Balancing Life-Style and Genomics Research for Disease Prevention

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the protein that is mutated in Huntington's disease, was discovered almost 10 years ago. Yet its normal function remains elusive, and it is still unclear how polyglutamine repeats in huntingtin cause selective pathology in discrete parts of the brain. Similarly, we already know that DISC-1 abnormalities are responsible for psychotic disturbances, but we have no idea as to the actions of normal or abnormal DISC-1. The combination of animal models and imaging technology may prove useful in resolving these dilemmas.

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VIEWPOINT

Balancing Life-Style and Genomics Research for Disease Prevention

Walter C. Willett

Genetic and environmental factors, including diet and life-style, both contribute to cardiovascular disease, cancers, and other major causes of mortality, but various lines of evidence indicate that environmental factors are most important. Overly enthusiastic expectations regarding the benefits of genetic research for disease prevention have the potential to distort research priorities and spending for health. However, integration of new genetic information into epidemiologic studies can help clarify causal relations between both life-style and genetic factors and risks of disease. Thus, a balanced approach should provide the best data to make informed choices about the most effective means to prevent disease.

The elucidation of the human genome sequence was an enormous achievement in biomedical research and will certainly lead to more effective disease prevention and treatment strategies. Among the anticipated advances are improved abilities to predict disease through identification of specific biochemical abnormalities that put individuals at risk. In principle, this information could more effectively focus screening and prevention strategies and also lead to "designer" interventions targeted at specific biochemical defects. However, overly enthusiastic expectations regarding the benefits of genetic research for disease prevention have the potential to distort research priorities and spending for health, resulting in both increased costs and suboptimal health. I argue here that the most effective strategies for disease prevention will be based on a balanced integration of new genetic information into epidemiologic studies.

Environmental and Genetic Contributions to Complex Human Disease

The relative contributions of genetic variation and nongenetic factors, here considered as "environmental" in the broadest sense, to common diseases such as cancer, heart disease, and psychiatric disorders have been the topic of much research and discussion for decades. These contributions can be expressed as the population-attributable risk percent, meaning the percentage of disease incidence that would be eliminated if the risk factor were removed. Often not appreciated in these discussions is that attributable risks for a complex disease can add to well over 100% because the disease can be avoided in more than one way. Statistically, this can be described as interactions among the various risk factors. As an extreme example, a genetic aberration may be necessary for a disease to occur, but the disease would not be manifest without the presence of an environmental risk factor. Thus, the attributable risks for the genetic aberration and the environmental factor would both be 100%. Phenylketonuria is a classic case: the clinical disease can be avoided either by not having the genetic mutation or by eliminating phenylalanine from the diet.

For most diseases contributing importantly to mortality in Western populations, epidemiologists have long known that nongenetic factors have high attributable risks, often at least 80 or 90%, even when the specific etiologic factors are not clear. This follows from observations that rates of cardiovascular diseases and major cancers differ 5- to 100-fold among various populations and that when groups migrate from low- to high-risk countries, their disease rates almost always change to those of the new environment (*1*, *2*). Dramatic changes in disease rates within a country over time also highlight the importance of environmental factors. For example, in the 1950s age-adjusted colon cancer mortality rates in Japan were less than one-fifth

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of those in the United States (*3*). However, rates among those with Japanese ancestry living in the United States were similar to U.S. Caucasian rates (*4*). In Japan today, colon cancer incidence and mortality rates have risen dramatically and are now as high as in the United States (*5*). This evidence has appropriately spurred efforts to identify the modifiable causes of colon cancer, with the hope that the historically low rates in Japan could be achieved by changes in diet or other environmental factors. Through this general strategy, considerable progress has been made for several important diseases. For example, we have been able to identify modifiable behavioral factors, including specific aspects of diet, overweight, inactivity, and smoking that account for over 70% of stroke (*6*) and colon cancer (*7*), over 80% of coronary heart disease (*6*), and over 90% of adult-onset diabetes (*8*) (Fig. 1).

