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 have 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.

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References