Genome-wide association studies need larger sample sizes

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While genome-wide association (GWA) studies have identified several genetic risk factors for common cancers, their predictive power is limited by their small effect sizes, according to a new study published online May 26 in the *Journal of the National Cancer Institute.*

In the past few years, several GWA studies have reported a large number of gene-disease associations with diverse cancers. But there is ongoing debate on the robustness of these studies and the expensive technology used to uncover the genetic associations.

To investigate the issues involved in this debate, John P.A. Ioannidis, M.D., of the Department of Hygiene and Epidemiology at the University of Ioannina School of Medicine in Athens, Greece and colleagues from Greece and Boston, reviewed 45 GWA studies, published between 2007 and 2010, listed in the National Human Genome Research Institute catalog. Ioannidis et al identified all discovered gene-cancer associations with robust statistical support. They also used these data in a simulation with 25,000 individuals per cancer type to determine what sample sizes would be needed to detect associations between these alleles and the risk of colorectal, prostate, testicular, and thyroid cancers.

The authors were able to glean 92 associations from the study that were eligible for evaluation. More than half of these pertained to prostate, colorectal and breast cancer. There was a slightly accelerated pace of discovery for the associations, with 15 occurring in 2007, 25 in 2008 and 50 in 2009, and another 2 in early 2010. This acceleration was due

primarily to the emergence of associations with cancers for which no previous discoveries had been made.

Most associations between risk factor genes and various cancers were for populations of European ancestry, with 69 associations; 16 associations pertained to both European and other populations, whereas 7 associations were identified for populations of Asian ancestry. Ioannidis et al. state that "…it is possible that additional loci will be discovered by performing GWA studies in non-European ancestry groups."

The authors conclude that although GWA studies have identified several genetic loci, particularly for breast, prostate and colon cancer, "the explanatory power of these loci to predict individual cancer risk is limited…." In other words, the average level of risk for associations identified by GWA studies, although statistically significant, is relatively small, even though other factors may increase the risk for any particular individual. Furthermore, they write: "Performing GWA studies using all currently available samples on common cancers would yield many more genetic loci, but almost all of them would also have small or very small effects."

In an accompanying editorial, David J. Hunter, M.D., of the Program in Molecular and Genetic Epidemiology at the Harvard School of Public Health, and Stephen Chanock, M.D., of the Division of Cancer Epidemiology and Genetics, at the National Cancer Institute, write that there have arguably been more discoveries of risk factors predictive of breast cancer in the past three years than in the previous three decades, largely thanks to discoveries using GWA. However, Hunter and Chanock point out that the harder challenges include transitioning to whole-genome sequencing, which would identify risk factors in the genomes of individuals, and performing genome-wide studies to hunt for rare gene variants, which will require larger sample sizes than studies of common variants. Hunter and Chanock also say that it will be necessary to

combine prognostic or predictive studies with those attempting to match disease causation with individual germline mutations.

"Clearly, statistically well-powered studies are needed to address gene-gene and gene-environment interactions," Hunter said. "The coming years promise to be an exciting time for the genetic epidemiology of cancer, even if they have more of a taste of consolidation, rather than the revolutionary flavor of the past three years."

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