EDITORIAL

Genetic and Epidemiologic Approaches to the Search for Gene-Environment Interaction: The Case of Osteoporosis

In this issue of the *Journal*, two Australian research groups report on twin studies of genetic and environmental contributions to bone mineral density. Nguyen et al. (1) analyzed data on 112 female twins 20–83 years old residing in Sydney and ascertained through the Australian Twin Registry. They looked at twin correlation in bone mineral density and related variation in it to lean mass and fat mass. They found evidence of a significant genetic component in bone mineral density as reflected in their heritability estimates. They also found evidence of environmental components in the relation between bone mineral density and fat mass. Hopper et al. (2) analyzed data on 215 pairs of female twins 10–26 years old ascertained through the Australian Twin Registry in Melbourne. They assessed genetic and environmental determinants of bone mineral density under the classic twin model of analysis of variance. They found strong evidence for a genetic component in variance that was modified by age, suggesting that gene-environment interaction plays a role in bone mineral density.

The study of the genetic and environmental factors affecting bone mineral density is important because bone mineral density is a strong predictor of osteoporosis later in life. Osteoporosis is a major public health problem, affecting more than 25 million people in the United States, mostly women. Bone fractures associated with osteoporosis (especially hip fractures) lead to significant morbidity and disability (3, 4). Yet the pathogenesis of osteoporosis starts early in life, leading some researchers to state that osteoporosis among the elderly is a pediatric disease (5). Prevention of osteoporosis through early intervention is becoming increasingly possible as more etiologic factors and therapeutic interventions are identified. Environmental risk factors associated with the genesis of osteoporosis including low calcium intake, vitamin D deficiency, and inadequate physical activity are amenable to early intervention designed to maximize peak bone density around menarche. Other suggested modifiable risk factors include smoking, alcohol consumption, and excessive protein consumption (3).

The role of genetic factors in osteoporosis has long been suspected. Twin studies like the ones reported in this issue strongly suggest that genetic factors influence bone mineral density. With advances in genetic technology, recent studies have been assessing the role of specific candidate genes in the etiology of osteoporosis (6), a notable one being the *vitamin D receptor* (*VDR*) gene (5). Since Morrison et al. reported that normal allelic variants in the *VDR* gene may account for a large fraction of the genetic effect on bone density (7), numerous studies have focused on this gene, with conflicting data in various populations, as shown in a recent meta-analysis of the literature (8). *VDR*, however, is not the only gene suggested to be related to bone density and osteoporosis. In December 1997, there were 67 genes associated with osteoporosis listed in the Online Mendelian Inheritance in Man (OMIM), a continuously updated catalog of Mendelian phenotypes authored by researchers at The Johns Hopkins University and available on the World Wide Web (9). This catalog has more than 8,000 of the estimated 50,000–100,000 human genes. More than 5,000 of these genes have been mapped to specific chromosomes. The list of osteoporosis genes in OMIM includes the *VDR* gene. However, many of these genes are associated with relatively rare conditions that include osteoporosis as one of their manifestations. Moreover, it is not clear how much of the etiology of osteoporosis can be explained by allelic variation in these genes and in yet to be discovered genes. Finally, it is not clear how these and other genes interact with the traditional risk factors for osteoporosis, such as calcium and smoking.

In many respects, the search for causes of osteoporosis is a paradigm of the search for the causes of most common chronic diseases of significant public health impact (such as cancer, diabetes, and heart diseases) that have multiple etiologies and considerable gene-
environment interaction. Assessing gene-environment interaction in chronic diseases will become an important public health research priority in the post-Human Genome Project era. The nature versus nurture controversy is being replaced by systematic evaluation of nature-nurture interaction. As more genes and their numerous allelic variants are discovered, it becomes crucial to assess how modifiable risk factors such as diet or drugs interact with genetic risk factors to influence disease risks. As most chronic disease risk factors have poor predictive value for disease occurrence, stratifying risk for disease among individuals with risk factors according to genetic susceptibility at one or more loci will improve the predictive value for disease occurrence among biologically susceptible individuals and may, thus, help target preventive and therapeutic interventions (10).

The methods used in genetics and epidemiology to study gene-environment interaction continue to evolve. The studies by Hopper et al. and Nguyen et al. illustrate classic twin designs with all their strengths and limitations, including selection biases and lack of generalizability of findings, as discussed by these authors and elsewhere. The purpose of such studies is to provide clues to the importance of genetic factors embodied in the concept of heritability and measured by analysis of variance or correlation. Neither environmental exposures nor specific genes are measured at this stage. Other traditional genetic analysis methods, such as linkage analysis and segregation analyses, are now evolving to include epidemiologic approaches of population-based study design, as well as measurements of specific gene variants and environmental exposures (11). Recent approaches include sequential family study sampling based on population-based case-control studies, family-based association studies that include affected relative pairs and that use parents as control subjects (12, 13). These and other approaches are emerging as ways of combining the methodological strengths of the fields of genetics and epidemiology.

In the final analysis, however, once specific genes are found using any number of techniques, and once allelic variations that lead to altered gene products are identified, it could become relatively simple to integrate such findings into traditional epidemiologic designs. While the usefulness of heritability studies will diminish, population-based epidemiologic studies will increasingly use genotype measurements at specific loci in addition to traditional risk factor information to identify interactions and refine risk estimates associated with infectious, chemical, or nutritional factors according to genetic susceptibility. As Shpilberg et al. noted recently, "The sequencing of the human genome offers the greatest opportunity for epidemiology since John Snow discovered the Broad Street pump" (14, p. 638). In spite of the limitations of epidemiologic studies, such studies do provide the key to assessing disease relative to absolute and attributable risks due to the interaction of measured genotypes and exposures. In the not too distant future, the classic epidemiologic paradigm of the two-by-two table, associating disease status with the presence or absence of a risk factor, will evolve into a two-by-four table that includes genotype measurements at one or more loci to measure nature-nurture interaction for virtually all human diseases.

REFERENCES


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