Potential Contributions of Genomic Research to Disease Prevention

Findings from modern molecular research have helped to clarify the genetic contribution to many diseases. Highly penetrant mutations, which account for conspicuous clustering of diseases within families, are rare and appear to account for less than 5% of major cancers and coronary heart disease (*9*). Examples of these highly penetrant mutations include those in BRCA1 and BRCA2, which greatly increase risk of breast cancer, and mutations in the gene encoding the low-density lipoprotein (LDL) receptor, which lead to dramatic elevations in LDL cholesterol and high probability of early coronary heart disease. The rare affected individuals can benefit from knowledge that they carry these mutations because early intervention can reduce disease incidence and mortality.

In contrast, the majority of the genetic contribution to cancer and coronary heart disease risk appears to result from a large number of low-penetrance variants in gene sequence, known as polymorphisms. Typically, these polymorphisms have relative risks less than two and are, thus, not strong enough to cause obvious clustering of disease within families. To date, the results of studies relating individual polymorphisms to disease outcomes have been disappointing overall. Often, strong associations are reported that are later not confirmed in larger and better-designed studies. For example, initial reports of strong associations between a polymorphism in the vitamin D receptor gene and risk of bone fractures, led to dozens of subsequent studies with variable findings and failure to support any relation in a large prospective study (*10*). Similarly, initial reports of associations between polymorphism in the apolipoprotein B gene and coronary heart disease were not supported in subsequent larger studies (*9*). Factors contributing to this phenomenon are the design of studies that are too small, the use of inappropriate control groups, and the propensity to publish only positive results. Failure to collect data on environmental factors that may modify the relation between genotype and disease can also lead to inconsistency and confusion.

Even though the population attributable risk for any one of these polymorphisms may be small, many different polymorphisms could collectively result in a substantial attributable risk due to genetic factors. Because most of these polymorphisms have yet to be identified and studied adequately in relation to disease risk, it is not possible to estimate directly their collective contribution to risk. However, classic heritability studies, such as investigation of twins, do provide some insight into their role in disease etiology. In a recent combined analysis of Scandinavian twin registries, the percent of risk accounted for by heritable factors was estimated to be 27% for breast cancer, 35% for colon cancer, and 42% for prostate cancer, with the remaining percentages due to noninherited environmental factors (*11*). But any conclusions drawn from such a study about the relative environmental contributions need to be considered cautiously for two reasons. First, in these types of calculations the relative contribution of environment is almost always underestimated because the studies are conducted in populations with limited variation in diet and other environmental factors. For example, within the modern Scandinavian countries few individuals have dietary and physical activity patterns typical of groups at low risk for these cancers, such as the traditional populations of Asia, Latin America, or Africa. Second, the calculations assumed no interaction between genetic and environmental factors. Therefore, it is still possible that the attributable risk for environmental contribution is close to 100%. Because the Scandinavian countries presumably represent high-risk environments but genotypes usually do not vary greatly among their populations, the estimates of genetic risk are probably close to maximal. Thus, the conclusion from twin studies is consistent with the conclusion from migrant studies: the majority—probably the large majority—of important cancers in Western populations are due to environmental rather than genetic factors.

The recognition that the genetic contribution to risk of major diseases is mostly accounted for by a large number of polymorphisms has important implications for some of the benefits anticipated from genomic knowledge. First, apart from the rare, highly penetrant mutations, individual genetic variants are not likely to be useful for screening and risk identification because they confer only small relative risks. For many purposes, relative risks of at least 10 are thought to be needed for effective screening (*12*). It may be possible to identify many polymorphisms that each weakly predict risk of disease and combine them into a risk score that more effectively predicts disease. For example, serum estrogen levels, which are moderately good predictors of breast cancer risk (relative risks of three to four for highest versus lowest quintiles), are probably slightly increased or decreased by many polymorphisms in the genes encoding factors involved in estrogen synthesis and metabolism. Genotyping these polymorphisms and combining this information in a long linear model could provide much better discrimination than any single genotype. However, this information may still be less useful than simply measuring serum estrogen, which summarizes all the genetic and environmental determinants. The same would apply to serum cholesterol for predicting cardiovascular disease.

