ did all statistical analyses. ZT checked for statistical inconsistency and interpreted data. LY, PT, and CZ contributed to data interpretation. PT drafted the report and all other authors (QW, LY, CZ, SYW, ZT, and LG) critically reviewed the article. All authors read and approved the final manuscript.

COMPETING INTERESTS
The authors declared no competing interests.

ACKNOWLEDGMENTS
This study was supported by the National Natural Science Foundation of China (Grant no. 81308855, 81200551, and 81300627), the Prostate Cancer Foundation Young Investigator Award 2013 and Foundation of Science and Technology Department of Sichuan Province (Grant no. 2013SZ0006 and 2015SZ0230). The funders had no role in study selection, data extraction, analysis or interpretation, writing of this article, or the decision to publish.

REFERENCES
1 National Cancer Institute. SEER Stat Fact Sheets: Prostate. Available from: http://www.seer.cancer.gov/statfacts/html/prost.html. [Last accessed on 2015 Apr 25].
2 Center MM, Jamal A, Lortet-Tieulent J, Ward E, Ferlay J, et al. International variation in prostate cancer incidence and mortality rates. Eur J Cancer 2012; 48: 2370–9.
3 He J, Chen WQ. Chinese Cancer Registry Annual Report 2012 by National Cancer Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, et al. SEER Stat Fact Sheets: Prostate. Available from: http://www.seer.cancer.gov/statfacts/html/prost.html. [Last accessed on 2015 Apr 25].
4 Browning DR, Martin RM. Statins and risk of cancer: a systematic review and meta-analysis. Int J Cancer 2007; 120: 833–43.
5 Dale KM, Coleman CI, Herlyn NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA 2006; 295: 74–80.
6 Bansal D, Undela K, D’Cruz S,Schifano F. Statin use and risk of prostate cancer: a meta-analysis of observational studies. PLoS One 2012; 7: e46691.
7 Bonovas S, Filoussi K, Sitaras NM. Statin use and the risk of prostate cancer: a metaanalysis of 6 randomized clinical trials and 13 observational studies. Int J Cancer 2008; 123: 899–904.
8 Park HS, Schoenfeld JD, Mailhot RB, Shive M, Hartman RL, et al. Statins and prostate cancer recurrence following radical prostatectomy or radiotherapy: a systematic review and meta-analysis. Ann Oncol 2013; 24: 1427–34.
9 Nordström T, Clements M, Karlsson R, Adolfsson J, Grönhögl. The risk of prostate cancer for men on aspirin, statin or anti-diabetic medications. Eur J Cancer 2015; 51: 725–33.
10 Lustman A, Nakar S, Cohen AD, Vinker S. Statin use and incident prostate cancer risk: does the statin brand matter? A population-based cohort study. Prostate Cancer Prost atic Dis 2013; 17: 6–9.
11 Jespersen CG, Norgaard M, Friis S, Skriver C, Børre M. Statin use and risk of prostate cancer: a Danish population-based case-control study, 1997–2010. Cancer Epidemiol Biomarkers Prev 2013; 38: 42–7.
12 Murtola TJ, Tammela TL, Maatianen L, Huhtala H, Platz EA, et al. Prostate cancer and PSA among statin users in the Finnish prostate cancer screening trial. Int J Cancer 2010; 127: 1650–9.
13 Boudreau DM, Yu O, Buist DS, Miglioretti DL. Statin use and prostate cancer risk in a large population-based setting. Cancer Causes Control 2008; 19: 767–74.
14 Deeks JJ, Dines J, D’Amico R, Rowden AJ, Sakarovitch C, et al. Evaluating non-randomised intervention studies. Health Technol Assess 2003; 7: 186.
15 Simon SD. Statistical evidence in medical trials: what do the data really tell us? New York: Oxford University Press, 2006. p. 122.
16 Sprancne SL, Reid JE, Grace M, Samore M. Hazard ratio in clinical trials. Antimicrob Agents Chemother 2004; 48: 2787–92.
17 de Lemos ML. How to survive the survival plots. Lancet 2002; 360: 954.
18 Coogan PF, Kelly JP, Strom BL, Rosenberg L. Statin and NSAID use and prostate cancer risk. Pharmacoeconomic Drug Saf 2010; 19: 752–5.
19 Aguiló I, Salinas CA, Harsten PD, Ostrandt EA, Stanford JL. Statin use and risk of prostate cancer: results from a population-based epidemiologic study. Am J Epidemiol 2008; 168: 250–60.
20 Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, 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: 1613–22.
21 The LIPI D Study Group. Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPI D trial follow-up. Lancet 2002; 359: 1379–87.
22 Serruys PW, de Feyter P, Macaca Y, Kokott N, Puel J, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA 2002; 287: 3215–22.
23 Strandberg TE, Pyorala K, Cook TJ, Wilhelmsen L, Faergeman O, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). Lancet 2004; 364: 711–7.
24 HPSC Group. The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: a randomised placebo-controlled trial (ISRCTN48489393). BMC Med 2005; 3: 6.
25 Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, et al. Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med 2007; 357: 1477–86.
26 Fowle JM, Motley SS, Barocas DA, Cookson MS, Concepcion R, et al. The associations between statin use and prostate cancer screening, prostate size, high-grade prostate intraepithelial neoplasia (PIN), and prostate cancer. Cancer Causes Control 2011; 22: 417–26.
27 Haukka J, Sankila R, Klaukka T, Lonnoqvist J, Niikanen L, et al. Incidence of cancer and statin usage-record linkage study. Int J Cancer 2010; 126: 279–84.
28 Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QRResearch database. BMJ 2010; 340: c2197.
29 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.
30 Murtola TJ, Tammela TL, Lahtela J, Auxiniam A. Cholesterol-lowering drugs and prostate cancer risk: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2007; 16: 2226–32.
31 Shannon J, Tweedores S, Garzotto M, Beer TM, Derenick R, et al. Statins and prostate cancer risk: a case-control study. Am J Epidemiol 2005; 162: 318–25.
32 Kuppaia J, Lamminpia A, Pukkela E, Statins and cancer: a systematic review and meta-analysis. Eur J Cancer 2008; 44: 2122–32.
33 Papadopoulos G, Delakas D, Nakopoulou L, Kassimatis T, Statins and prostate cancer: molecular and cellular aspects. Eur J Cancer 2011; 47: 819–30.
34 Konstantinoupolos PA, Karamovzis MV, Pavapasiosilou AG. Post-translational modifications and regulation of the RAS superfamily of GTPases as anticancer targets. Nat Rev Drug Discov 2007; 6: 541–55.
35 Zhuang L, Kim J, Adam RM, Solomon KR, Freeman MR. Cholesterol targeting alters lipid raft composition and cell survival in prostate cancer cells and xenografts. J Clin Invest 2005; 115: 959–68.
[36] Vainio P, Lehtinen L, Mirtti T, Hilvo M, Seppanen-Laakso T, et al. Phospholipase PLA2G7, associated with aggressive prostate cancer, promotes prostate cancer cell migration and invasion and is inhibited by statins. *Oncotarget* 2011; 2: 1176–90.

