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The epidemic of nonmelanoma skin cancer and the widespread use of statins

Is there a connection?

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Abbreviations: NMSC, nonmelanoma skin cancer; NHANES, national health and nutrition examination survey; Tregs, regulatory T cells; 4S, scandinavian simvastatin survival study; HPS, heart protection study

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We hypothesize that some of the mechanisms involved in the "epidemic" of nonmelanoma skin cancer might also be due to widespread use of cholesterol lowering statin drugs.

It has recently been reported that the incidence of nonmelanoma skin cancer (NMSC) in the United States has substantially increased from 1992 through 2006 with a 4.2% yearly average increase cases.[1] Although exposure to ultraviolet radiation is an important initiating factor in skin cancer, the exact relationship between NMSC risk and nature, extent and timing of exposure remains poorly understood. An emerging important risk factor for NMSC is immunosuppression, which can justify the increase prevalence of these tumors in the elderly who are relatively immunosuppressed.[2] In fact, immunosuppressive treatments seem to act as a catalyst for skin carcinogenesis as they increase the frequency, number and aggressiveness of such tumors.[3] In a population of kidney graft recipients it has been reported an approximately 90-fold increased risk of NMSC 3 years after transplantation than the general population,[4] and an approximately 52-fold risk 10 years after transplantation than in an age and sex-adjusted general population.[5] Furthermore, in a population of heart transplant patients, whose age at transplant is older than in individuals undergoing renal transplant,[6] it has been found a very high burden of NMSC compared to general population.[6,7]

In this setting, we hypothesize that some of the mechanisms involved in this "epidemic" of NMSC might also be due to the widespread use of cholesterol lowering statin drugs. A recent analysis using National Health and Nutrition Examination Survey (NHANES) data found that only in the period 1999–2006 the use of statins significantly increased from 8.0% to 13.4% of the screened population.[8]

It is widely acknowledged that statins have immunomodulatory properties,[9] and their use has been just proposed for the prevention of pediatric graft coronary artery disease after cardiac transplantation.[10] In fact, statin drugs have been shown to modulate the immune system through coordinated activity in various arms of the immune reaction. In particular, one of the mechanisms involved in this immunosuppressive action is related to the statin-induced increase in the peripheral blood concentration of regulatory T cells (Tregs) by increasing the expression of the transcription factor, forkhead box P3.[11,12] This unique pleiotropic action of statins may be a mixed blessing among certain adult populations taking statin therapy for dyslipidemia.[13] A statin-induced increase in Tregs may be beneficial by decreasing the function of effector T cells in the atherosclerotic plaque, resulting in a more stable plaque.[14] On the contrary, an increase in Tregs may impair host anti-tumor immune response by suppressing the tumor specific effector T cell response, leading to an increased risk of cancer.[15] Indeed, in situ analysis of Tregs in cutaneous premalignant and malignant squamous lesions has demonstrated that the population of Tregs and dendritic cells

were increased in Bowen's disease and cutaneous squamous cell carcinoma compared to actinic keratosis.[16] Furthermore, Tregs infiltration was closely related with the number of infiltrating dendritic cells, and Tregs were also located in direct proximity to dendritic cells, thus suggesting that Tregs are related to cutaneous squamous tumor progression.

Data from statin trials are revealing. In the two first simvastatin trials, the Scandinavian Simvastatin Survival Study (4S),[17] and the Heart Protection Study (HPS),[18] NMSC was observed more often in the treatment groups. In the 4S, there were 13 NMSC in the statin group (0.6%), and 6 (0.3%) in the placebo group.[17] In the HPS, in simvastatin-allocated participants were diagnosed 243 NMSC (2.4%), vs. 202 (2.0%) in placebo-allocated individuals.[18] The difference is statistically significant if the results from both studies are combined (in simvastatin groups, 256 of the 12,490 participants; and in control groups, 208 of the 12,490 participants; p = 0.028). For unknown reasons, NMSC have been excluded in all reports from subsequent statin trials.

Therefore, it is plausible that the epidemic of NMSC might be related to the widespread use of statin drugs. We feel this information is important since there is a push to treat wider segments of the population with higher doses of statins.[19]

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