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# Comment on 'Statin use and all-cancer survival: prospective results from the Women's Health Initiative'

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**Sir,**

Recently, Wang *et al* (2016a) published a paper the conclusion of which was that statin treatment protects against cancer. In their response (Wang *et al*, 2017) to Mascitelli's and Goldstein's comment to their paper (Mascitelli and Goldstein, 2017), Wang *et al* refer to several large cohort studies, which apparently are in support of their own study. However, in all of these studies, including the one by Wang *et al*'s own paper, statin-treated patients have been compared with non-treated individuals. As mentioned by Mascitelli and Goldstein, this method is associated with a serious bias because many untreated individuals have lived most of their life with low cholesterol, and there is even more evidence that low cholesterol predisposes to cancer than mentioned by Mascitelli and Goldstein.

For instance, Newman and Hulley found that in almost all experiments on rodents both fibrates and statins produced cancer (Newman and Hulley, 1996), and at least nine cohort studies have found that cancer was inversely associated with cholesterol levels measured in healthy people from 10 to more than 30 years earlier (Ravnskov *et al*, 2012). Several cohort and case-control studies have also shown that cancer patients have used statin drugs significantly more often than control individuals of the same age and sex (Ravnskov *et al*, 2012). The reason may be that LDL inactivates most types of microorganisms and their toxic products (Ravnskov and McCully, 2009;2012), and viral infections are the cause of almost 20% of all cancer types (Parkin, 2006).

Furthermore, cancer was seen significantly more often in the treatment groups in several statin trials, not only in PROSPER (Shepherd *et al*, 2002), but also in CARE (Sacks *et al*, 1996) and SEAS (Rossebø *et al*, 2008). In 4S (Scandinavian Simvastatin Survival Study Group, 1994) and HPS (Heart Protection Study Collaborative Group, 2002) non-melanoma skin cancer was observed more often in the treatment groups and with statistical significance if the results in the two trials are calculated together.

Furthermore, Wang *et al.* have not adjusted their result for prior treatment with clofibrate, although cancer was an adverse effect in WHO's clofibrate trial (Oliver 2010). Nor have they updated the participants' medication continuously, which may induce another bias because a substantial number of statin-treated patients stop the treatment without informing their doctor (Jackevicius *et al*, 2002). It is noteworthy that in a nationwide study, mentioned by Wang *et al*, the lowest rate of cancer among the statin-treated patients was seen among those on the lowest statin dose (Nielsen *et al*, 2012).

Wang *et al* suggest that statins may have cancer-protective effects, but, as mentioned by Mascitelli and Goldstein, some of their effects may also increase the risk of cancer. However, as seen from the decade-long observation studies of the healthy people mentioned above (Ravnskov *et al*, 2012), the increased risk of cancer is not associated with statin treatment, but with low cholesterol. A more likely explanation is therefore that many of those without statin treatment have lived most of their life with low cholesterol and thus have had a higher risk of cancer compared with the statin-treated patients, most of whom have lived most of their life with high cholesterol.

Very few statin trials have continued for more than 5 years, and it takes many more years before exposure to a cancer-promoting factor, in this case low cholesterol, may result in clinically detectable cancer. An exception is skin cancer, because it is easily detected at an early stage, which explains the finding by Wang *et al* in their 10.5 years follow-up of postmenopausal women (Wang *et al*, 2016b), where statin use at baseline was associated with an increased risk of non-melanoma skin cancer ($P<0.002$).

The hypothesis that it is the low cholesterol and not the very statin treatment that increases the risk of cancer is supported by a Japanese study of 47 294 hypercholesterolaemic patients treated with 5–10 mg simvastatin per day (Mabuchi *et al*, 2002). Six years later the number of cancer deaths was more than three times higher in patients whose total cholesterol was $<160\ \mathrm{mg\ dl^{-1}}$ at follow-up compared with those whose cholesterol was normal or high ($P<0.001$).

## CONFLICT OF INTEREST

The author declares no conflict of interest.

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