COMMENTARY

Genetic susceptibility and the common cancers

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The review of d'Errico *et al.* (1996, this issue) summarizes the major epidemiological studies that have evaluated putative associations of susceptibility genes and cancers. The growing field of molecular epidemiology is concerned with biomarkers of exposure, effect (disease), and susceptibility. It is the area of genetic susceptibility that is outlined in the paper, and some perspective regarding the rationale for this approach is useful. Traditionally, studies that aim to explain the aetiology of the common cancers have focused on the environment. Genetics was given much less emphasis since it was rationalized that disorders in this category would be rare, and once identified, not easily prevented or treated. Exposure information is gathered in the context of an appropriate epidemiological study design (i.e., case-control) typically using a standardized questionnaire. Studies in this vein have established causal associations such as tobacco and lung cancer, DES and clear cell carcinoma of the vagina, and oestrogens (reproductive factors) and breast cancer. The methodologic armamentarium of the epidemiologist has grown more sophisticated with improved tools for dealing with bias and statistical limitations. Unfortunately, in spite of advances in aetiologic understanding, certain limitations are apparent. For certain cancers (i.e. prostate, lymphoma and brain) understanding of major risk factors is limited. In general, there is a poor appreciation of factors that control individual susceptibility. Approaches to expand the understanding of the role of exposure include larger and better designed studies using traditional questionnaire approaches, or focused study of specific critical time periods, i.e. where prenatal or adolescent exposures may be important. More recently, proposals to explore new and old risk factors using biomarkers have been suggested. Specific advantages of biomarkers in the evaluation of exposures have been noted by many authors and include integration of doses from different routes, an evaluation of effective dose reaching a target organ (e.g. DNA adducts), and the ability to make more rational inferences from animal work (Vineis and Caporaso 1988, Hulka 1990). Of particular interest is the opportunity to exploit biomarkers to better understand the influence of genetics on human disease. For a variety of reasons, genetics is understood to play some role in virtually all cancer (Table 1) but the role of pure hereditary factors has been thought to be limited by the relatively small number of cancers (e.g. retinoblastoma) that exhibit clear (familial) mendelian patterns of inheritance. Beyond this group, a subset of common cancers have been associated with specific genes that account for a high proportion of disease among familial affecteds. Some prominent examples include BRCA1 in familial breast/ovarian cancer (Miki *et al.* 1994) , and loci accounting for microsatellite instability in hereditary non-polyposis colon cancer (HNPCC) (Bronner *et al.* 1994). An understanding of the role of 'familial' genes in sporadic disease is an active area of investigation. The '2 hit' paradigm of Knudson offers one mechanism for a broad connection between hereditary and somatic mutations (Knudson *et al.* 1971). The results of large scale population studies to understand the role of these genes in the non-familial setting is an active area of investigation. For other common tumours, risk in relatives is generally elevated compared with suitably selected controls, but a specific genetic aetiology remains obscure. While rare and yet undiscovered genes may account for individual variation in susceptibility (e.g. based on segregation analyses) to lung (Sellers *et al.* 1990), smoking-related (Sellers *et al.* 1994), and prostate (Carter *et al.* 1992) cancers, there is growing interest in the possibility that polymorphic genes important in metabolism have relevance based on their ability to direct potential carcinogen substrates towards either damaging or harmless intermediates. It is mechanistically plausible that individuals who carry a more active version of a gene that activates carcinogens will be at increased risk of a specific malignancy, given similar exposure. A satisfying aspect of this scheme is that a role for both the gene and the exposure is accommodated, i.e. a true gene–environment interaction must exist and we have recently described how the implications of this contrast with traditional 'genetic' disease (Table 2) (Caporaso *et al.* 1995). Genes and the environment jointly account for many pharmacogenetic conditions (e.g. G6PD deficiency and fava beans resulting in haemolytic anaemia), but studies investigating their role in chronic diseases such as cancer are more recent. The concept has gained favour as susceptibility type alleles have been identified for cardiovascular disease and Alzheimer's, as recent examples. Over a decade ago, the early studies in this field employed phenotyping approaches to examine the roles of underlying genes: CYP2D6 (debrisoquine given to subjects and a phenotype was determined based on a ratio of metabolites) (Ayesh *et al.* 1984), CYP1A1 (aryl hydrocarbon hydroxylase inducibility assayed in lymphocytes) (Kellermann *et al.* 1973), GSTM1 (*trans*-stilbene activity in erythrocytes) (Seidegard *et al.* 1986), and NAT2 (sulphonamide in urine and blood) (Lower *et al.* 1979). An important development that derives from the revolution in molecular biology is the widespread use of DNA-based assays to directly identify the genotype. This approach is more efficient and avoids certain sources of bias. For example, a phenotype assay may be distorted because of poor nutrition associated with the disease under study. For these reasons the use of genotyping is appropriately increasing. However, the phenotype will always retain a role since it is the only way to understand the action of the gene in the organism. Therefore the relationship of genotype and phenotype remains complementary (Table 2).

