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RESPONSE

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In our original paper we found that the seven genome-wide statistically significant genetic determinants of telomere length from the largest genome-wide association study of telomere length (1) also influence melanoma risk and that their effects on both traits were highly correlated (Pearson's correlation = 0.92), clearly establishing the existence of shared biology underlying the two traits. However, we concluded that "Our findings do not imply that telomere length acts directly on cancer risk and could reflect pleiotropic effects of telomere-length loci (such as the ease with which telomerase is reactivated in a melanocytic nevus)." Despite acknowledging that they are underpowered to detect pleiotropy, and indeed without any investigation of pleiotropy, Shen and Zhang assume that the effect of the single-nucleotide polymorphisms (SNPs) on melanoma risk is entirely mediated by telomere length. This is the crux of the matter: If you assume that there is no pleiotropy, then, yes, telomere length is a direct determinant of melanoma risk. But making the assumption that leukocyte telomere length (LTL) should have a direct impact on melanoma risk seems biologically implausible to us. For instance, given that telomere lengths in different tissues are highly correlated despite consistent differences in length (2,3,4), it is likely that these SNPs influence telomere length in a variety of cell types, such that LTL is strongly correlated with telomere length in melanocytes. Melanocytic telomere length may then have a direct or indirect effect on melanoma risk.

Whether or not you accept the authors' assumption, extrapolating results based on genetic variants that explain only 1.2% of the variation in LTL to estimate the effect of LTL directly on melanoma risk appears to us overly optimistic, and the confidence intervals reported here do not reflect the huge uncertainty inherent in the modeling assumptions made.

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