Counterpoint: Genetic Risk Feedback for Common Disease—Time to Test the Waters

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Status of Common Polymorphisms as Measurable Determinants of Cancer Risk

A recent news article in the Journal of the National Cancer Institute “SNPs not Living Up to Promise: Experts Suggest New Approach to Disease ID” (1) speaks to the general failure thus far to identify common disease-causing gene variants in the human population. The article speaks directly to the lack of success in finding genetic variants that, by themselves, affect the risk of sporadic cancers in a manner that is consistent across studies or of sufficient effect size to justify the cost of testing and counseling. This somewhat undesirable view supports the longstanding notion that any given individual’s risk of expressing a cancer occurs as the result of complex gene × gene (G) interactions and the interaction of these genes with the environment (E; for example, see ref. 2 and associated correspondences; refs. 3-5). If we work from the assumption that a significant number of human cancers arise from G × E interactions, these G × E interactions are proving hard to detect (1), and in simple 2 × 2 relationships, not clinically informative and likely not reflective of the expected complexity of tumorigenesis. Although better appreciated in 2007, these relationships remain as complex and recalcitrant as when originally conceived. Perhaps most troublesome is the disagreement among ourselves on the overall contribution, and therefore, the importance of common or shared allelic variation as potentially clinically useful determinants for assessing individual cancer risk (2, 6).

Is the Common Disease Gene Hypothesis Holding Up for Cancer?

At present, there are no sufficiently strong or consistently reproducible G or G × E combinations that, if present, sufficiently explain individual risk for the sporadic cancers or for cancers of specific organ types. An additional emergent consideration in genetic studies of cancer end points, which is clearly a challenge to the field, is the accumulating evidence that many of the sporadic cancers are in fact subsets of discrete and etiologically distinct subtypes (see refs. 7, 8 for examples). As we move forward as a field, we are quickly watching the cancer risk/gene story evolve away from a common gene/common disease hypothesis to a rare gene/rare disease hypothesis. As we refine our G and G × E discovery activities using high-density genotyping technologies (i.e., construction of haplotypes and diplotypes), improved exposure measurement tools, and better-defined cancer end point phenotypes, we are faced with the realization that a rare gene/rare disease hypothesis may be a truer reflection of the relationship between genetic background and an individual’s risk of expressing a particular cancer phenotype. The good news is that with improved tumor classification, there is immediate potential to define susceptible genotypes and G × E associations that will enable us, for example, to identify gene carriers at increased risk for specific cancer subtypes (i.e., estrogen receptor–positive breast tumors; ref. 8). This emerging scenario (8-10) although exciting, suggests the presence of potentially large numbers of statistically significant low-to-moderate cancer risk genes, G × G and G × E combinations that will prove elaborately complex, difficult to discover, and time-consuming, at best, to convey in the traditional risk counseling setting. It is important to recognize the recency of progress in this field and the immediate challenges. This may be best illustrated in the closing comments of the recent report in Nature (10) by Easton et al., in which the authors report statistically strong and reproducible evidence for five novel SNPs as weak-acting breast cancer risk alleles. However, even though one of the most exciting of these SNPs is relatively common (minor allele frequency of 0.14) and seems to act in a codominant manner “at this stage”, the authors state that, “it is unlikely that these SNPs will be appropriate for predictive genetic testing, either alone or in combination with each other.” However, they conclude that, “as further susceptibility alleles are identified, a combination of such alleles together with other breast cancer risk factors may become sufficiently predictive to be important clinically.” The challenge here is to temper our own scientific enthusiasm for what these strong associations mean in terms of tangible clues about events that give rise to sporadic cancers in humans and communicating the effect of these weak-acting cancer risk genes to an anxious public in the form of “tests.”
Challenges with the Best Case Common Risk Gene/Cancer Scenario

A more positive viewpoint is the one that favors the presence of commonly acting and occurring gene variants that modify individual cancer susceptibility to environmental exposures such as obesity, chemical carcinogens, or tumor growth factors. These types of “general risk” cancer genes are thought to operate in mechanistic pathways that are common across tumor types (initiation, growth promotion, angiogenesis, metastasis) and potentially modifiable because of their dependence on an exposure. Given the complexity of these events and the number of potential players in these “pathways”, any one allelic variant of this kind is widely believed, if present, to confer very modest effects on individual cancer susceptibility (e.g., MTHFR and low folate status). Thus, even in the best case scenario of a common “cancer” pathway, we are talking about many weak-to-modest acting genetic risk factors that likely depend on environmental triggers and interactions with other gene variants; a scenario akin to the breast cancer risk gene example discussed above. Thus, in spite of the availability of microarray and other highly parallel genomic technologies and the ability to readily reduce such multidimensional data to a combined genotype-risk factor questionnaire test, the real challenge ultimately lies in determining which of this uncertain information is useful and appropriate to develop as risk counseling tools for an individual.