There are a number of new considerations since the last review of this literature that considered these studies from an epidemiological perspective (Caporaso *et al.* 1991). First, the number and mechanisms of the proposed susceptibility genes has broadened. Many new genes and conditions have been

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studied. Although the current review is limited to cancer, new findings are being reported for many common conditions. A few recent examples include: apolipoprotein E and late-onset Alzheimer's (Polvikoski *et al.* 1995), cardiovascular disease and paraoxonase (Ruiz *et al.* 1995), and monamine oxidase A mutations and psychiatric conditions (Brunner *et al.* 1993), to highlight some recent work. It is remarkable to note that with regard to cancer, initial studies began with the straightforward idea of a polymorphic gene that would differentially activate (AHH, CYP2D6), or deactivate (NAT2, GST) carcinogens. The paradigm has now widened considerably to consider genes involved in DNA repair (ataxia telangiectasia heterozygotes and breast cancer), vitamin metabolism (vitamin D polymorphism and prostate cancer), oncogene regulation, i.e. H-ras1 vtr rare alleles and various tumours (Sugimura *et al.* 1990) hormone metabolism (oestrogen polymorphism and breast cancer), and others.

Second, the accumulating data supporting for a causal role for some of these associations has now reached a point where the evidence must be considered convincing. The clearest example, as summarized in the D'Errico review, is the case for GSTM1 null genotype as a susceptibility factor for lung cancer (also bladder cancer). The study reported here indicates that fully half the general population is at a 40 – 70% increased risk of lung cancer (and likely bladder cancer) if they smoke cigarettes. Many questions remain unanswered: the role of smoking in risk, whether null subjects are at increased risk of only lung cancer, all-smoking related cancer, all-smoking related disease, or possibly all cancer. The latter possibility is suggested by scattered findings suggesting some degree of increased risk in breast, skin, colon, and prostate cancers.

A third issue involves the role of exposure, and how this influences the role of the susceptibility gene. For certain genes, data suggest the genotype has the biggest impact on risk at low levels of exposure, e.g. NAT2 (Vineis *et al.* 1990), CYP1A1 (Nakachi *et al.* 1991). For others, that risk due to the gene is

Specific cancer genes ('single genes') have been identified and shown to account for specific tumours in individuals in the families who inherit them
A number of chromosome fragility syndromes are characterized by greater rates of certain tumours (i.e. xeroderma pigmentosa and skin cancer)
Most cancers exhibit increased risk of cancer in relatives
Virtually all tumours exhibit somatic mutations
Specific chromosomal changes characterize a variety of haematopoietic malignancies
Many carcinogens damage the genetic material

Table 1. General evidence for a genetic role in cancer aetiology.

	Phenotype	Genotype
Advantages	— depicts biochemical 'reality' at physiological level — historically well studied	— usually simple assay based on germline DNA — PCR-based assays increasingly simplifying approaches — can identify heterozygotes directly — most suitable to population and field studies
Disadvantages	— often requires probe drug and collection of timed samples — depending on genetic mechanism, some phenotypes may be indistinguishable — assay subject to various types of error — effect–cause bias, i.e. disease state may distort phenotype — other factors: diet, medications, etc. may influence phenotype procedure — may subject hospitalized or ill patients to risk	— requires DNA with attendant ethical difficulties — assumes mutations and their functional status are known — differences in gene frequency and type complicate studies in different ethnic/racial groups — danger of 'reductionism'

Table 2. Advantages and drawbacks to the use of genotype and phenotype in population studies.

	Single gene	Susceptibility gene
Definition	Necessary and sufficient for disease	Alters risk but is neither necessary nor sufficient for disease causation
Example	BRCA1 (breast/ovary) APC (polyposis coli) RB (retinoblastoma)	CYP1A1 (lung) CYP2D6 (lung) GST-M1 (lung, bladder)
Gene prevalence	Low	Often high
Gene type	Mutation	Polymorphism or mutation
Study setting	Family	General population or epidemiological studies
Strength of association	Very high	Low to moderate
Absolute risk	High	Low
Population attributable risk	Low	High
Gene–environment interaction	Secondary and variable	Primary and implicit
Role of environmental exposure	Secondary and variable	Crucial

Table 3. Single and susceptibility genes in cancer aetiology.

