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Editorial

# Statins – No more cream for cancer

In this issue of the *European Journal of Cancer*, Shao *et al.* and Van Rompay *et al.* [1,2] report that statins and, in the latter manuscript, also non-statin lipid-lowering medications appear to improve prostate cancer outcomes, both by retrospective analyses. This adds to the large body of epidemiological studies suggesting a favourable role for statins on the clinical outcomes of men with prostate cancer, but the precise nature of the anticancer effect of these drugs remains controversial. Retrospective studies have an inherent bias because all these men received the statin (or any other lipid-lowering drug) for a medical condition that may influence their prognosis or receiving a statin could be a surrogate for being under more 'intensive' medical care. Up to now, there are no randomized data published to confirm the favourable effect of statins in men with prostate cancer.

The metabolic status of prostate cancer is important because, even in early prostate cancer, a 'Warburg Switch' has been suggested and the consequent ongoing metabolic stress can induce a sequence of events, leading to mitochondrial mutation, gene fusion and increasing genomic disruption as the energy requirement of the cancer cells increases. Enhanced *de novo* lipogenesis in prostate cancer is well established [3] and has underpinned recent efforts to target lipogenesis clinically. However, recent data have demonstrated that extracellular fatty acids are a major contributor to intracellular lipogenesis in prostate cancer cells, supplying a major energy source [4].

The most common effect of statins and other lipid-lowering medications is to decrease serum cholesterol, low-density lipoproteins and triglyceride [5]; however, lipidomic profiling demonstrates that these drugs downregulate a wide spectrum of lipid species including sphingolipids/ceramides [6]. The routine clinical lipid panels may only be surrogates for the wider changes in lipid metabolism. A variety of biological processes have been implicated downstream of these metabolic changes including inhibition of prostate cancer inflammation, cell proliferation, angiogenesis, cell migration and invasion while promoting apoptosis [5]. That direct serum cholesterol/lipid-mediated mechanisms may be important in the anticancer effect is supported by both of the present studies. Shao *et al.* suggest that statins that are more effective in lowering triglycerides and low-density lipoprotein cholesterol have a stronger effect on reduction of prostate cancer mortality, and Van Rompay *et al.* suggest in their study that an effect on prostate cancer mortality is also seen with non-statin lipid-lowering drugs. These results have to be interpreted with caution because they are based on non-powered subgroup analysis but are certainly of interest.

Cancer is commonly considered in isolation from the rest of the body—as a parasitic growth in an otherwise normal host. But there is increasing evidence that the 'host' environment including its cellular metabolic function plays a significant role in cancer development and progression. A recent study has demonstrated that upregulation of circulating sphingolipids/ceramides across the lipidome in metastatic castration-resistant prostate cancer is associated with significantly poorer cancer survival [7]. The poor prognostic lipid signature is more likely to be due to the 'host' metabolism than a direct consequence of the cancer metabolism; however, it is also targetable by statins [6].

Essentially, statins result in effects across the human lipidome that may affect how the 'host' body responds to the cancer as well as affect lipid metabolism within the prostate cancer cells. Furthermore, the aforementioned circulating poor prognostic lipid signature is present in only 25–30% of men with metastatic castration-resistant prostate cancer (mCRPC). Consequently,

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current randomised controlled trials may be underpowered to identify an effect from statin therapy if only a proportion of men are metabolically deranged in the first place. Precision medicine may be just as important in targeting metabolic aberrations as it is in choosing the correct drug, for example, in epidermal growth factor receptor–mutant lung cancer. There may also be some prostate cancers that have already acquired early mutational changes that lead to aggressive behavior and are, therefore, not amendable to metabolic therapies alone. Epidemiological data may demonstrate effects due to the larger sample size, while the effect may be diluted in smaller randomized trials if only a proportion of the trial population is likely to benefit.

In addition to the aforementioned potential anticancer effects, statins can potentially mitigate some of the known metabolic side effects of androgen-deprivation therapy that is still a mainstay in the treatment of advanced prostate cancer.

Ultimately, only large prospective randomized trials including translational research such as planned with, for example, the PEACE-4 study will be able to solve the question if statins have a positive effect on prostate cancer outcomes and which are the subgroups of patients who profit most from such a metabolic intervention.

## Conflict of interest statement

S.G. is a member of advisory boards/Independent Data Monitoring Committee (IDMC) (compensated) of AAA International, Active Biotech AB IDMC, Astellas Pharma, Bayer, Bristol-Myers Squibb, Clovis, CureVac, Dendreon Corporation, Ferring, Innocrin Pharmaceuticals, Janssen Cilag, MaxiVAX SA, Millennium Pharmaceuticals, Orion, Roche and Sanofi Aventis Group; advisory boards (uncompensated) of Astellas Pharma, Bayer, ESSA Pharmaceuticals Corp., Nectar, ProteoMediX and Sanofi; speakers bureau (compensated) of Janssen and Novartis and speakers bureau (uncompensated) of Astellas Pharma, Janssen and Sanofi Aventis Group. Patent pending: patent application for a method for biomarker WO 2009138392 A1.

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