Genetic Variation is Just Another Risk Factor to Consider

With the expected complexity of the information to be obtained from these efforts, it could be argued that it is “time to test the waters” of the effects of such information on weak-to-modest acting cancer risk genes on individual beliefs about risk and motivation to change risk-associated behaviors. One could argue, however, that we already know how to communicate information on individual risk factors (gene or other) when the basis of the association between a risk factor and the disease state contains sufficient and reliable content that physicians, genetic counselors, and patients understand the implications of carrier status. This is true for any number of risk factors for which the disease association is well established (e.g., high cholesterol levels and cardiovascular disease). This is true even for those factors that only modestly but consistently affect risk (e.g., obesity and cardiovascular disease). Still further, we know how to integrate multiple data points into a summary risk statistic when one risk factor occurs in the presence of other risk factors (hypertension + obesity + family history and cardiovascular disease). When a link has been clearly established between a risk factor and a disease state and there is evidence that the risk can be mitigated with an intervention appropriate to the level of risk (i.e., exercise and obesity, prophylactic oophorectomy and BRCA1 carriers), we have well-established mechanisms for communicating risk to patients. Thus, in the absence of strong or consistent associations and importantly proven effective and risk-appropriate means of risk reduction, we should be highly selective and extremely cautious in delivering cancer risk information, genetic or other, to the individual in either the current research or clinical settings. This is particularly true in cases in which the scientific evidence is weak and no data exists on whether risk reduction options are in fact beneficial and not adverse. For the cancer field, such activities would seem, at present, to be unduly premature. At some point, the scientific community for each disease discipline will be called on to develop disease-specific guidelines for the use and clinical practice of low-to-moderate risk gene testing (i.e., when is the strength of the evidence sufficient, what magnitude of risk warrants clinical consideration, what defines harm?). Perhaps the big question is whether or not it is time to test these waters?

The Risk of Confusing the Public about the Importance of Genes in Cancer Risk

In general, from this author’s perspective, the problem with genes as risk factors is that we have given them some special status and, in essence, have used them to distract ourselves, myself included, and the public from the harder issues of affecting change in established risk behaviors that contribute to cancer risk (i.e., smoking, sun exposure, energy balance). At present, there exists significant potential to confuse the public about the relative importance of common genetic variation in cancer risk and worse, lead non–gene carriers with risky behaviors to believe they may be “off the hook.” Worse yet, in the absence of regulation of genetic testing, the abundance of weak, largely unreplicated, G and G × E cancer association studies serves to prematurely propagate commercial tests that poorly inform risk and capitalize on novelty, public curiosity, and individual worry. The commercialization of genetic tests on the basis of current evidence for common genes and disease risk generally has attracted relatively low opposition from the scientific community. Thus, in spite of weak scientific evidence, a rapidly expanding medley of direct-to-consumer (DTC) genetic tests continues to emerge unchecked in the marketplace, particularly in the U.S. This is best illustrated in the area of Nutrigenomics with promises, for example, “to link the dietary practices of a consumer with their genetic profile to produce advice aimed at the individual (11).”

Opportunities to Evaluate Public Uptake of Genetic Information with DTC Gene and Risk Assessment Tests

Although present DTC practices seem solely profit-motivated and predatory, the interest in such DTC tests by the investment community suggests a remarkably high public interest level in knowing how genes affect disease risk at an individual level. One has to consider the scientific community largely responsible for the propagation of the public’s interest for individualized risk assessment and gene testing with perhaps overstated promises from the human genome effort. Perhaps the relevant opportunity and challenge to the cancer research community is to evaluate and understand the current beliefs, motivation, and knowledge level of consumers seeking DTC genetic testing; tests that are
based on low-to-modest supposed risk elevations. In spite of the debatable current validity of these DTC activities, they do represent a revolutionary and fundamentally different approach of providing low-cost, minimal provider contact risk assessment and communication of prevention and screening messages. This DTC approach is likely to emerge as a societal mainstay as medical costs continue to increase and disease treatment costs overwhelm resources to conduct primary prevention. This is likely to become particularly true for those genetic and lifestyle risk factors that act modestly to affect disease risk and, because of the complex interaction with the environment and biology, are time-consuming to explain. Administered in a regulated fashion with high-quality information compiled by physicians, genetic counselors and user advocates, and high-quality testing and exposure measurements, such DTC approaches may prove a useful, low-cost strategy for communicating risk and risk-reducing behavior strategies. The DTC model, which has the potential to be highly personalized and private, may prove of particular value, for example, in communicating the effect of low-risk genotypes that modify the relationship between obesity and cancer, smoking and cancer, and aging and cancer. Given their potential to bridge a growing gap between high consumer expectation and low scientific evidence, the DTC model deserves consideration from the cancer research community as a device to link the emerging science of risk assessment, risk factor validation, and delivery of medical information on low-to-moderate risk cancer genes to the individual. Early evaluation of the Nutrigenomics field by the cancer community may allow the development of effective means to communicate parallel information to individuals regarding low-to-moderate risk genes for which simple lifestyle changes offer risk modification.

Remembering to Communicate What We Already Know about Modifiable and Established Cancer Risk Factors

Although we continue to pursue low-to-moderate risk genetic determinants of cancer, it remains clear that lifestyle and environmental factors play the much larger role in determining cancer risk (12), and that the adoption of healthy lifestyles and behaviors is good for humans regardless of their individual genotype. The overemphasis of the research community on a future of individualized healthcare based on genetic testing not only seems overly optimistic at present but it also diverts attention from the immediate need to develop effective and simple health messages for the public and community planners; messages targeted at counteracting the highly prevalent disease aspects of the “Western” lifestyle.

In a healthcare system that is increasingly burdened with environmental/lifestyle-driven illnesses that affect many, we are more than remiss in our public health duties to spend efforts prematurely on practicing the delivery of messages that ultimately look to increase testing costs and perhaps ultimately are too tenuous in nature to effectively motivate behavior change. Although I am actively involved in the ongoing pursuit of the genetic determinants of cancer risk along with my colleagues, I daily feel that my time and effort to improve public health would be better spent in an elementary school classroom with a clear and simple message on tobacco use, sun protection, physical activity, and energy balance. In my opinion, we should be cautious in communicating our expectations of genetics to explain disease risk and its ultimate public health impact. We should be globally diligent in engaging national leaders to continue to direct resource and policy change to community leaders, planners, and educators to deliver broadly acting societal support for healthy lifestyles and choices; a strategy derived from the tobacco control policies with proven value (13, 14).

References

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