Editorial

Statins - the Holy Grail for cancer?

Preet Paul Singh[1*], Siddharth Singh[2*]

[1]Department of Medical Oncology and [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

*Both authors contributed equally to drafting the manuscript.

Corresponding to: Preet Paul Singh, M.D. Department of Medical Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA. Email: singh.preetpaul@mayo.edu.

Submitted Nov 08, 2012. Accepted for publication Dec 13, 2012.
doi: 10.3978/j.issn.2305-5839.2012.12.02
Scan to your mobile device or view this article at: http://www.atmjournal.org/article/view/1330/1822

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have been used for primary and secondary prevention of cardiovascular diseases and currently are the most commonly prescribed drug class in the world. Besides cholesterol reduction, pre-clinical studies have shown that statins may exert antineoplastic effects, through both HMG-CoA reductase-dependent and HMG-CoA reductase-independent pathways. By competitive inhibition of HMG-CoA reductase, statins prevent post-translational prenylation of the Ras/Rho superfamily, which are important mediators of cell growth, differentiation and survival (1). In addition, statins exert proapoptotic, antiangiogenic, and immunomodulatory effects, which may prevent cancer growth (1,2). Indeed, several observational studies and meta-analyses have shown that statin use may be associated with reduced risk of prostate cancer (3), hepatocellular cancer (4) and esophageal cancer (5) but not others (6,7). More recently, there has been greater interest in the potential role of statins in modifying cancer outcomes and mortality. Early data from post-hoc individual patient data meta-analysis of randomized controlled trials (RCTs) of statins for cardiovascular outcomes has not shown reduction in the risk of cancer mortality with statin use, but these studies are limited by short follow-up and insufficient power to detect a significant difference in cancer outcomes between placebo and statin group (8).

In the November issue of the *New England Journal of Medicine*, Nielsen *et al.* (9) studied the relationship between statin use (prior to cancer diagnosis) and cancer-related mortality in the entire Danish population from 1995-2009 in adults >40 years of age. Through record linkage between the Danish Registry of Medicinal Products Statistics (which records information on all drugs dispensed from Danish pharmacies), the Danish Cancer Registry (which tracks data on 98% of all incident cancers in Denmark) and the Danish Register of Causes of Death, in 1,072,503 person-years of follow-up on 295,925 patients with incident cancer, they observed 195,594 deaths, of which 162,067 were cancer-related. As compared to statins non-users, patients using statins prior to cancer diagnosis were 15% less likely to die from any cause [adjusted hazard ratio (HR), 0.85; 95% CI, 0.83-0.87] or cancer specifically (adjusted HR, 0.85; 95% CI, 0.82-0.87). On evaluating risk of mortality from 27 individual cancers comparing 18,721 statin users and 277,204 statin non-users, they observed improved survival with statin exposure for 13 cancers, including the 4 most common cancers - lung (adjusted HR, 0.87; 95% CI, 0.83-0.92), colorectal (adjusted HR, 0.79; 95% CI, 0.75-0.85), prostate (adjusted HR, 0.81; 95% CI, 0.75-0.88) and breast (adjusted HR, 0.88; 95% CI, 0.80-0.99). The hazard ratios for cancer death in statin users ranged from 0.64 (95% CI, 0.46 to 0.88) for cervical cancer to 0.89 (95% CI, 0.81 to 0.98) for pancreatic cancer. These results were stable across a nested 1:3 matched case-control study of statin users *vs.* statin non-users with matching for sex, age at cancer diagnosis, cancer type and year of diagnosis to adjust for the evolving cancer treatments and increasing use of statins over the follow up period. Their robust study design adjusted for multiple confounding factors including age at diagnosis, sex, level of education, residential area, cancer stage, presence of cardiovascular disease or diabetes before cancer diagnosis and whether they received chemotherapy and/or radiotherapy. They also accounted for probability of prescribing statins through propensity score analysis.

