Egyptian Journal of Surgery Vol. (21), No. (4), Oct., 2002

PROFESSIONAL DEVELOPMENT

Research Design

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This series of articles is aimed at enhancing your surgical research skills. Research design will be covered over two issues of the journal. In this issue we present the categories of research design and a detailed description of observational research. The forthcoming issue of the journal will cover experimental research (clinical trial) in detail.

INTRODUCTION

Research can be crudely divided into observational and experimental studies. In observational studies we collect information about one or more groups of subjects, but do nothing to affect them. Observational studies can be prospective, where subjects are recruited and data are collected about subsequent events, or retrospective, where information is collected about past events. Observational studies include surveys, case-control studies and cohort studies. Experimental studies are those in which the researcher affects (controls) what happens to all or some of the individuals.

In most research we wish to extrapolate the results from a study to the population in general. There are two aspects that require particular attention in this respect. First, the sample(s) studied should be representative of the population(s) of interest; this applies especially to observational studies. Secondly, groups being compared should be as alike as possible, apart from the features of direct interest; this applies particularly in experimental studies, such as clinical trials, but is also relevant in many observational studies, such as case-control studies.

CATEGORIES OF RESEARCH DESIGN

Research designs can be classified in several ways:

1. observational or experimental;
2. prospective or retrospective;
3. longitudinal or cross-sectional.

These terms are explained below. The first classification relates to the purpose of the study, while the others describe the way in which the data are collected. Not all combinations of these classifications are possible, but most are.

OBSERVATIONAL OR EXPERIMENTAL

In an observational study the researcher collects information on the attributes or measurements of interest, but does not influence events. An example would be a study to discover the prevalence of peptic ulcer disease among patients with portal hypertension. Observational studies include surveys and most epidemiological studies. By contrast, in an experimental study the researcher deliberately influences events and investigates the effects of the intervention. Experimental studies include clinical trials and many animal and laboratory studies. In general, stronger inferences can be made from experimental studies than from observational studies.

PROSPECTIVE OR RETROSPECTIVE

There is a clear distinction between prospective studies, in which data are collected forwards in time from the start of the study, and retrospective studies, in which data refer to past events and may be acquired from existing sources, such as

hospital notes, or by interview. Experiments are prospective, but observational studies may be prospective or retrospective. Of course, retrospective data can be obtained to compare different treatments, for example different types of mastectomy, but such a study would not be an experiment as it was not a pre-specified study performed under standardized conditions.

LONGITUDINAL OR CROSS-SECTIONAL

Longitudinal studies are those which investigate changes over time, possibly in relation to an intervention. Observations are taken on more than one occasion, although they may not all be used in the analysis. Clinical trials are longitudinal because we are interested in the effect of treatment commencing at one time point on outcome at a later time. Cross-sectional studies are those in which individuals are observed only once. Most surveys are cross-sectional, as are studies to construct reference ranges. Observational studies may be longitudinal or cross-sectional, but experimental studies are usually longitudinal.

STUDY DESIGN INTER-RELATIONSHIPS

Figure (1) summarizes the most likely possible combinations of design features. There is a clear distinction between experimental studies which are nearly all prospective and longitudinal, and observational studies which can be either retrospective or prospective, and also either cross-sectional or longitudinal.

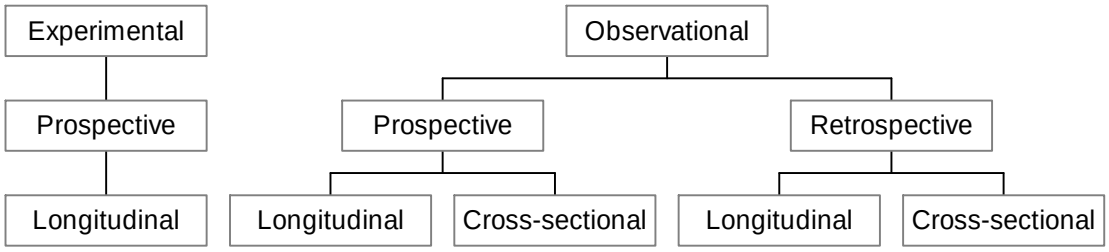

Figure (1): Types of research design.

