Primary prevention of cardiovascular disease with statins: cautionary notes

Sir,

In his informative commentary on the importance of primary prevention in reducing the burden of vascular disease, Dr Miller states that compliance problems with lifestyle changes facilitate the pharmacologic treatment with statins to achieve low-density lipoprotein (LDL) cholesterol lowering goals. It’s noteworthy that prominent thought leaders now suggest that 100 million Americans should be on statin therapy (instead of the 16 million Americans presently on statin therapy) and everyone should have a LDL cholesterol level <100 mg/dl for the primary prevention of vascular disease. However, there are potential problems with the long-term use of statins, which have been inadequately evaluated in the relatively short-term prevention trials.

It is interesting that in vitro studies have shown statins to exhibit anti-proliferative, pro-apoptotic, anti-invasive and radio-sensitization properties mediated by a statin induced reduction in mevalonate and downstream geranygeranylated proteins. These pleiotropic effects of statins might actually prevent the initiation and promotion of cancer. However, statins have other pleiotropic actions that might promote existing cancer. For example, the short-term beneficial effect of statin therapy after cardiac transplantation has been attributed to a statin induced reduction in natural killer (NK) cell cytotoxicity. However, a chronic attenuation of NK cell function will decrease the innate cell-mediated immune response to tumor cells.

It is known that statin therapy increases circulating bone marrow derived endothelial progenitor cells (EPCs) with enhanced functional activity. Although EPCs might augment the neovascularization of ischemic tissue and wounds, they might promote tumor growth by supporting angiogenesis. Not surprisingly, the levels of circulating EPCs correlate directly with the stage of invasive breast cancer, and circulating EPCs are significantly higher in stages III and IV when compared with stages I and II breast cancer patients. Likewise, circulating EPC levels are much higher in patients with aggressive compared with less aggressive non-Hodgkin’s lymphoma.

Recently, statins have been shown to increase the numbers and functionality of peripheral regulatory T-cells (Tregs), in vivo, by inducing the transcription factor forkhead box P3. Even though this unique pleiotropic effect of statins might help stabilize the atherosclerotic plaque by attenuating the effector T-cell response within the atheroma, enhanced Treg numbers and functionality might impair the host anti-tumor immune response. Additionally, Tregs have been shown to promote the induction of alternatively activated monocytes/macrophages which contribute to hampered anti-tumor immunity. Compared with normal controls, peripheral Treg numbers are increased significantly in cancer patients. In numerous solid tumor types, the accumulation of Tregs predict a reduction in patient survival, and the quantification of tumor Treg numbers identifies high-risk breast cancer patients and those at risk for late relapse. Moreover, it is possible that statin-induced Treg increases will impede cancer immunotherapies. Furthermore, statins alter interferon signaling which might potentiate the already impaired interferon signaling seen in cancer.

What is the clinical significance of the aforementioned pleiotropic effects of statins in reference to cancer promotion? Observational data suggest that overall cancer incidence is unchanged by statin therapy. Meta-analyses of large randomized statin trials in the prevention of cardiovascular disease have revealed mixed results. A recently published meta-analysis demonstrated a significant inverse relationship between achieved LDL cholesterol levels in statin trials and cancer incidence. Other meta-analyses have not shown that statin therapy increases overall cancer incidence.
However, close inspection of individual statin trials yields some disturbing trends regarding cancer promotion. The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) is the only statin trial that was specifically designed for elderly subjects. PROSPER was 3.2 years in duration and randomized subjects (mean age at entry: 75 years) with known vascular disease or risk factors for vascular disease to pravastatin or placebo. Total cancer incidence was significantly increased (P = 0.02) in those randomized to pravastatin, and the resulting increase in cancer mortality equaled in magnitude the decrease in cardiovascular mortality, leaving overall mortality unchanged. Similarly, post hoc analysis of the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, a 6-year prospective randomized trial of pravastatin vs. placebo, demonstrated an increase in cancer incidence (P = 0.012) in the elderly subgroup (aged 65–75 years) randomized to pravastatin. These data suggest that the elderly might be particularly sensitive to some of the aforementioned pleiotropic effect of statins. Elderly subjects are more likely to harbor microscopic foci of cancer cells and, furthermore, they are already relatively immunosuppressed. Perhaps, long-term statin therapy in the elderly is more likely to promote existing cancers by decreasing NK cell function, increasing peripheral Treg numbers, enhancing Treg functionality, increasing peripheral EPC numbers and altering interferon signaling.

