Letter to the Editor

Cancer Epidemiology, Biomarkers & Prevention

The Heritability of Prostate Cancer—Letter

John L. Hopper[1,2] and Thomas M. Mack[3]

Hjelmborg and colleagues (1) present an exceptional prospective population-based twin study, but in our opinion their estimates of the "heritability of prostate cancer" (the title of their paper) are meaningless, whether they be based on "risk" or "liability." Whatever they have estimated, it is not the "proportion of disease due to genes" even though many, including prominent authors of genome-wide association studies (2), misinterpret it this way. Furthermore, "missing heritability," which refers to the proportion of a measured concept (familial aggregation) assigned to "known" genetic factors, has nothing to do with the concept of "heritability," which is variation in a trait attributable to "all" genetic factors (known and unknown) as a proportion of total variation.

In 1918, Ronald Fisher (3) defined heritability—for a measured continuously distributed trait—as the proportion of population variance attributable to genetic factors. For a disease, which is a binary trait, the concordance for monozygotic twin pairs defines the maximum variance in underlying "risk" attributable to genetic factors.

But how can one ever know the total variance, and therefore the variance due to all non-genetic factors, let alone estimate the latter to be 42% (95% CI, 37–48) of the former, which is what the authors have in effect done? This is incredulous.

For any observed familial risk (increased risk for relatives of an affected), there are an infinite set of possibilities for (i) the correlation between relatives in underlying risk and (ii) the gradient in underlying risk across the population (see, e.g., refs. 4–6). That is, a given increase in risk for the monozygotic co-twin of an affected twin is consistent with 100% heritability and one gradient of risk, or any heritability <100% and a corresponding (smaller) gradient of risk. It all depends on the variation in risk explained by nonfamilial factors, which could vary across populations and time, and be caused by more than what is known to date about "environmental" risk factors.

To derive their "heritability" estimate, Hjelmborg and colleagues (1) make three critical assumptions: (i) There is an unmeasured "liability"; (ii) it has a normal distribution; and (iii) risk is 100% for people above a given threshold. Suppose disease prevalence is 10% and there is a 5-fold increased risk associated with having an affected monozygotic twin. The correlation in "all-or-nothing liability" is approximately 0.5. However, if instead risk is 50% for those above a threshold, the correlation is approximately 0.3, whereas if it is 25%, the correlation is 0.1.

Therefore, their estimates of "heritability of liability" depend on the presumed model. However, there are no degrees of freedom to conduct a statistical test of these assumptions, so virtually any scenario is possible. In addition, the "all-or-nothing" liability model they choose to work with just happens to give the largest "heritability"!

On the broader issue of heritability, it is a characteristic of a population in a chronologic environment and a crude measure of the impact of genes on population incidence, not an inherent characteristic of the disease. Fisher showed that the genetic component of variance is transmitted to future generations and thereby related Mendelian inheritance of qualities to genetic variance of quantities. The "absolute" genetic variance, not a percentage, is what was important. When it comes to "heritability of a continuous trait," Fisher referred to the "hotch-potch of a denominator," and admonished that "loose phrases about the 'percentage of causation,' which obscure the essential distinction between the individual and the population, should be carefully avoided" (7). When it comes to heritability of a disease, there is not even a denominator!

As Lewontin cogently argued 40 years ago, "In view of the terrible mischief that has been done by confusing the spatiotemporally local analysis of variance with the global analysis of causes, I suggest that we stop the endless search for better methods of estimating useless quantities. There are plenty of real problems" (8).

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