Emerging diseases – the need for a new research framework

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Past achievements

The twentieth century saw an enormous growth in understanding of the contribution of individual risk factors to health and disease. Classic epidemiological studies demonstrated the link between smoking and lung cancer,[1] and cholesterol and heart disease.[2] Other work uncovered the specific effects of a myriad of other less widely distributed risk factors, such as radiation and asbestos. This research was based on a model drawn originally from the germ theory, and then enshrined in the biomedical model of disease causation, in which exposure of a susceptible host to a particular agent led to the onset of disease. The exposures studied were clearly defined and easy to measure, such as smoking status, cholesterol level, or blood pressure. The causal pathway was easily understood, at least in retrospect.

Future challenges

The importance of these studies should not be underestimated. Collectively they have paved the way for policies that have brought about enormous reductions in premature mortality. They do, however, have many limitations and, specifically, they provide only a partial answer to the question of why a particular person has a specific disease, or why a certain disease is more common in one population than another.

There are many reasons for this. The first is that they often have limited ability to explain the entire variation of disease in a population. The classic example is Marmot's research on civil servants in the Whitehall study, in which the then conventional risk factors explained only a small amount of the observed variation in heart disease.[3] However they also fail to explain the huge variation in death rates between countries, such as the two-fold difference in rates of death from ischaemic heart disease in Spain and the United Kingdom, or why the rate in the United Kingdom has fallen by almost 50% in the past three decades.

Second, knowledge of the impact of specific risk factors on disease says nothing about the distribution of those risk factors within a population, which is often socially patterned. Exposure to many adverse factors is more common among the poor than the rich. A policy to reduce cancer requires knowledge not only that smoking causes lung cancer but also of why certain groups or categories of people smoke. This involves understanding the role that smoking plays in the lives of the disadvantaged, often functioning as a coping mechanism in adverse circumstances. It must also consider the contradictory messages that they are exposed to, in particular tobacco advertising that seeks to glamorise this unhealthy behaviour.

Third, it is increasingly recognised that some factors act over very long time periods, illustrated by the growing volume of work on early life determinants of adult disease.[4] There is now compelling evidence to link a range of adult diseases to conditions in early childhood. The mechanisms vary. Rates of stomach cancer reflect levels of *Helicobacter pylori* infection that are usually acquired in childhood. Cerebrovascular disease arises as a consequence of hypertension, which is closely associated with poor foetal growth, with babies of low birth weight much more likely to have high blood pressure in adulthood. Thus the very high death rates from stroke and stomach cancer in contemporary Portugal compared to Spain can only be understood by comparing the relative economic development of the two countries fifty years ago.[5]

Fourth, many potential risk factors are difficult to define, let alone measure. For example, even where only a single agent is being studied, measurement of exposure is problematic where this is intermittent, as with binge drinking[6] or ambient temperature,[7] where the frequency of exposure may be as important as the level of exposure. The ability to classify someone as a binge drinker or not at entry to a study only provides part of the picture. If the probability of death is related to the amount of time when the individual is severely intoxicated that a small change in the frequency of binging, say from once a month to once a week, will have a substantial impact on the probability of death. It is easy to see how changing circumstances could leed to such a change in behaviour over the course of a longitudinal study. Thus the risks associated with such exposures are particularly difficult to study with traditional cohort studies but case-control studies also face significant obstacles, especially where the outcome of interest is death.

Fifth, the single agent model has difficulty addressing situations in which multiple factors, whether genetic or environmental, interact. The complexity of these relationships can be illustrated by the case of stomach cancer. As already noted, it is now widely accepted that most cases are caused by infection with *Helicobacter pylori*. But those infected are not equally at risk of disease. The risk of stomach cancer is lower in individuals with certain genetic polymorphisms for interleukin-1[8] and among those with high intakes of dietary antioxidants.[9] In both cases the mechanism is likely to be their impact on the degree of inflammation of the stomach wall, and thus interference with regulation of gastric acid secretion. Thus, one's individual risk of getting stomach cancer depends on whether you were infected with Helicobacter, most often as a child, as well as your genetic make up and your diet. The rate of gastric cancer in Crete is much lower than would be expected given the prevalence of helicobacter infection.[10] Is it the genes or is it the diet? At least it is now possible to begin to sort this out.