apparently greatest at higher levels of exposure, e.g. CYP2D6 (Caporaso *et al.* 1995) and GSTM1 (Kihara *et al.* 1994). A crucial challenge for future well designed large studies (i.e., nested case-control studies from cohorts) will be to resolve this question. The implications of the available findings has scarcely begun to be considered. Assuming for a moment that GSTM1 only increases risk of lung cancer, the attributable risk due to this one gene easily exceeds BRCA1 and HNPCC together since a substantial proportion of lung cancer *in smokers* is likely due to this gene. Yet, unlike other genetic risk factors, the implications are quite different. Risk to the individual is only slightly increased in individuals who bear the gene, while the public health implications due to the widespread nature of the trait are potentially greater. Paradoxically, the genetic trait identifies a group where environmental exposures may be more relevant. The differences between the metabolic genes considered in this review that alter susceptibility, and the single genes that are largely determinant in causing disease are outlined (Table 2). These contrasts highlight the different implications of single and susceptibility genes from the individual and from the public health perspective. Specifically, rare highly penetrant genes such as BRCA1 have important implications for individuals, but overall the gene only accounts for a small proportion of the disease. For the common low penetrance genes, the gene itself has minor implications for risk in an individual (i.e. the result of a 'gene test' is less important than avoiding the exposure), but the attributable risk may be high.

It can be predicted with confidence that DNA based approaches to characterizing genes will continue to improve, and applications exploiting these advances will proliferate. Genes with an impact on human cancer will continue to be identified from cancer families, but studies in the wider population should accelerate. The availability of both improved technical methods for blood collection (e.g. cards with blood spots, 'mouthwash' techniques for DNA collection (Hayney *et al.* 1995)) and PCR-based methods for characterization will allow increasing investigation of candidate genes in the general population. To efficiently address aetiologic questions, studies will be larger and include systematic collection of exposure, cofactor, and clinico-pathologic data as well as other relevant biomarkers. Ethical considerations will receive increased attention, but since the positive predictive value for the individual (how the individual's risk changes by knowing the status of the gene) of the high prevalence susceptibility genes is low, the constraints that limit study of genetic factors in families should be appropriately modified for the population setting (Clayton *et al.* 1995). There is a danger on the one hand, of rushing to commercialize gene tests that have been well-characterized in families, but incompletely studied in the general population. On the other hand, if constraints appropriate to high penetrance genes are applied to the study of low penetrance genes, it will render the design of large-scale studies impossibly burdensome and expensive. Further discussion regarding the appropriate level of informed consent and other safeguards for genetic testing in population-based studies is urgently needed.

Finally, the larger implications of this work imply a rejection of both the idea that the influence of genes on disease is limited to rare disorders as well as a nihilistic approach towards genetic disorders in general. The mechanistic involvement of environmental factors in genetic mechanisms suggests, paradoxically, that identification of genetic susceptibility factors may provide hints for environmental risk factors. The long term benefit of understanding gene–environment relationships is increased understanding of mechanisms, and identification of subsets at altered risk, these insights should contribute to relieving the burden of cancer on humanity in ways we can hardly imagine today.

References

Ayesh, R., Idle, J.R., Ritchie, J.C., Crothers, M.J. and Hetzel, M.R. (1984) Metabolic oxidation phenotype as markers of susceptibility to lung cancer. *Nature*, **312**, 169-170.

Bronner, C.E., Baker, S.M., Morrison, P.T., Warren, G., Smith, L.G., Lescoe, M.K., Kane, M., Earabino, C., Lipford, J., Lindblom, A., Tannergard, P., Bollag, R.J., Godwin, A.R., Ward, D.C., Norgenskjold, M., Fishel, R., Kolodner, R. and Liskay, R.M. (1994) Mutation in the DNA mismatch repair gene homologue hMLH1 is associated with hereditary non-polyposis colon cancer. *Nature*, **368**, 258-259.

Brunner, H.G., Nelen, M., Breakfield, X.O., Ropers, H.H. and van Oost, A. (1993) Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase. *Science*, **262**, 578-580.

Caporaso, N. and Goldstein, A. (1995) Cancer genes: single and susceptibility: exposing the difference. *Pharmacogenetics*, 5, 59-63.

Caporaso, N., Landi, M.T. and Vineis, P. (1991) Relevance of metabolic polymorphisms to human carcinogenesis: evaluation of the epidemiologic evidence. *Pharmacogenetics*, **1**, 4-19.

Caporaso, N., DeBaun, M.R. and Rothman, N. (1995) Lung cancer and the CYP2D6 (the debrisoquine polymorphism); sources of heterogeneity in the proposed association. *Pharmacogenetics*, **5**, 129-134.

Carter, B.S., Beaty, T., Steinberg, G.D., Childs, B. and Walsh, P.C. (1992) Mendelian inheritance of familial prostate cancer. *Proceedings of the National Academy of Sciences* , **89**, 3367-3371.

Clayton, E.W., Steinberg, K.K., Khoury, M.J., Thomson, E., Andrews, L., Kahn, M.E., Kopelman, L.M. and Weiss, J.O. (1995) Informed consent for genetic research in stored tissue samples. *Journal of the American Medical Association*, **274**, 1786-1792.

d'Errico, Taioli, E., Chen, X. and Vineis, P. Genetic Metabolic Polymorphisms and the Risk of Cancer: A Review of the Literature. *Biomarkers*, **1**, 149–173.