OBSERVATIONAL STUDIES

As shown in Figure (1), observational studies can take different forms. Many studies are carried out to investigate possible associations between various factors and the development of a particular disease or condition. Example are studies of the relation between passive smoking and lung cancer, the use of oral contraceptive pills and breast cancer, and alcohol consumption and liver disease.

There are two main types of observational studies that are used to investigate causal factors - the case-control study and the cohort study. Figure (2) indicates the basic structure of these designs. In a retrospective case-control study, a number of subjects with the disease in question (the cases) are identified along with some unaffected subjects (controls). The past history of these groups in relation to the exposure(s) of interest is then compared.

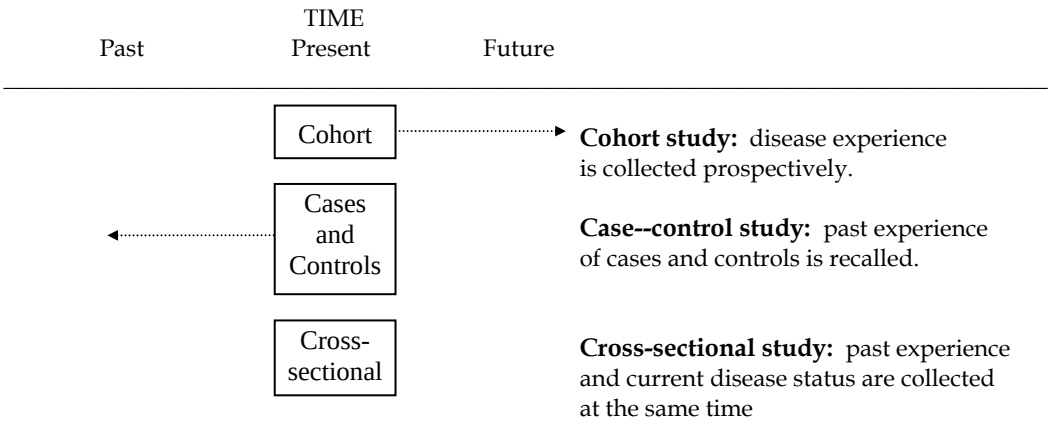

Figure (2) : Basic structure of the case-control study, the cohort study and the cross-sectional study.

In contrast, in a prospective cohort study a group of subjects is identified and followed prospectively, perhaps for many years, and their subsequent medical history recorded. The cohort may be subdivided at the outset into groups with different characteristics to study which subjects go on to develop a particular disease. (There is also the historical cohort study, in which a past cohort is identified, and their experience up to the present is obtained. Few studies like this are carried out as the necessary data are rarely available.)

Also shown in Figure (2) is the cross-sectional study, in which subjects are investigated on one occasion only. The advantages and disadvantages of the retrospective case-control study, the prospective cohort study and the cross-sectional study are described in the next three sections.

I - CASE-CONTROL STUDIES

As shown in Figure (2), in the case-control study we identify a group of subjects (cases) with the disease or condition of interest, say lung cancer, and an unaffected group (controls), and compare their exposure to one or more factors of interest, such as smoking. If the cases report greater exposure than the controls, we may infer that exposure is casually related to the disease of interest, for example that smoking affects the risk of developing lung cancer.

The prime advantages of the case-control approach are practical: it is relatively simple, and thus quick and cheap. The case-control design is also valuable when the condition of interest is very rare. The disadvantages of this design relate to possible biases in the comparison of cases and controls.

SELECTION OF CANTROLS

The main difficulty with the case-control study is the selection of an appropriate control group as it is desirable for the controls to be as similar as possible to the cases, except that they do not have the disease being investigated. Obtaining such a group is not straightforward. Subjects who do not have the outcome of interest may as well differ in other ways from the cases, and in particular may be atypical with regard to the exposure of interest.

