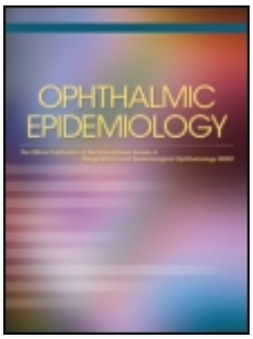

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EDITORIAL

The Value of Population-Based Studies in the Genomic Era

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Since the landmark Framingham Study in the 1950s, there have been many large population-based studies conducted in the United States and around the world. For over half a century, the contribution to medical knowledge from these population-based studies has been immense. In ophthalmology and vision research, we have benefited from studies done in diverse communities in Beaver Dam, Wisconsin; Salisbury and Baltimore, Maryland; the Blue Mountains and Melbourne, Australia; Rotterdam, the Netherlands; and the Latino communities of Los Angeles and Arizona, among others. These studies have provided us with estimates of disease prevalence and incidence, the natural history and prognosis of diseases, the burden on health care demand, and the socioeconomic impact of visual impairment. They have further confirmed the importance of key risk factors in different populations (e.g., smoking and age-related macular degeneration [AMD][1]), generated new hypotheses (e.g., inflammatory markers and AMD,[2] inhaled steroids and posterior subcapsular cataracts[3]), and helped define health care policies (e.g., screening for diabetic retinopathy).[4]

However, with the completion of the human genome project and the shift toward understanding the genetic basis of disease, along with increasing competition for limited research funding, we need to ask ourselves tough questions: Is there still a need for population-based studies? What is the unique value of these studies in the current genomic era? Are alternative, less costly methods available? Answers to these questions have far-reaching implications on how the National Eye Institute (NEI) at the National Institutes of Health (NIH) and other funding agencies around the world would approach and prioritize population-based research. In fact, the NEI has already announced a moratorium on funding research proposals that uses a population-based methodology until these questions and issues are addressed.[5]

In the genomic era, one of the key challenges facing scientists is how to resolve the complex etiologies of chronic diseases that cannot be explained by a single genetic or environmental risk factor. Even now, the degree of complexity is difficult to comprehend,[6] because multiple gene variants (polymorphisms), multiple environmental factors, and multiple possibilities of interactions between genes (gene-gene interaction), and between genes and environmental factors (gene-environmental interaction), appear to work together to shape an individual's susceptibility to certain diseases. What we do know is that genetic variants alone do not account for most cases of chronic disease.[6,7] We also know that for many chronic diseases, the penetrance of genes is usually low, and an individual's susceptibility to nongenetic (i.e., environmental and lifestyle) factors is conversely high.[8] In fact, our inability to identify strong correlations between specific genes and disease phenotypes indicates that in most diseases, there is unlikely to be a one-to-one correlation, but multiple genes or multiple genes and environmental factors are responsible for a specific phenotype.[6] To understand this complex etiological picture for any given chronic disease, we would require study samples covering the whole spectrum of the disease phenotype (early to late, subclinical to clinical), the whole spectrum of the gene variants, and information on as many environmental risk factors as possible. Only when such comprehensive data are available can we explore the multifaceted interactions between these factors.

These types of information are clearly available in population-based studies,[9] but can these data be collected from less costly alternatives? Let's consider the case-control study, which may be the cost-effective alternative in the genomic era to population-based studies. In a hypothetical case-control study, we would select cases with the disease (e.g., wet AMD) and

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a control group and measure the frequency of a genetic marker (e.g., complement factor H gene) in cases and controls. Does this obviate the need for population-based studies? There are several issues that should be considered. First, case-control studies focus on cases with a particular disease at a specific stage in its natural history. This limits the ability of case-control studies to detect associations with different disease phenotypes and to assess penetrance of genes. In our hypothetical case-control study, we will not be able to determine the association of complement factor H gene with early AMD (e.g., drusen) or with a different manifestation of late AMD (e.g., geographic atrophy). Second, prospective follow-up of population-based samples ensures the correct temporal relationship of risk factors/exposures and outcomes; thus, behavior change after clinical diagnosis of disease is not a factor. In contrast, case-control studies are retrospective in nature and likely to be subjected to important biases, such as recall and indication bias. Although genetic characteristics will not change and are not susceptible to these biases, lifestyle and environmental factors may and often do change, and the reporting of them may vary after diagnosis of a disease. Therefore, there is the potential for measurement error, which may lead to either nondifferential biases (toward the null) or differential bias that can either conceal a true association or spuriously reveal one that does not really exist. In our example, cases with AMD may overreport smoking behavior compared to controls. Third, selection of controls in case-control studies is critical to the quality of evidence that these studies provide. Hospital-based case-control studies or any other case-control study using a convenient, non-population-based source of controls will be subjected to selection biases and provide, at best, supporting evidence only. Fourth, the case-control study cannot accurately estimate the impact of a risk factor on the community (i.e., the population attributable risk of a factor). We may find a very significant association with a risk factor with an apparently high odds ratio, but if the prevalence of this risk factor in the population is low, then interventions targeted at this risk factor will not reduce disease burden by much. Only population-based studies can provide the information about the frequency of risk factors or genetic markers, and only then can we predict whether statistically significant findings are likely to have a major public health impact. Finally, with regards to cost, although a single case-control study will naturally cost less than a single large-scale population-based study, these isolated case-control studies can only study one disease outcome. Population-based studies, in contrast, can simultaneously investigate multiple disease outcomes and their associations with multiple risk factors. Thus, the ultimate cost of conducting many small case-control studies may add up and even exceed that of a single well-conducted population-based study with comprehensively collected data.

Of course, case-control studies are useful in answering research questions involving rare outcomes. It is often not appreciated that population-based studies are also useful for studying associations with rare diseases. Participants of population-based studies are valuable control samples for case-control studies of other diseases, as long as these diseases also arise from the target population from which the population controls were sampled. Baseline information from this population-based study will provide unbiased estimates of exposure to the main potentially confounding environmental and lifestyle factors, and stored genetic material can be tested on randomly selected subgroups whenever they are required as controls for a case-control study. Thus, the population-based study will not only answer primary questions regarding common disease outcomes but may provide controls for subsequent case-control studies with rare outcomes. Importantly, such case-control studies using population-based controls will allow more accurate assessment of the public health importance of new findings because the population controls will allow estimates of risk factor prevalence.

Population-based studies have been playing a key role in biomedical research for many years and must continue to be an integral part of any research strategy in the future. These studies allow translation of genetic discoveries into the patient community and are critical to understanding the complex gene-environmental etiology of diseases in the genomic era. We believe that providing the infrastructure for such research through the funding of existing and new population-based studies should be viewed as vital and as integral as the building and maintenance of core laboratory facilities for genetic research. It is time to recognize that population-based epidemiological research and basic genetic research are not mutually exclusive. The merging of these two disciplines, each with their complementary strengths, will substantially enhance the capability of biomedical research to answer key questions regarding health and disease in the genomic era.[10,11]

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