The existence of many weak variants that account for much of genetic risk also greatly reduces the likelihood that "designer" interventions will have a major impact on disease prevention. For example, correction of a metabolic alteration caused by a low-penetrance polymorphism would have only a small effect on dis-

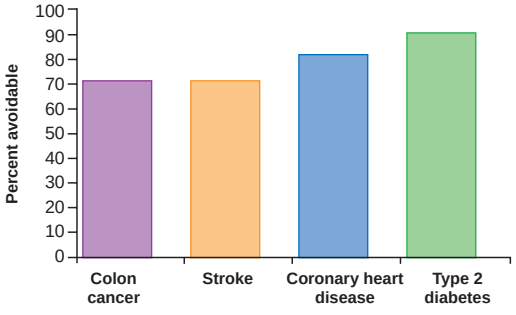

Fig. 1. Percentage of colon cancer, stroke, coronary heart disease, and type 2 diabetes that is potentially preventable by life-style modifications. For colon cancer (*7*), the low-risk definition includes body mass index <25 kg/m^2, physical activity equivalent to >30 min per day of brisk walking, folic acid supplement of 100 μg per day or more, less than three alcoholic drinks per day, lifetime nonsmoking, and fewer than three servings of red meat per week. For stroke (unpublished data) and coronary heart disease (*6*), the low-risk definition includes nonsmoking, a good diet (incorporating low intake of saturated and trans fat and glycemic load and adequate intake of polyunsaturated fat, N-3 fatty acids, cereal fiber, and folic acid), body mass index <25 kg/m^2, physical activity equivalent to > 30 min per day of brisk walking, and moderate alcohol consumption. For diabetes (*8*), the low-risk definition was similar to that for coronary heart disease except that the dietary score did not include folic acid or N-3 fatty acids.

ease risk, and abnormalities due to different polymorphisms in different genes may not be corrected by the same intervention. Also, many of the important environmental risk factors act by multiple mechanisms and affect more than one disease. For example, the effects of smoking on coronary heart disease risk are mediated by both nicotine and carbon monoxide, and the effects on cancers are mediated by other unrelated pathways. Thus, even with new genomic knowledge to come, the idea that we should identify persons who are genetically more susceptible to the deleterious effects of smoking is a distraction from efforts to avoid smoking in the whole population. The same applies to sedentary life-styles and many aspects of diet.

Integration of Genomics into Epidemiologic Studies

Integration of genomic research into epidemiologic studies of environmental factors should provide additional insight and health benefits. One major challenge in research on human disease prevention is that randomized trials are often not feasible, either for ethical or practical reasons. Though observational epidemiologic studies have become increasingly stronger and with less potential for bias (*13*), in some cases additional evidence that associations represent causal effects would be valuable and increase the justification for intervention. In this situation, documentation that a polymorphism in a gene specifically involved in the metabolism of an environmental factor is associated with disease risk can provide strong evidence that the environmental factor is causally related to disease. Because individuals are usually unaware of their polymorphism status, this evidence can come close to the strength of a randomized trial, and indeed has been referred to as "Mendelian randomization." Although such genomic information can strongly support an etiologic role of an environmental factor, in isolation this conveys little about the environmental dose-response relation or even the direction of the environmental effect. The epidemiologic data on the environmental exposure can provide this.