Despite the comprehensive nature of the analysis and well thought out adjustments for confounding factors, several important limitations remain. Firstly, no data was available on smoking that affects cancer incidence and related mortality. Conceivably patients may stop smoking after starting statin for a recent acute myocardial infarction, which may favorably modify the relationship between statin use and mortality from smoking-related cancers. Secondly, the healthy user effect and the healthy adherer effect needs to be considered while interpreting the results of this study. Statin users are more likely to be health-conscious and be more compliant with cancer screening leading to early cancer detection and treatment, translating into improved survival. This may partially be addressed by the study adjusting for cancer stage (tumor size and spread to the lymphatic system), but as nearly one-third of the patients in the statin use group and three-quarters of the no-statin use group had missing data pertaining to tumor size and lymphatic spread, residual confounding cannot be excluded. Also, no data is provided in terms of incident cancers or mode of cancer diagnosis - it is plausible that more cancers in the statin users were detected on screening exams in asymptomatic individuals. Besides early diagnosis, statin use prior to cancer diagnosis may also reduce the risk of cancer metastases. In an *in vitro* study, Brown and colleagues observed that lipophilic statin use reduced the formation and spread of metastatic prostate colonies (10). This reduction in the risk of cancer metastases has also been observed with aspirin use, and has been implicated in the early reduction in cancer deaths observed in trials of daily aspirin versus control (11).

Thirdly, the study does not take into account the potential for concomitant use of other drugs with known anti-proliferative activity and anti-neoplastic potential. Statin users in the study had a significantly higher proportion of patients with cardiovascular disease (70% *vs.* 21%, P<0.001) and diabetes mellitus (18% *vs.* 3%, P<0.001) and conceivably would have a disproportionately higher use of aspirin or metformin that could have led to significant confounding. Aspirin as well as anti-diabetic medications like metformin use has been associated with reduced cancer-related mortality (11-14). In a post-hoc individual patient data meta-analysis of 51 RCTs, aspirin users were 15% less likely to die from cancer (OR, 0.85; 95% CI, 0.76-0.96), with a more profound effect seen with >5 years of aspirin use (OR, 0.63; 95% CI, 0.49-0.82) (15). Aspirin may inhibit cancer cell proliferation and promote apoptosis through cyclo-oxygenase 2 (COX2) mediated and COX2 independent effects (16). Likewise, metformin use may improve colorectal cancer mortality in observational studies (13), with its anti-neoplastic effects being mediated by activation of adenosine monophosphate-activated protein kinase (AMPK) and consequent inhibition of the mammalian target of rapamycin (mTOR) pathway, a downstream effector of growth factor signaling which is frequently activated in malignant cells (17). In addition, metformin may also inhibit cell growth and promote cell senescence by inhibiting cyclin D1 expression and pRb phosphorylation (18).

Additionally, while Nielsen and colleagues identified a consistent reduction in mortality across various cancer types and various sub-groups of patients, there was no clear dose-response relationship with statin use. The reduction in all-cause mortality was similar in patients with defined daily dose of statins of 0.01-0.75 (HR, 0.82; 95% CI, 0.81-0.85), 0.76-1.50 (HR, 0.87; 95% CI, 0.83-0.89) and >1.50 (HR, 0.87; 95% CI, 0.81-0.91). This partially could be accounted for by the increased cardiovascular mortality of patients who were on higher defined daily dose of statins, however, there was similar lack of gradient even for cancer-related mortality. This could be secondary to a threshold effect but based on Hill's criteria for causality, presence of a biological gradient or dose-response effect helps to strengthen a causal association. Moreover, they have not explored the potential effects of statins as adjuvant therapy after cancer diagnosis and this merits further evaluation. Lastly, as 97% of their study population was comprised of white persons of Danish descent, their results are not generalizable to other ethnic populations, especially in USA.