For example, when the cases are hospital patients with a particular condition, it is common to take as controls patients in the same hospital with different conditions. Patients in hospital may be expected to have other conditions that are also affected by the exposure of interest. For example, in a study of lung cancer and smoking, use of hospital controls may well lead to an underestimate of the relation because many other medical conditions are related to smoking.

The alternative approach is to select community controls. It is, however, not straight-forward to select a representative control group from the general population, especially if, for example, a certain age and sex distribution is required. There is also likely to be less willingness among healthy people to participate in a study than among hospital patients, which would introduce a further bias.

Some studies use both hospital and community controls, which is a desirable approach when there is doubt about the validity of hospital controls.

One way to make cases and controls more comparable is to match for some variables that might confuse the comparison. Matching means that each case is individually paired with a control subject. For example, for each case we might seek a control subject of the same age, sex and occupation. Matching is only useful for variables that are strongly related to both the exposure, and the outcome of interest. Further, it is important to appreciate that any variable used for matching cannot be investigated as a possible risk factor for the outcome.

For rare events, the strength of the study can be increased by having more controls than cases (3:1). Where matching is used, each case can have several matched controls.

SELECTION OF CASES

The selection of cases should also be considered carefully as many diseases such as cancer are heterogeneous in cause, nature and degree. The choice of cases with respect to type of disease and other factors such as age, determines the degree of generalizability of results.

RECALL BIAS

An important source of bias is due to the differential recall by cases and controls. In many case-control studies retrospective information is obtained by interviewing the subjects. People with a particular disease or condition, in comparison to healthy individuals, may have thought a lot about a possible link with their past behaviour especially with respect to widely publicized risk factors.

Although it may not always be present, there is enormous scope for recall bias in case-control studies. In general, the bias is due to under-reporting of exposure in the control group. Usually there are no records against which to check reports, but efforts should be made to evaluate and minimize the effect of recall bias.

INACCURACY OF RETROSPECTIVE DATA

In addition to biased recall of events, there is the possibility of a general inaccuracy in recalled information. Studies requiring recall of detailed habits are prone to this problem, as are those requiring a precise breakdown of subjects' working history to evaluate total exposure to a hazard. A related problem is that data obtained from hospital notes will suffer from incompleteness due to missing information and missing notes.

ASCERTAINMENT BIAS

Another form of bias can arise through a relation between the exposure and the probability of detecting the event of interest. For example, women taking oral contraceptive pills will have more frequent cervical smears than women not on the pill, and as a consequence are more likely to have cervical cancer detected, if it is present (and it is likely to be detected at an earlier age). Thus, in a case-control study comparing women with cervical cancer and a control group, an excess of pill taking among the cases may be (at least partly) due to the ascertainment bias (or detection bias) related to more frequent screening.

II - COHORT STUDIES

The prospective cohort study (or follow-up or longitudinal study) is the method of choice for an observational study, but there are certain difficulties with this design too. The essence of the cohort study is to identify a group of subjects of interest, and then follow them up to see what happens. Because of the need to observe unaffected individuals until a fair proportion develop the outcome of interest, cohort studies can take a long time, and may thus be very expensive. They are usually unsuitable for studying rare outcomes, as it would be necessary to follow a huge number of subjects to get an adequate number of events.

There is usually one particular event of interest, such as death or recurrence of disease, but there may be several. There may be subgroups of subjects identified at the outset whose experience is to be compared, such as smokers and non-smokers, or patients with different stages of breast cancer. Alternatively, the purpose of the study may be to use the information gained to try to identify those subjects most at risk of developing the outcome of interest. For example, we could follow patients with cirrhosis of the liver, identify those developing carcinoma of the liver over, say, ten years, and compare their characteristics with those who do not get a carcinoma. Because the study is prospective, the nature and quality of the data recording can be carefully controlled.