In several cases, genotyping has contributed to our understanding of disease etiology in this way. In epidemiologic studies, folic acid intake has been inversely associated with risk of colon cancer, perhaps by influencing DNA synthesis or methylation (*14*). Moreover, a polymorphism in the gene for methylenetetrahydrofolate reductase (MTHFR), which results in reduced activity of this enzyme involved in folate metabolism, has been associated with lower risk of colon cancer (*15*). If this genetic association is confirmed, it would provide powerful evidence for a causal role of folate in colon carcinogenesis. Interestingly, though, it had originally been hypothesized that the slow metabolizing MTHFR genotype would be associated with increased cancer risk, because the same genotype is positively associated with risk of neural tube defects (*16*). In other epidemiologic studies, folic acid intake has also been inversely, and serum homocysteine levels positively, associated with risk of coronary heart disease. One possible mechanism is that folic acid is a cofactor for the enzyme that re-methylates homocysteine to form methionine. Studies of the same MTHFR polymorphism and risk of coronary heart disease have been numerous but inconsistent. However, given the known relations between the MTHFR polymorphism and serum homocysteine levels and between serum homocysteine level and risk of coronary heart disease risk, the expected relative risk for the MTHFR polymorphism and incidence of coronary heart disease would be only about 1.1 to 1.2. Few studies have had the statistical power to detect such an association, and inconsistency among studies would also be expected because the strength of association is likely to depend on the folate intake of the population. Thus, resolution of this relation will require thousands of cases of coronary heart disease, most likely from the combined results of many studies. A clear, positive conclusion would be important to understanding of disease etiology, but this would have no implications for screening because of the small relative risk. Also, as illustrated by these examples, a specific genotype can be beneficial for one outcome (cancer), but detrimental for another (birth defects), which adds complexity to any clinical application.

Additional evidence that an association between an environmental factor and disease risk is causal is provided when an interaction between the environmental factor and relevant genotype is documented. For example, moderate alcoholic beverage consumption has been inversely associated with risk of coronary heart disease in many studies. Although some have hypothesized that constituents of red wine are the primary explanation, the benefits are probably mainly due to the ability of alcohol to increase serum HDL cholesterol levels and antithrombotic factors (*17*). The association of alcohol with risk of coronary disease has recently been shown to be strongest among persons homozygous for a polymorphism in the alcohol dehydrogenase type 3 gene (*ADH3*) that results in slower alcohol metabolism (*18*) (Fig. 2). Also, this polymorphism was significantly associated with coronary heart disease (CHD) risk only among those who consume one or more drinks of alcohol daily, and similar interactions have also been seen with HDL cholesterol as the outcome. Because these interactions would be improbable were alcohol consumption not causally related to CHD risk, this adds further weight to the already-strong evidence that moderate alcohol consumption per se reduces risk of coronary heart disease.

Even if a genetic polymorphism is not specific for the metabolism of the environmental factor under study, documentation of a clear interaction can provide evidence of causality. As an example, greater intake of cruciferous vegetables such as cabbage and broccoli is hypothesized to reduce the risk of lung cancer because their high content of isothiocyanates, which inhibit carcinogenesis in animals. In a recent study in China (*19*), individuals with detectable isothiocyanates in the urine were found to have a lower risk of lung cancer. Further, the strongest reduction in risk was observed among persons with polymorphisms in the genes for two glutathione *S*-transferases that result in delayed elimination of isothiocyanates and many other compounds. Although this finding needs to be reproduced, this interaction would not have been expected were cruciferous vegetables not protective for lung cancer risk.

Until recently, most cancers have been considered homogeneous entities in epidemiologic studies, whereas molecular pathology now indicates substantial heterogeneity. Further support for causality can be gained if an environmental factor is associated with a specific mutation in the DNA of tumors, often referred to as "fingerprinting." A classical example has been the association between aflatoxin exposure and a specific *P53* mutation in human liver cancers (*20*), which largely resolved a conflicting literature on this topic. In diseases with complex etiologies, relations between environmental exposures and a mutation may not always be completely specific, but a clear association can still be highly informative. Although the frequency with which associations between environmental factors and specific mutations in tumors will be convincingly documented is unclear, exploitation of this strategy has only just begun.

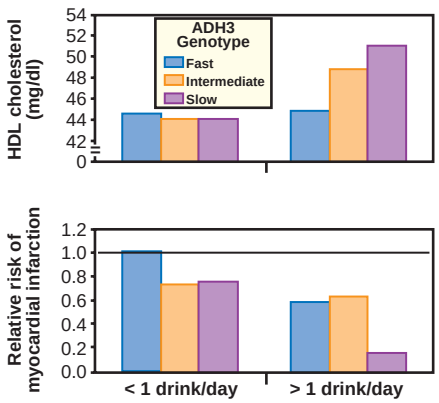

Fig. 2. Adjusted high-density lipoprotein levels and relative risks of myocardial infarction according to *ADH3* genotype and level of daily alcohol consumption among men. [Adapted with permission from (*18*). Copyright 2001, Massachusetts Medical Society. All rights reserved.]

