Lecture September 04

Non-Experimental Studies [Fletcher Ch5 "Risk"]

NONEXPERIMENTAL STUDIES
{excerpt from Rothman & Greenland]

The limitations imposed by ethics and cost restrict epidemiologic research to nonexperimental studies in most circumstances. While it is unethical for an investigator to expose a person to a potential cause of disease simply to learn about etiology, people often willingly or unwillingly expose themselves to many potentially harmful factors. The extent of such exposures has been eloquently described by MacMahon (1979):

> They choose a broad range of dosages of a variety of potentially toxic substances. Consider the cigarette habit to which hundreds of millions of persons have exposed themselves at levels ranging from almost zero (for those exposed only through smoking by others) to the addict's three or four cigarettes per waking hour and the consequent two million or more deaths from lung cancer in the last half century in this country alone. Consider the fact that fewer than half of American women pass through menopause without either having their uterus surgically removed, being liberally dosed with hormones that are known to increase cancer risk in animals, or both. Consider the implications of the fact that more than fifty million women worldwide take regularly for contraceptive purposes a combination of hormones that essentially cuts off the function of their own ovaries.

The goal of all research is to obtain valid evidence regarding the hypothesis under study. **Ideally, we would want the quality of evidence from nonexperimental research to be as high as that obtainable from a well designed experiment, had one been possible**. In an experiment, however, the investigator has the power to assign exposures in a way that enhances the validity of the study, whereas in nonexperimental research the investigator cannot control the circumstances of exposure. If those who happen to be exposed have a greater or lesser risk for the disease than those who are not exposed, a simple comparison between exposed and unexposed will not reflect accurately the effect of the exposure. **Since the investigator cannot assign exposure in nonexperimental studies, he or she must rely heavily on the primary source of discretion that remains, the selection of subjects**.

If the paradigm of scientific observation is the experiment, then the paradigm of nonexperimental epidemiologic research is the "natural experiment," in which nature emulates an experiment. By far the most renowned example, the prototype of all natural experiments, is the elegant study of cholera in London conducted by John Snow. In London during the mid- nineteenth century, there were several water companies that piped drinking water to residents. Snow's natural experiment consisted of comparing the cholera mortality rates for residents subscribing to two of the major water companies: the Southwark and Vauxhall Company, which piped impure Thames river water contaminated with sewage, and the Lambeth Company, which in 1852 changed its collection from opposite Hungerford Market to Thames Ditton, thus obtaining a supply of water free of the sewage of London. As Snow (1860) described it,

> . . . the intermixing of the water ***supply*** of the Southwark and Vauxhall Company with that of the Lambeth Company, over an extensive part of London, admitted of the subject being sifted in such a way as to yield the most incontrovertible proof on one side or the other. In the subdistricts...supplied by both companies, the mixing of the ***supply is*** of the most intimate kind. The pipes of each company go down all the streets, and into nearly all the courts and alleys. A few houses are supplied by one company and a few by the other, according to the decision of the owner or occupier at the time when the Water Companies were in active competition. In many cases a single house has a supply different from that on either side. Each company supplies both rich and poor, both large houses and small; there is no difference in either the condition or occupation of the persons receiving the water of the different companies...it is obvious that no experiment could have been devised which would more thoroughly test the effect of water supply on the progress of cholera than this.
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> The experiment, too, was on the grandest scale. No fewer than three hundred thousand people of both sexes, of every age and occupation, and of every rank and station, from gentle folks down to the very poor, were divided into two groups without their choice, and, in most cases, without the* knowledge; one group being supplied with water containing the sewage of London, and amongst it, whatever might have come from the cholera patients, the other group having water quite free from impurity.
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> To turn this experiment to account, all that was required was to learn the supply of water to each individual house where a fatal attack of cholera might occur….

There are two primary types of non-experimental studies in epidemiology.

The first, the ***cohort study*** (also called ***the follow-up study*** or ***incidence study), is*** a direct analogue of the experiment; different exposure groups are compared, but (as in Snow's study) the investigator does not assign the exposure.