These complex interactions do, however, mean that knowledge gained in one setting may simply not apply in another, quite different one. Understanding the reasons for the high death rate from heart disease in Russia is complicated by the finding that the relationship between blood lipids and heart disease seen in studies in western populations is not present in Russians, [11] possibly because of interactions with other dietary factors. Indeed, high density liporotein extracted from blood of Russians and Americans has different effects on cholesterol metabolism in cell cultures. [12]

Interactions with genetic factors are especially interesting. The frequency of a gene in a population may have its origin long in the past, where a particular genetic characteristic conferred a selective survival advantage on certain individuals, thus increasing the frequency of that gene in the contemporary population. [13] Thus, many single genetic mutations that cause disease when present as homozygotes may have persisted because the heterozygous form conferred some benefit. Examples include sickle cell disease and malaria, cystic fibrosis and cholera, and Tay-Sachs Disease and tuberculosis.

Problems may arise when circumstances change. Thus, westernisation of lifestyle has had a particularly adverse effect on some populations, such as those on Pacific islands and the Amerindian descendants of those who survived the slow crossing of the

Bering Strait around 20,000 years ago, where exposure to intermittent famine over millennia appears to have caused preferential survival of genes that promote fat storage, the so-called "thrifty genotype". [14] A plentiful food supply has led to a dramatic increase in diabetes and cardiovascular disease that would not have been seen in a western population consuming a similar diet.

The way ahead?

Given the complex nature of these relationships and the resulting difficulty we have in explaining existing patterns of health, how can we hope to address some of the larger questions now being asked of us? As politicians have belatedly come to understand that many of their policies in non-health sectors do have unexpected consequences for health there is a growing demand for health impact assessments. How does one assess the current, let alone future health impact of, for example, global climate change, enhanced international movement of goods and people, conflict and violence, and international trade policy? Each has characteristics that make elucidation of their health effects especially difficult. Their impact is typically indirect and often dependent on local context. Exposure is frequently difficult to define and causal pathways are complex. And research often challenges strong vested interests that invest considerable effort in making the picture even more confusing than it already is.

But these complex issues are susceptible to well designed research that draws on a range of methods and disciplinary paradigms, and assesses evidence from many different sources. Some of the best examples come from those working on the health effects of climate change.[15] They have quantified the impact of changes in temperature and rainfall on outcomes as diverse as deaths from heatstroke, [16] the distribution of malaria-carrying mosquitoes,[17] and climate-induced "natural" disasters, such as those resulting from El Niño.[18] In doing so they have imaginatively brought together diverse data sets, on weather patterns, mortality, and many other subjects. They have also connected their empirical research with scenario-based mathematical models, to improve the forecasting of likely health impacts over coming decades.

Those working on the health effects of climate change have also learned about the power of vested interests, in their case some major oil companies such as

ExxonMobil, which is currently developing a major, but subtle, campaign to persuade Europeans that the Kyoto Treaty is unnecessary.[19] Those working in other fields must contend with the efforts of other sectors of industry. One of the best documented example is the tobacco industry.[20] For example, when confronted by compelling evidence from the International Agency for Research on cancer (IARC) of a link between exposure to environmental tobacco smoke (passive smoking) the industry adopted a three point strategy. First, under its scientific strategy, industry lawyers identified direction of research and commissioned research to 'confound' it. Second, under its communication strategy, it promoted 'good epidemiology practice', which, despite sounding laudable, would have made epidemiological research prohibitively difficult ant which would, specifically, discount relative risks less than 2, which would thus exclude the typical values found for the health effects of environmental tobacco exposure. It also included selective leaking of initial results pre-publication to ensure the actual paper was 'old news' and to prevent IARC responding as the paper was not yet published. Third, its governmental strategy involved lobbying governments to oppose restrictions on indoor smoking bans

The tobacco industry is not, however, unique and similar tactics have been pursued at times by producers of, among others, foodstuffs,[21] chemicals, and asbestos.[22]

At this point it is necessary to reflect on one of the greatest obstacles to progress, lack of relevant data on populations and mortality. Many governments have only the vaguest idea of how many people live on their territory. Some have not undertaken censuses for many years,[23] in some cases because large areas are outside their effective control. Population registration systems are often fragmentary, and even in some advanced industrialised countries there are significant gaps in coverage of some groups. [24]

Thus, a substantial proportion of the world's population never officially exist, in that neither their death nor their birth will ever be recorded by any government agency. This is especially likely in areas of conflict, where there are often large-scale movements of population and where registration systems are a low priority. As a consequence, those who are most vulnerable to the changes that we seek to assess the impact of are most likely to be invisible.

Conclusion

The 21st century will bring an unprecedented demand from policy makers for an understanding of the diversity in levels of health in the world and an explanation of the impact of human activity on it. This poses many challenges to the epidemiology and demography communities. It will require new ways of working, drawing on diverse methods and the skills of many different disciplines, as well as a gift for lateral thinking.

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