Future Directions

Now that the human genome has been largely sequenced, one can expect that the most common polymorphisms will be identified over the next several years. Given the momentum of ongoing research, we will determine how these genetic variants are related to risks of important human diseases. However, to do so without interminable inconsistency in results will require carefully designed studies and probably the pooling of results unaffected by publication bias to obtain the best overall estimate of associations. These results will no doubt lead to better increase understanding of the pathogenesis of human disease and to the development of new pharmacologic agents and more individualized interventions. These benefits are likely to be greatest for treatment rather than prevention because in treatments a single disease and biological pathway is targeted and adverse effects of powerful agents are appropriately more acceptable. Recognizing that more effective treatments are desirable, our resources allocated to treatment already massively outweigh those spent for disease prevention, and even preventive strategies are heavily biased toward pharmacology rather than supporting improvements in diet and life-style that could be more cost-effective (*21*). For example, treatment of serum cholesterol with statins (*22*) alone could cost approximately 30 billion dollars per year in the United States and will have only a modest impact on coronary heart disease incidence (*23*). The inherent problem is that most pharmacologic strategies do not address the underlying causes of ill health in Western countries (Fig. 1), which are not drug deficiencies. (An effective pharmacologic treatment of obesity may be an exception because the adverse health consequences are so numerous and the condition of being overweight has become the norm.) The use of research approaches that integrate environmental factors including diet and other life-style variables with genetic information has the potential to clarify the roles of both environment and genotype in disease causation. This balanced approach should provide the best data to make informed choices about the most effective means to enhance health.

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23. The overall effect of using statins for primary prevention on rates of coronary heart disease in the U.S. population (*22*) may be modest because treatment reduces risk by about one-third in those receiving the drug and a substantial proportion of cases will occur among untreated persons. For example, on the basis of data from the MRFIT study (*24*), 35% of coronary heart disease occurred among the 20% of men in the population with the highest serum cholesterol; if this is reduced by one-third, the total population rate is reduced by 35% x 0.33 = 12%. The annual cost of treating 20% of U.S. adults over the age of 40 is roughly $1400 per person per year (*21*), multiplied by 24 million persons equals ~$34 billion annually. Prosser *et al.* have documented that widespread use of statins for primary prevention is not cost-effective at present prices with the use of widely accepted criteria (*21*). Use among patients with existing coronary disease or diabetes is better justified.
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VIEWPOINT

Complex Disease and the New Clinical Sciences

Jonathan Rees

Medical research today is dominated by a genocentric point of view. At the same time, clinical discovery and patient-oriented research have become less common. Here, I suggest that these developments are interdependent, each representing the flip side of an inaccurate view of how clinical advance occurs.

The last 25 years has seen medical research dominated by a genocentric view of discovery. The icon of the biological sciences, if not of everyday life, has been DNA. Today, even sunblock manufacturers feature images of the double helix on their advertising material. We have, we are told, entered a new golden-period of medical discovery. Medical research funding and personnel have grown as never before; it is implied that, now that we have solved the easy problems (that is, identified genes that cause a myriad of Mendelian disorders), we need new postgenomic approaches to solve "complex disease" and move from "bench to clinic." No longer are we to be satisfied with discovering the causes of rare diseases, but we must now set in place new strategic structures to study the big three: cancer, psychiatric disorders, and cardiovascular disease. For this, it is said, we need human-genome-project-like science, sequencing of a range of model organisms, and a host of "omic" projects—proteomics, metabolomics, etc. A giant cataloging of molecular natural history is entertained, a move from the small to the large scale, all to solve disease.

At the same time, an alternative set of views is being given more credence(*1–3*). Despite the mushrooming of basic research, clinical breakthroughs have become less common. The therapeutic revolution that transformed medicine in the 1950s and 1960s has petered out. New drugs to market are fewer than ever, the range of diseases of interest to the major pharma diminishing, and the success rate of either pharma or biotech is low (*4*). Clinical discovery and patient-orientated research are also noteworthy, because of their relative absence

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