The other, the incident case- control study, or simply the ***case-control study,*** employs an extra step of sampling according to the outcome of individuals in the population. This extra sampling step can make a case-control study much more efficient than a cohort study of the entire population, but it introduces a number of subtleties and avenues for bias that are absent in typical cohort studies.

Cohort Studies

In the classic cohort study, the investigator defines two or more groups of people that are free of disease and that differ according to the extent of their exposure to a potential cause of the disease. These groups are referred to as the study ***cohorts*** (from the Latin word for one of the ten divisions of a Roman legion). In such studies, there is at least one cohort thought of as the exposed cohort—those individuals who have experienced the putative causal event or condition—and another cohort thought of as the unexposed) or reference cohort. There may be more than just two cohorts, but each cohort would represent a group with a different level or type of exposure. For example, an occupational cohort study of chemical workers might comprise cohorts of workers in a plant who work in different departments of the plant, with each cohort being exposed to a different set of chemicals. The investigator measures and compares the incidence rate of the disease in each of the study cohorts.

In Snow's natural experiment, the study cohorts were residents of London who consumed water from either the Lambeth Company or the Southwark and Vauxhall Company and who lived in districts where the pipes of the two water companies were intermixed. Snow was able to estimate the frequency of cholera deaths, using households as the denominator, separately for people in each of the two cohorts (Snow, 1860):

> According to a return which was made to Parliament, the Southwark and Vauxhall Company supplied 40,046 houses from January I to December 31, 1853, and the Lambeth Company supplied 26,107 houses during the same period; consequently, as 286 fatal attacks of cholera took place, in the first four weeks of the epidemic, in houses supplied by the former company, and only 14 in houses supplied by the latter, the proportion of fatal attacks to each 10,000 houses was as follows: Southwark and Vauxhall 71, Lambeth 5. The cholera was therefore fourteen times as fatal at this period, amongst persons having the impure water of the Southwark and Vauxhall Company, as amongst those having the purer water from Thames Ditton.

Many cohort studies begin with but a single cohort that is heterogeneous with respect to exposure history. Comparisons of disease experience are made within the cohort across subgroups defined by one or more exposures. Examples include studies of cohorts defined from membership lists of administrative or social units, such as cohorts of doctors or nurses, or cohorts defined from employment records, such as cohorts of factory workers.

Prospective Versus Retrospective Studies

Studies can be classified further as either prospective or retrospective. We define a prospective study as one in which exposure and covariate measurements are made before the cases of illness occur. In a retrospective study these measurements are made after the cases have already occurred.

The distinction between the classification as cohort or case-control and prospective or retrospective should be firmly drawn, because these two axes for classifying epidemiologic studies have often been confused: Early writers referred to cohort studies as prospective studies and to case-control studies as retrospective studies because cohort studies usually begin with identification of the exposure status and then measure disease occurrence, whereas case-control studies usually begin by identifying cases and controls and then measure exposure status. **The terms *prospective* and *retrospective,* however, are more usefully employed to describe the timing of disease occurrence with respect to exposure measurement.** For example, case-control studies can be either prospective or retrospective. A prospective case-control study uses exposure measurements taken before disease, whereas a retrospective case-control study uses measurements taken after disease. Both cohort and case-control studies may employ a mixture of prospective and retrospective measurements, using data collected before and after disease occurred.

The prospective/retrospective distinction is sometimes used to refer to the timing of subject identification***, rather than measurement of exposure and covariates. With this usage, a retrospective (or historical) cohort study involves the identification and follow-up of subjects, but the subjects are identified only after the follow-up period under study has ended. The identification of the subjects, their exposure, and their outcome must be based on existing records or memories.

Experiments are always prospective cohort studies, because the investigator first assigns the exposure and then must wait until disease events occur. On the other hand) many occupational cohort studies are retrospective, in the sense that subjects are selected after the disease occurred. [end of excerpt]

***** e.g. Hennekens and Buring Fig 2-3**