SELECTION OF SUBJECTS

In follow-up studies, the probability of the event of interest occurring may be strongly related to how the sample was obtained. Clinic-based studies of some disease may bias the study towards selecting higher risk patients, as they are the ones who need to seek medical advice at outpatient clinics. In some cases, however, studying attenders at special clinics may give an optimistic picture as they represent the cases that have survived and are able to attend such clinics. Population samples, although the solution, are difficult and expensive to carry out.

LOSS TO FOLLOW-UP

The main difficulty encountered in cohort studies is that some subjects will not be followed up for the full length of the study. They may move to another area or lose interest, or they may even die. The longer the study, the more subjects will be lost. Losses to follow-up reduce the numbers supplying information, and thus weaken the analysis slightly. The main worry, however, is that subjects are lost to follow-up for some reason that is related to the outcomes being studied or to pre-defined risk categories. There is a considerable risk of this type of bias, and so strenuous efforts are needed to try to contact as many

people as possible. Some losses are inevitable, and it is useful to compare the characteristics of these subjects on entry to the study with those with whom contact is maintained.

OTHER PROBLEMS

Long-term studies may suffer from problems associated with change in habits. For example, people may change jobs (and hence exposure to risk) or become unemployed, or may change the consumption of cigarettes, alcohol or specific items of food. It is, though, a strength of the cohort study that repeated assessments of risk status can be made.

Perhaps a more serious problem is that different groups may not be investigated equally closely. In particular, a high risk group may be studied more carefully, resulting in advantageous earlier detection of medical problems. Conversely, intensive investigation of the high risk group may lead to the greater discovery of conditions that are actually equally common in the low risk group. Surveillance bias is eliminated when all subjects are investigated identically, preferrably with the assessors being unaware of each person's risk status.

III - CROSS-SECTIONAL STUDIES

In a cohort study, subjects with different characteristics are identified and followed to see what happens. By contrast, in a cross-sectional study all the information is collected at the same time because subjects are only contacted once. Many cross-sectional studies are descriptive, and these are often called surveys. For example, we might ask surgeons about their smoking consumption, carry out a survey of the use of evidence-based practice in a particular area, or investigate the ability of a particular blood test to give a correct diagnosis.

The cross-sectional study does not suffer from many of the difficulties that affect these other designs, such as recall bias and loss to follow-up. It is relatively cheap and easy to carry out. Needless to say, there are different special problems associated with cross-sectional studies.

SAMPLE SELECTION

Cross-sectional studies share the problems of sample selection with cohort studies. Although research is carried out on a limited number of individuals, the interpretation of results is usually extended widely. A survey of surgical practice, or health education in one area, will probably be taken as an indication of what happens nationally. However, the nature of hospital inpatients, clinic attenders, general practice attenders and those not attending may vary enormously. Apart from affecting the observed prevalence of a disorder, the choice of sample may have a strong effect on the observed relation with other factors. Clearly, the validity of the extrapolation depends crucially on the representativeness of the sample. It is an inherent weakness of most observational studies that the sample is not representative of the population. In some cases, however, we can select a random sample for a survey, which is the ideal method.

RESPONSE RATES

Many cross-sectional studies obtain most of their information from postal questionnaires. Non-response can be a big problem, with perhaps only 50% to 80% of questionnaires being returned. Many studies have found that there are marked differences between those who do or do not respond to a questionnaire, with the non-responders usually being less healthy. This is sometimes known as volunteer bias.

CAUSE OR EFFECT ?

The particular difficulty associated with cross-sectional studies looking at associations with disease concerns the sequence in time of the disorder of interest and the possible risk factor. For example, if we were to carry out a study of the relation between employment status and health, we would probably find that the unemployed have worse health than those in employment. We might conclude that being unemployed leads to poorer health, but an equally valid possibility is that poor health leads to being unemployed, or both statements might be true. Because we have collected both sets of information at the same time, we cannot draw a clear inference of causality.

CHANGE OVER TIME

The last point to be considered is that two or more independent sets of cross-sectional data can be used to make inferences about changes over time.