Re: Commonly Studied Single-Nucleotide Polymorphisms and Breast Cancer: Results From the Breast Cancer Association Consortium

In a recent pooled analysis of breast cancer data from up to 12 case-control studies from the Breast Cancer Association Consortium (1), five of 16 common single-nucleotide polymorphisms (SNPs) were associated with modest increases in risk. The authors interpreted their findings, with P values ranging from .06 to .0088, as failing to meet a level of statistical significance appropriate to genetic association studies. There were no associations for the other SNPs evaluated.

To us, these analyses and interpretation represent a growing divergence in perspective between investigators approaching disease from a statistical genetics viewpoint and those approaching it from a molecular epidemiologic viewpoint. Carcinogenesis is a dynamic process, usually the result of both exogenous and endogenous exposures, and we would not expect, for most pathways, to observe main effects for common genetic variants without consideration of relevant exposures. Moreover, because of the complex nature of carcinogenesis pathways, it is unlikely that a SNP in one single low-penetration gene alone would be associated with an increase in cancer risk, without consideration of potential interactions with other polymorphic genes.

Genetic processes, and interactions with exposures, are far from simple. In addition to SNPs modifying risk associated with exposures, the impact of exposures on relationships between genetic variants and phenotype, through enzyme induction or inhibition, must also be considered. For example, effects of dietary exposures on relationships between catalase genotypes and enzyme activity have been demonstrated (2). Although genotype predicted phenotype overall, relationships varied by levels of fruit and vegetable consumption, with genotype/phenotype correspondence only among consumers of low levels of fruits and vegetables, suggesting feedback mechanisms. Similarly, in a study of glutathione peroxidase genotype, erythrocyte activity, and breast cancer risk (3), although genotype predicted glutathione peroxidase activity overall, relationships between genotype and activity were modified by alcohol consumption and smoking, with changes in activity according to levels of exposure varying by genotypes. These data illustrate the dynamic biologic systems in which the effects of SNPs on cancer risk are evaluated. Genotypes are not static variables, and the ultimate impact of SNPs on phenotype, and, more important, on cancer risk, will be modified by exogenous and endogenous exposures.

Accumulating evidence illustrates the importance of exposures for breast cancer risk. It is notable that cancer rates are rising in Japan with westernization and that migrants to the United States from low-risk countries have increased breast cancer risk with subsequent generations (4). Clearly, genes are not changing; rather, lifestyle factors, perhaps interacting with genetics, are likely the cause of these rising cancer rates. The consortia authors noted heterogeneity in results among the pooled studies and commented that it is “likely due to some unexplained artifact” and that “it seems unlikely that there are associations in one population and not others.” We would argue that, when examining the effects of genotypes without consideration of other exposures, it is highly likely that results from different populations would in fact differ, if there are important differences in the relevant exposures in the populations. For example, results from assessment of the main effects of alcohol dehydrogenase 1C (ADHC1), which is involved in metabolism of alcohol, would likely vary widely if one population included a large proportion of heavy consumers of alcoholic beverages and the other did not.

In summary, examination of common single SNPs in the absence of data on exposures, and expectations to see main effects, may not be appropriate. We suggest that considerable caution be exercised in the interpretation of main effects of common polymorphisms on risk of cancer. Genome-wide association studies are now yielding results and offer promise for identification of genetic variants that may play a role in cancer risk. However, null results from such studies will only mean that the gene, in and of itself, is not associated with cancer risk and should not rule out further investigation of the effects of the genetic variants in modifying relationships between exposures and cancer risk.

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The Breast Cancer Association Consortium did a remarkable job of pooling data from various studies to investigate the association of 16 single-nucleotide polymorphisms (SNPs) and breast cancer (1). The result was no association between the 16 SNPs and cancer after an adjustment for the type I error with 16 tests (2), although one
could argue for a much more stringent adjustment based on the type I error needed for a low false-positive report probability (3,4).

Two competing conclusions can be drawn. One is that methods building on this approach should be applied to more genes and that it is only a matter of time before a confirmed discovery of a true association will be made. The opposite conclusion is that the results of no association support other evidence of very weak or no association between common genetic variants and cancer (4), including 1) studies showing that many cancers arise from defects in communication between stromal and parenchymal cells (5), rather than mutations in parenchymal cells; 2) migration studies that find that populations moving from one country to another generally experience the cancer rates of the new country within a generation or two (6), which is too soon to be the result of an inherited genetic mutation; and 3) a twin study showing that genetic contributions to common cancers are small and likely arise from rare mutations, not commonly occurring gene variants such as SNPs (7).

If the first conclusion is drawn and larger gene–cancer association studies are undertaken, an important consideration is how small a relative risk would be worthwhile (in terms of net health benefit) to detect. To put this question in perspective, one needs to consider the sequence of events leading to a worthwhile clinical benefit: 1) the genetic variant must suggest a modifiable risk factor; 2) an intervention must be developed or identified based on this modifiable risk factor; 3) the intervention must be tested in an extremely large randomized cancer prevention trial; and 4) there must be no side effects whose harms would outweigh the small benefits. It is important to realize that larger gene–cancer association studies to detect smaller relative risks yield diminishing net returns due to the larger cost of the gene identification study, larger cost of the resulting cancer prevention trial, and smaller future clinical benefits compared to potential harms.

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important interacting exposures. However, such differences are unlikely to explain the heterogeneity we observed for several SNPs, given that there were not substantial differences between the findings of studies carried out in populations of Asian origin and those based on subjects of European descent.

Baker suggests that one conclusion that might be drawn from our data is that they “support other evidence of very weak, or no association between common genetic variants and cancer.” This conclusion seems premature given that we have studied just 16 common variants out of several million across the genome, of which five showed some evidence, albeit weak, of association. Several genome-wide association studies in breast cancer are ongoing, and over the next year or so, it should become clearer whether or not this conclusion is justified. Baker additionally suggests that it is not worth detecting alleles with small effect, even if they do exist, because of their limited clinical significance. We agree that the clinical significance of individual markers is likely to be small. However, the combined effect of multiple alleles may well be substantial and of clinical importance (5). Furthermore, although practical application in prevention is an important consideration, it is not the only justification for such research. Important insights into cancer biology are likely to come from identifying novel genes, and these may have wider implications for prevention and cure beyond simply identifying individuals at high risk.

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References


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This response has been seen and approved by all Breast Cancer Association Consortium contributors.

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