Hayney, M.S., Diamanlig, P., Lipsky, J.J. and Poland, G.A. (1995) Utility of a 'Swish and Spit' technique for the collection of buccal cells for TAP haplotype determination. *Mayo Clinic Proceedings*, **70**, 951-954.

Hulka, BS. (1990) Overview of Biological Markers. In *Biological Markers in Epidemiology*. (Oxford University Press), New York. pp. 3-15.

Kellermann, G., Shaw, C.R. and Luyten-Kellermann, M. (1973) Aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma. *New England Journal of Medicine*, **298**, 934-937.

Kihara, M., Kihara, M. and Noda, K. (1994) Lung cancer risk of GSTM1 null genotype is dependent on the extent of tobacco smoke exposure. *Carcinogenesis*, **15**, 415-418.

Knudson, A.G., Jr. (1971) Mutation and cancer—Statistical study of retinoblastoma. *Proceedings of the National Academy of Sciences*, **68**, 820.

Lower, G.M., Jr., Nilsson, T., Nelson, C.E., Wolf, H., Gamsky, T.E. and Bryan, G.T. (1979) *N*-Acetyltransferase phenotype and risk of urinary bladder cancer: approaches in molecular epidemiology. Preliminary results in Sweden and Denmark. *Environmental Health Perspectives*, **29**, 71-79.

Miki, Y., Swensoen, J., Shattuck-Eidens, D., Futreal, P.A., Harshman, K., Tavigian, S., Liu, Q., Cochran, C., Bennett, L.M., Ding, W., Bell, R., Rosenthal, J., Hussey, C., Tran, T. *et al.* (1994) A strong candidate for the breast and ovarian cancer susceptibility gene, Brca1. *Science*, **266**, 66-71.

Nakachi, K., Imai, K., Hayashi, S., Watanabe, J. and Kawajiri, K. (1991) Genetic susceptibility to squamous cell carcinoma of the lung in relation to cigarette smoking dose. *Cancer Research*, **51**, 5177-5180.

POLVIKOSKI, T., SULKAVA, R., HALTIA, M., KAINULAINEN, K., VUORIO, A., VERKKONIEMI, A., NIINISTO, L., HALONEN, P. AND KONTULA, K. (1995) Apolipoprotein E, Dementia, and Cortical deposition of B-Amyloid Protein. *New England Journal of Medicine*, **333**, 1242-1247.

RUIZ, J., BLANCHE, H., JAMES, R.W., BLATTER GARIN, M-C., VAISSE, C., CHARPENTIER, G., COHEN, N., MORABIA, A., PASSA, P. AND FROGUEL, P. (1995) Gln-Arg192 polymorphism of paraoxonase and coronary heart disease in type 2 diabetes. *Lancet*, **346**, 869-872.

SEIDEGARD, J., PERO, R.W., MILLER, D.G. AND BEATTIE, E.J. (1986) A glutathione transferase in human leukocytes as a marker for the susceptibility to lung cancer. *Carcinogenesis*, **7**, 751-753.

SELLERS, T.A., BAILEY-WILSON, J.E., ELSTON, R.C., WILSON, A.F., ELSTON, G.Z., OOI WL. ET AL. (1990) Evidence for Mendelian Inheritance in the Pathogenesis of Lung Cancer *Journal of the National Cancer Institute*, **82**, 1272-1279.

SELLERS, T.A., CHEN, P-L., POTTER, J.D., BAILEY-WILSON, J.E., ROTHSCHILD, H. AND ELSTON, R.C. (1994) Segregation Analysis of Smoking-Associated Malignancies. *American Journal of Medical Genetics*, **52**, 308-314.

SUGIMURA, H., CAPORASO, N.E., MODALI. R., HOOVER, R.N., RESAU, J.H., TRUMP, B.F., LONGERAN, J.A., KRONTIRIS, T.G., MANN, D.L., WESTON, A. AND HARRIS, C.C. (1990) Association of rare alleles of the Harvey ras protooncogene locus with lung cancer. *Cancer Research*, **50**, 1857-1862.

VINEIS, P. AND CAPORASO, N. (1988) Applications of biochemical epidemiology in the study of human carcinogenesis. *Tumori*, **74**, 19-26.

VINEIS, P., CAPORASO, N., TANNENBAUM, S.R., SKIPPER, P.L., GLOGOWSKI, J., BARTSCH, H., CODA, M., TALASKA, G. AND KADLUBAR, F. (1990) Acetylation phenotype, carcinogen-hemoglobin adducts, and cigarette smoking. *Cancer Research*, **50**, 3002-3004.

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