

“Study Design and Analysis Methods for Complex Pathways in Molecular Epidemiology: Applications to Folate Metabolism and DNA Repair Pathways”

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ABSTRACT

The field of molecular epidemiology has evolved from testing associations with single functional variants, to exhaustive examination of genetic variation within a gene region using haplotype tagging SNPs, to testing multiple candidate genes and their interactions (gene-gene and gene-environment) simultaneously, to genome-wide association scans (GWAS), and is now moving into the post-GWAS era aimed at trying to uncover causal variants responsible for GWAS hits. In contrast to these “agnostic” GWAS approaches, pathway-based methods are aimed at a comprehensive treatment of all the genetic and environmental components of a postulated pathway. I will discuss two general approaches to this problem -- one empirical based on hierarchical models, one deterministic based on physiologically-based pharmacokinetic models -- and will discuss some ideas about marrying to two approaches and incorporating biomarker measurements. Examples will be drawn from studies of colorectal cancer and adenomas in relation to folate metabolism and second breast cancers in relation to radiotherapy doses and DNA repair pathways. Ultimately, our hope is to be able to use pathway knowledge to inform the analysis of GWAS data and to use GWAS data to discover novel pathways.