Statins reduce the risk of cancer-related mortality in cancer-diagnosed patients. A true phenomenon?

Stella Trompet[1,2,3], Anton JM de Craen[1,2], J Wouter Jukema[1,3]

[1]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; [2]Department of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands; [3]Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands

Corresponding to: Prof. J. Wouter Jukema. Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands. Email: j.w.jukema@lumc.nl.

Submitted Nov 19, 2012. Accepted for publication Dec 26, 2012.
doi: 10.3978/j.issn.2305-5839.2012.12.03
Scan to your mobile device or view this article at: http://www.atmjournal.org/article/view/1610/2287

This editorial refers to 'Statin use and reduced cancer-related mortality' by S.F. Nielsen *et al*., published in the *New England Journal of Medicine* (1).

The association between cholesterol and cancer has been studied for decades, since it is known that cholesterol is essential for cellular proliferation of cancer cells (2). In some observational studies low levels of cholesterol has been associated with an increased risk of cancer mortality, while other studies showed a reduced risk (3). However, when the association between cholesterol and cancer is studied in an observational research design, the findings may be influenced by confounding or reverse causality. We previously demonstrated in a Mendelian randomization study, that overcomes the problems of confounding and reverse causality (4), that the reported relations between low cholesterol levels and increased risk of cancer mortality is likely to be explained by reverse causality (4).

In theory, statins could have a beneficial effect on cancer incidence and mortality since cholesterol levels are lowered by statins and thus the cholesterol cannot be used for cancer proliferation. The question whether treatment with statins has a beneficial (or detrimental) effect on cancer is under debate for already a long time (5). Observational studies and randomized controlled trials assessing this association have shown contradictory results. For example, the PROSPER study, a randomized controlled trial in the elderly, found an increased risk for cancer incidence and mortality for the statin users compared to placebo users (6). However, various meta-analyses, also including the PROSPER study, did not reveal any effect of statins on cancer incidence and mortality after using statins (7,8).

Nielsen *et al*. investigated whether statin treatment in 295,925 subjects diagnosed with cancer is associated with reduced cancer-related mortality (1). They found that statin use in patients with cancer is associated with reduced all-cause mortality and cancer-related mortality with a hazard ratio of 0.85 (95% CI, 0.82-0.87). This study varies from other observational studies in that they only investigated the relation between statin use and cancer mortality in cancer patients instead of subjects free from cancer at baseline. Moreover, they convincingly showed that their finding is robust since in many additional subgroup analyses (to 'get rid of' confounding by indication) the protective effect of statins is present. However, although these additional analyses did not show different results compared to the main analysis, we are not convinced that all residual confounding is removed from the study by performing these analyses. Subjects given statin treatment are different from subjects not receiving statin treatment in various aspects. The statin users will have more cardiovascular risk factors and a higher history of cardiovascular diseases. The prognosis for cancer mortality, for example by the higher number of smokers within the statin user group, is therefore unequally balanced between the statin users and the non-users. As already mentioned by Nielsen *et al*., the only proper study design to study this association is a randomized controlled trial in which there is no imbalance in prognostic factors between users and non-users of statin treatment. Such kind of randomized controlled trial in only cancer patients has not been performed yet.

Nielsen *et al*. could have performed an additional analysis in their study to show that their results are not confounded.

For example, they could have reported the results of a similar analysis with another cardiovascular treatment, for example blood pressure lowering medication. If no effect of blood pressure medication on the risk of cancer mortality was shown, they could have argued that the unequal balance of cardiovascular risk factors had no effect on the cancer mortality outcome and that the effect found with statin treatment is not affected by confounding by indication. Since they have not done such analysis, the issue whether there is residual confounding or not remains unresolved and subscribes the need for a prospective randomized trial to settle the issue of statin therapy in cancer-diagnosed patients.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med 2012;367:1792-802.
2. Vitols S, Gahrton G, Björkholm M, et al. Hypocholesterolaemia in malignancy due to elevated low-density-lipoprotein-receptor activity in tumour cells: evidence from studies in patients with leukaemia. Lancet 1985;2:1150-4.
3. Cowan LD, O'Connell DL, Criqui MH, et al. Cancer mortality and lipid and lipoprotein levels. Lipid Research Clinics Program Mortality Follow-up Study. Am J Epidemiol 1990;131:468-82.
4. Trompet S, Jukema JW, Katan MB, et al. Apolipoprotein e genotype, plasma cholesterol, and cancer: a Mendelian randomization study. Am J Epidemiol 2009;170:1415-21.
5. Jukema JW, Cannon CP, de Craen AJ, et al. The controversies of statin therapy: weighing the evidence. J Am Coll Cardiol 2012;60:875-81.
6. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623-30.
7. 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.
8. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581-90.

Cite this article as: Trompet S, de Craen AJ, Jukema JW. Statins reduce the risk of cancer-related mortality in cancer-diagnosed patients. A true phenomenon? Ann Transl Med 2013;1(1):2. doi: 10.3978/j.issn.2305-5839.2012.12.03