In conclusion, statins are being looked at as the Holy Grail for multiple non-cardiac indications including cancer. The results of this large nationwide observational study are encouraging and show that statin use is associated with reduced cancer mortality across different subgroups and cancer sites. However, there are several confounding variables which merit further evaluation and it still is a long way from changing clinical practice. Although cancer risk and mortality have been studied in secondary analyses of many RCTs to assess the efficacy of statins for cardiovascular indications (8,19,20), clinical trials evaluating cancer as primary outcome are lacking. Well-designed, prospective, randomized trials of statins with cancer incidence or mortality as the primary endpoint are needed. These must take into account various other factors that tend to cluster in statin users and may independently modify cancer risk. Certainly, focusing on high risk populations or patients with pre-existing cancer may be a first step

towards the right direction. Nonetheless, as we await data from ongoing RCTs where statins are being investigated for primary cancer prevention (NCT01500577), preventing recurrent cancer (NCT01011478) or reduced cancer mortality when combined with conventional chemotherapy for different cancers (NCT00433498 and NCT01238094), Nielsen and colleagues' notable data moves us probably another step closer to broadening recommendations for statin use. Statins as well as other commonly used and safe drugs like metformin and aspirin may cause a paradigm shift in how we approach cancer prevention and treatment in the years to come.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Demierre MF, Higgins PD, Gruber SB, et al. Statins and cancer prevention. Nat Rev Cancer 2005;5:930-42.
2. Chan KK, Oza AM, Siu LL. The statins as anticancer agents. Clin Cancer Res 2003;9:10-9.
3. 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.
4. Singh S, Singh PP, Singh AG, et al. Statins Are Associated With a Reduced Risk of Hepatocellular Cancer: A Systematic Review and Meta-analysis. Gastroenterology 2012. [Epub ahead of print].
5. Singh S, Singh AG, Singh PP, et al. Statins and the Risk of Esophageal Cancer: A Systematic Review and Meta-analysis. Am J Gastroenterol 2012;107:S11-2.
6. Bonovas S, Filioussi K, Flordellis CS, et al. Statins and the risk of colorectal cancer: a meta-analysis of 18 studies involving more than 1.5 million patients. J Clin Oncol 2007;25:3462-8.
7. Undela K, Srikanth V, Bansal D. Statin use and risk of breast cancer: a meta-analysis of observational studies. Breast Cancer Res Treat 2012;135:261-9.
8. Cholesterol Treatment Trialists' (CTT) Collaboration, Emberson JR, Kearney PM, 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.
9. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med 2012;367:1792-802.
10. Brown M, Hart C, Tawadros T, et al. The differential effects of statins on the metastatic behaviour of prostate cancer. Br J Cancer 2012;106:1689-96.
11. Rothwell PM, Wilson M, Price JF, et al. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet 2012;379:1591-601.
12. Currie CJ, Poole CD, Jenkins-Jones S, et al. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care 2012;35:299-304.
13. Garrett CR, Hassabo HM, Bhadkamkar NA, et al. Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. Br J Cancer 2012;106:1374-8.
14. Jacobs EJ, Newton CC, Gapstur SM, et al. Daily aspirin use and cancer mortality in a large US cohort. J Natl Cancer Inst 2012;104:1208-17.
15. Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 2012;379:1602-12.
16. Langley RE, Burdett S, Tierney JF, et al. Aspirin and cancer: has aspirin been overlooked as an adjuvant therapy? Br J Cancer 2011;105:1107-13.
17. Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 2001;108:1167-74.
18. Ben Sahra I, Laurent K, Loubat A, et al. The antidiabetic drug metformin exerts an antitumoral effect in vitro and in vivo through a decrease of cyclin D1 level. Oncogene 2008;27:3576-86.
19. Bonovas S, Filioussi K, Tsavaris N, et al. 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.
20. Dale KM, Coleman CI, Henyan NN, et al. Statins and cancer risk: a meta-analysis. JAMA 2006;295:74-80.

Cite this article as: Singh PP, Singh S. Statins - the Holy Grail for cancer? Ann Transl Med 2013;1(1):1. doi: 10.3978/j.issn.2305-5839.2012.12.02