[37] Sivaprasad U, Abbas T, Dutta A. Differential efficacy of 3-hydroxy-3-methylglutaryl CoA reductase inhibitors on the cell cycle of prostate cancer cells. *Mol Cancer Ther* 2006; 5: 2310–6.

[38] Sekine Y, Furuya Y, Nishii M, Koike H, Matsu H, et al. Simvastatin inhibits the proliferation of human prostate cancer PC-3 cells via down-regulation of the insulin-like growth factor 1 receptor. *Biochem Biophys Res Commun* 2008; 372: 356–61.

[39] Hamelin BA, Turgeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. *Trends Pharmacol Sci* 1998; 19: 26–37.

[40] Prowell TM, Stearns V, Trock B. Lipophilic statins merit additional study for breast cancer chemoprevention. *J Clin Oncol* 2006; 24: 2128–9; author reply 2129.

[41] Shibata MA, Ito Y, Morimoto J, Otsuki Y. Lovastatin inhibits tumor growth and lung metastasis in mouse mammary carcinoma model: a p53-independent mitochondrial-mediated apoptotic mechanism. *Carcinogenesis* 2004; 25: 1887–98.

[42] Watanabe M, Koike H, Ishibashi T, Okada T, Sui S, et al. Synthesis and biological activity of methanesulfonamide pyrimidine- and N-methanesulfonyl pyrrole-substituted 3,5-dihydroxy-6-heptenoates, a novel series of HMG-CoA reductase inhibitors. *Bioorg Med Chem* 1997; 5: 437–44.

[43] Chen-Pin W, Javier H, Lorenzo C, Downs JR, Thompson IM, et al. Statins and finasteride use differentially modify the impact of metformin on prostate cancer incidence in men with type 2 diabetes. *Ann Transl Med Epidemiol* 2014; 1: pui1004.

[44] Bush DM, Lorenzo C, Hernandez J, Wang CP. Statin use as a moderator of metformin effect on risk for prostate cancer among type 2 diabetic patients. *Diabetes Care* 2012; 35: 1002–7.

[45] Olivan M, Rigau M, Colas E, Garcia M, Montes M, et al. Simultaneous treatment with statins and aspirin reduces the risk of prostate cancer detection and tumorigenic properties in prostate cancer cell lines. *Biomed Res Int* 2015; 2015: 762178.

[46] Morote J, Celia A, Planas J, Placer J, de Torres I, et al. Role of serum cholesterol and statin use in the risk of prostate cancer detection and tumor aggressiveness. *Int J Mol Sci* 2014; 15: 13615–23.

[47] Platz EA, Tangen CM, Goodman PJ, Till C, Parnes HL, et al. Statin drug use is not associated with prostate cancer risk in men who are regularly screened. *J Urol* 2014; 192: 379–84.

[48] 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.

[49] Freedland SJ, Hamilton RJ, Gerber L, Banez LL, Moreira DM, et al. Statin use and risk of prostate cancer and high-grade prostate cancer: results from the REDUCE study. *Prostate Cancer Prostatic Dis* 2013; 16: 254–9.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

©The Author(s) (2017)