Statin Treatment Does Not Cause Cancer*

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In a previous issue of the Journal, Alsheikh-Ali et al. (1) reported a meta-analysis of data from large-scale randomized clinical trials of statins. In that analysis, dealing only with the statin arms of the studies, they reported that the subjects with the lowest on-treatment levels of low-density lipoprotein (LDL) cholesterol had a significantly higher risk of developing cancer than those with higher on-treatment LDL levels. Needless to say, this report occasioned some unease among patients taking statins and also among physicians (see comments by LaRosa [2], DeMaria and Ben Yehuda [3], and Kjekshus [4]). In this issue of the Journal, the same authors now publish their analysis of data from subjects in the control arms of statin trials (5). They find almost exactly the same relationship, namely, that the randomly recruited subjects who entered the studies with low LDL levels but were not treated with statins also had a significantly higher cancer risk. Moreover, the slope of the curve relating cancer risk to LDL level was almost identical to that in the statin-treated group. In other words, as the authors point out, it turns out that the statins really had nothing to do with it. Untreated subjects with low LDL levels on entry into the studies showed the same “low-LDL/higher cancer risk” relationship. The authors now conclude that “…statin therapy, despite producing marked reductions in LDL-C, is not associated with an increased risk of cancer” (5). This is, of course, in agreement with an extensive literature on the safety of statins, including the conclusions of other meta-analyses (6,7). Here we have yet another example of an epidemiologic correlation mistakenly interpreted as possibly representing a causal connection. No, statin treatment does not cause cancer.

What accounts then for the apparent association between low LDL and cancer risk reported in the first article? Mostly it reflects what Rose and Shipley (8) referred to over 30 years ago as the “unsuspected sickness phenomenon” (i.e., the lowering of cholesterol levels by subclinical disease). We know that cancers can significantly lower cholesterol levels as much as 10 years before they surface clinically (9). The randomly recruited cohorts in the large statin trials undoubtedly included some subjects who had low LDL levels at the time they entered the study because they already had cancer. It is well recognized that the curve describing the relationship between initial LDL (or total cholesterol) and subsequent cancer incidence is J-shaped. In other words, if you measure serum cholesterol levels in a large, randomly chosen population and then simply follow that population for 5 years—without intervention of any kind—there will be more cancer deaths in those who had the lowest cholesterol levels to begin with. Much of this (but perhaps not all) can be attributed to the fact that subclinical cancer is lowering the LDL levels in those subjects. This is especially true for leukemias and other cancers of the hematopoietic system but to some extent for all cancers. Tumor cells express high levels of the LDL receptor and catabolize LDL at a higher than normal rate (10). Thus, low LDL is the result, not the cause, of the cancer. Subjects with latent cancers and very low initial LDL levels probably respond to statin therapy to the same extent as the rest of the cohort. Consequently, they would still be in the statin-treated group with the lowest LDL levels. The excess cancer incidence in that low LDL group would then reflect their pre-existing disease, and the same would be true in both the statin-treated group and the control subjects. This is exactly what Alsheikh-Ali et al. (5) found. It is unfortunate that this analysis of the control cohorts was not included in the first article. It should be emphasized that what Alsheikh-Ali et al. (5) observed was that cancer risk correlated with the on-treatment level of LDL. It did not correlate with the extent of LDL reduction induced by the statins, whether expressed in relative terms (percentage fall) or in absolute terms (fall in mg/dl). Incidentally, the title of the first report was misleading in this respect: “Effect of the Magnitude of Lipid Lowering [emphasis added] on Risk of . . . Cancer.” They were observing not an effect of statin treatment, but the “unsuspected sickness phenomenon” with the distribution curve for LDL shifted to the left by statin treatment.

While pre-existing cancer can account for most of the J-shaped curve, it may not account for all of it. When cancers surfacing during the first few years are excluded from consideration, on the assumption that those cancers must have been already present at the time the study began, the LDL/cancer relationship weakens considerably but does not reach zero. Even after eliminating all cancers that surface during the first 5 years, there is a small residual excess in the low LDL group (11). However, there is evidence that low initial LDL values can be observed for as long as 10 years before the cancer surfaces (9). Also, other chronic diseases, such as alcoholism or cirrhosis, can lower
cholesterol levels and also predispose to cancer, possibly accounting for the sometimes long gap between the initial lowering of LDL and the ultimate expression of the cancer.

The central question for the clinician is whether a low LDL carries with it any intrinsic danger of cancer or other serious consequences (leaving aside for the moment possible side effects of the therapeutic intervention). Almost certainly not. Most mammals have LDL levels around 40 to 50 mg/dl all their lives (12). Our cord blood LDL levels are in that range. Some patients with hypobetalipoproteinemia do very nicely (even demonstrate longevity) with LDL levels as low as 10 to 20 mg/dl (13). Cellular levels of cholesterol are jealously guarded by the LDL receptor pathway of Brown and Goldstein (14), and the LDL receptor in peripheral tissues is still 50% saturated at a plasma LDL of only 10 mg/dl. Thus, the cells continue to take up as much LDL as they need even when LDL levels are extremely low. There should be no hesitation in aiming for LDL levels of 50 to 70 mg/dl in high-risk patients. Indeed a strong case can be made for even earlier and more aggressive treatment of hypercholesterolemia (15).

Neither statin treatment itself nor the low LDL levels induced by statins increases the risk of cancer.

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