Letter to the Editor

Cancer Epidemiology, Biomarkers & Prevention

The Heritability of Prostate Cancer—Response

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We thank Professors Hopper and Mack (1) for their correspondence in reference to our study (2), and in particular for recognizing the richness of the Nordic Twin Study of Cancer data that provide diverse opportunities to investigate cancer. The rationale for commenting on our article (2) seems to be to illustrate general arguments about the inadequacy and inappropriate use of the heritability statistic, rather than comment specifically on our study. Although we agree that heritability can be misused and misunderstood, there are several examples drawn from our article by Hopper and Mack to articulate their general perspective that do not accurately reflect the specific information we have provided. Indeed, we do not believe that our article misuses or misrepresents the heritability statistic, and therefore we believe that the letter (1) is misleading. For example, our definition of heritability is identical to that of Fisher and to the definition referred to in their letter. There seems to be a misattribution in their text suggesting that we define heritability by our statement explaining that precise estimates of heritability allow for the calculation of the extent to which variability in liability to develop cancer is explained by established risk loci. We do not define heritability in this way, but rather we are simply saying that if we estimate the heritability of prostate cancer (that is the variance due to all genetic factors) and we know the variability due to established risk loci, then we can calculate how much of the genetic variance is due to those known loci.

To provide a more balanced presentation, Hopper and Mack might want to recognize that we estimate the heritability of prostate cancer "risk." Our strategy does not load heavy modelling assumptions; it is a recent contribution as noted in the article, and is a strategy not yet well integrated by behavior geneticists. This, we believe, exactly fulfills their request for a measure of heritability. We encourage Hopper and Mack to examine our model in greater detail.

A twin analysis is based on comparing the dependence for monozygotic and dizygotic twins, here the concordance estimates and derived measures such as case-wise concordance and recurrence risk. The comparison of these then leads to "heritability." In the article, we suggest different ways of looking at these measures of dependence. One common and sensible approach is to do this via structured random-effect models (such as ACE components for the liability threshold model). We agree that the size of these random effects is not the whole story. Researchers are familiar with these twin modeling methods, and the assumptions underlying the decompositions are well known in twin research. We state these assumptions clearly in the article. If the article is read without the crusade against the liability threshold heritability, one cannot avoid seeing that we show various other summary measures of the dependence and the differences between them.

The main methodologic point in our article is that when one computes dependence measures for diseases with variable age of onset that contains censored observations, as is the case for prostate cancer, then one needs to adjust for the fact that there are censored observations. Censored subjects are twins that are alive without the disease. Because these twins may develop disease later in life, it is critical that this censoring is taken into account. If one does not do this, then the estimates can be seriously biased, and then all the basic measures that we agree on computing do not make sense and are not comparable across studies. We suggest a solution for this important problem.

An overarching theme of our article is that by taking into consideration the timing of events, one can give a more accurate account from twin studies of traits with variable age of onset than previously seen before. We respectfully believe that Hopper and Mack misunderstand our article, misinterpret it, and only focus on liability scale heritability. Their own suggestion for a model is clearly insufficient for the cancer data, and it would be far more fruitful to spend energy in collaborating with us on developing a theory that adapts to the situation of influences varying over time, for instance seen from epigenetic causes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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