There are data regarding statin therapy in women that are equally disturbing. Among women randomized to pravastatin (mean age: 59 years) in the Cholesterol and Recurrent Events (CARE) trial, a 5-year prospective randomized secondary prevention trial, breast cancer was significantly increased. Breast cancer occurred in 1 patient of 290 in the placebo group and 12 patients of 286 in the pravastatin group (P = 0.002) over the trial duration, and some of the cancers were recurrences. This was not reported in other prospective statin trials, but, it is of concern since there are observational data suggesting an increase in breast cancer of 28% among elderly women on statin therapy >three years. It has been recently reported that higher 3-hydroxy-3-methylglutaryl-coenzyme-A reductase (HMG-CoAR) expression in breast cancer cells, in vivo, is associated with a less aggressive phenotype. Therefore, the inhibition of HMG-CoAR by statins might increase the aggressiveness of breast cancer. Additionally, statins have been found to activate PI3K and ERK1/2 signaling pathways, which could promote the invasive growth of ductal carcinoma in situ. These data are particularly disturbing since the prevalence of microscopic breast cancer at autopsy has been reported to be 39% among women 40–49 years dying without clinically diagnosed cancer. Furthermore, among women, the propensity of statins to promote cancer might be dose related. Post hoc analysis of women (median age: 63.5 years) in the Treating to New Targets (TNT) study, a 4.9 year secondary prevention trial comparing atorvastatin 10 mg daily to 80 mg daily, was noteworthy for an increase in noncardiovascular disease death (P = 0.004), cancer death (P = 0.006) and overall death in the women randomized to atorvastatin 80 mg/day.

The increase in cancer incidence as a result of statin therapy might not become evident for more than a decade in some cancers. Follow-up of the West of Scotland Coronary Prevention Study (WOSCOPS), 10 years after the completion of the 5-year primary prevention trial of hypercholesterolemic men comparing pravastatin to placebo, revealed an increase in prostate cancer (P = 0.03) in the pravastatin group. Similar to breast cancer in women, this is of concern since autopsy data have likewise revealed a high prevalence of microscopic prostate cancer in the middle-aged men dying without a clinical history of cancer.

In conclusion, we have concerns regarding the use of statins to prevent cardiovascular disease in certain segments of the population. They include the elderly, women and those individuals with a clinical history of cancer. Primary and secondary prevention trials largely have excluded patients with a history of cancer. In real practice situations, statins are commonly used in patients with prevalent cancer. We feel this is a leap of faith, and the short- and long-term safety of these agents needs further prospective evaluation among patients with a history of cancer. It is unlikely that trends will be noticed as these drugs are routinely used in clinical practice, since the reporting of side effects of drugs is incomplete and the prevalence of cancer is large. Likewise, more prospective data need to be produced on the safety of statins in the elderly population, who are more likely susceptible to the immunosuppressive and tumor promoting effects of statins, because of their age-related immunosuppressive state and increased chance of harboring microscopic foci of cancer cells. Equally important, more prospective data are needed on the safety of statins in women, particularly regarding breast cancer promotion and high-dose statin use, in general.
Additionally, more data are needed on the safety of long-term statin therapy. Will the immunosuppressive effects of decades of statin therapy do more harm than good in those with a strong family history of malignancy? Finally, we agree with Dr Miller\(^1\) that compliance issues with lifestyle change encourage the rapid use of statins to lower LDL cholesterol in the primary prevention of cardiovascular disease. However, physicians should do as much as they can to encourage the lifestyle change to prevent cardiovascular disease and realize that those same lifestyle changes might prevent both cardiovascular disease and cancer.

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References


doi:10.1093/qjmed/hcp099

Advance Access publication 20 July 2009

**Embolic complication of Tako-Tsubo cardiomyopathy**

Sir,

We present a case of an 81-year-old female presenting with one week worsening dyspnea on exertion.