

Common Approaches in Medical Research

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ABSTRACT

The cohort study, case-control study and randomized control trial are commonly used in medical research. Each type has its own strength and weakness. All doctors, no matter whether they are actively involved in research or not, should be familiar with these study designs. Understanding the principles can help them to be more critical when reading medical journals.

Keywords: Case-control study, cohort, randomized control trial

INTRODUCTION

There are many different approaches in medical research, ranging from molecular studies to population-based studies. In this article, three common study designs, which are regarded as fundamental concepts in medical research, will be discussed. Clinicians who are interested in doing research should have thorough knowledge in them, especially the strength and weakness of each study design. These three study designs include cohort study, case-control study and randomized control trial.

COHORT STUDY

"I work under the sun every day. What will happen to my skin in the future?" This kind of question can be answered by the cohort study. The cohort study is a form of observational analytic epidemiological study.¹ It is also called longitudinal study. There are two main types of cohort studies, namely the prospective cohort study and retrospective cohort study.

Prospective cohort study

A group of subjects are selected. They are all free of disease at the start. The exposure status is determined. The risk factors in the study can be multiple and the outcomes, characterized by onset of certain diseases, can also be multiple. The data collected is then analyzed. The example of sun exposure may be used to illustrate the concept. We recruit 10000 healthy subjects into the study. We then assess their average sun exposure and classify the subjects into high exposure and low exposure groups. Follow up these subjects for 50 years and record the incidence of various skin diseases such as skin cancers, wrinkles and atrophy. By comparing the incidence of various skin diseases in the high exposure and low exposure groups, we can draw the conclusion whether sun exposure is associated with certain skin diseases.

Relative risk

To express the effect of the exposure on the outcome, the term 'relative risk' is often used.² The relative risk is the ratio of the risks of disease for those with the risk factor to those without the risk factor. It indicates the likelihood of developing the disease in the exposed group relative to the non-exposed group. The usage of 'relative risk' is synonymous with 'risk ratio'. From the data collected in a cohort study, a two by two table can usually be constructed:

	Disease	No disease
Exposed	a	b
Unexposed	c	d

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Relative risk (RR) =

$$\frac{\text{Incidence of disease in the exposed group}}{\text{Incidence of disease in the unexposed group}}$$

$$RR = \frac{a / (a + b)}{c / (c + d)}$$

When the relative risk is greater than one, it means there is an increased chance of developing the disease among those exposed to the risk factor. When the relative risk is equal to one, it means there is no association between the risk factor and the disease. When the relative risk is smaller than one, the factor is actually protective.

Attributable risk

Another term with which one should be familiar is 'attributable risk'. It is defined as the rate of an outcome in exposed individuals that can be attributed to the exposure. It is derived by subtracting the rate of the outcome among the unexposed from the rate among the exposed individuals.

$$\text{Attributable risk} = \text{Incidence of disease in exposed group} - \text{Incidence of disease in unexposed group}$$

A hypothetical example can illustrate the different implications of the terms 'relative risk' and 'attributable risk'.

Assume:

Incidence of lung cancer in smokers
= 900 / 1000000 / year

Incidence of lung cancer in non-smokers
= 100 / 1000000 / year

Incidence of myocardial infarction in smokers
= 3200 / 1000000 / year

Incidence of myocardial infarction in non-smokers
= 1000 / 1000000 / year

For lung cancer, the relative risk of smoking
= 900 / 100 = 9

For myocardial infarction, the relative risk of smoking
= 3200 / 1000 = 3.2

It seems that smoking is not so important in causing myocardial infarction when compared with lung cancer.

However, if we look at the attributable risks, the picture will be different.

For lung cancer, attributable risk of smoking
= (900 - 100) / 1000000 / year
= 800 / 1000000 / year

For myocardial infarction, attributable risk of smoking
= (3200 - 1000) / 1000000 / year
= 2200 / 1000000 / year

It means that quitting smoking can prevent 800 cases of lung cancer in one million person-years. On the other hand, quitting smoking can prevent 2200 cases of myocardial infarction in one million person-years.

The relative risk measures the strength of the association between the risk factor and the disease. The attributable risk indicates how many cases can be prevented by eliminating a risk factor; it is important in health care planning.

Odds ratio

In a cohort study, the relative risk can be determined. Another way to express the increased risk is the odds ratio.

	Disease	No disease	Total
Exposed	a	b	a+b
Unexposed	c	d	c+d
Total	a+c	b+d	a+b+c+d

$$\text{Odds for exposed} = \frac{Pe}{1 - Pe} = \frac{a / (a + b)}{b / (a + b)}$$

$$\text{Odds for unexposed} = \frac{c / (c + d)}{d / (c + d)}$$

Odds ratio (OR):

$$OR = \frac{a / b}{c / d} = \frac{ad}{bc}$$

It is easier to understand the term 'relative risk'. Why should we use odds ratio?

In a case-control study, which will be discussed later, the participants are selected on the basis of disease status. One does not know the incidence of the disease in the presence or absence of the risk factor. The formula for calculating the relative risk cannot be applied. Only the odds ratio can be calculated.

Let us compare the two formulae:

Relative risk:

$$RR = \frac{a / (a + b)}{c / (c + d)}$$

Odds ratio:

$$OR = \frac{a / b}{c / d} = \frac{ad}{bc}$$

When the disease is rare, (a + b) is approximately equal to b, and (c + d) is approximately equal to d.

Thus,

$$RR = \frac{a / (a + b)}{c / (c + d)} \approx \frac{a / b}{c / d} \approx OR$$

The odds ratio is a good approximation of the relative risk when the disease is rare.

The prospective cohort study is the most powerful observational study design to define the causal relationship. It can assess the exposure accurately. Information on the confounding variables can also be collected. Multiple outcomes can be assessed. However, the main disadvantage is that if the latency period between the exposure and the outcome is long, it will take a very long time to get the conclusion. In the example of sun exposure and skin changes, it takes 50 years to get the result!

Retrospective cohort study

A cohort study can be retrospective. All relevant events have occurred. The identification of past exposure status depends on previously collected data. The disease status is determined by current examination or investigation. It is cheap and quick to get the results. It is especially efficient for diseases with long latency. However, because the data of exposure was not specifically collected for the study purpose, the quality may not be ideal. Moreover, information on the confounding factors is usually unavailable.

CASE-CONTROL STUDY

The basic concept is that one collects patients with

a particular disease and a control group without the disease.³ One then studies the frequency of the risk factor in these two groups and compares the results. Let us take an example to elaborate the concept. Suppose we have the question: "Will having multiple sexual partners increase the risk of the cervical cancer in women?" We collect all cases of cervical cancer in Hong Kong. We then take a random sample of normal control. In both groups, we ask how many sexual partners they have in their lives. We can construct a 2 x 2 table as follows:

	Case	Control
Multiple sexual partners	a	b
Single or no sexual partner	c	d

$$\text{The odds ratio} = \frac{ad}{bc}$$

If the odds ratio is greater than one, having multiple sexual partners does increase the risk of getting cervical cancer.

Although the design seems to be fairly simple, one of the most challenging and difficult parts is the selection of the control series. Theoretically, the controls should be randomly selected from the same source of the patients. If the cases are from the general population, selection of true community controls is ideal. It involves obtaining a sampling frame, the costly exercise of contacting and interviewing and effort of minimizing non-response bias. Moreover, the controls should be assessed by some means to exclude cervical cancer so that they are really 'normal controls'.

If the cases are not from the general population, for example from one teaching hospital, it will be rather difficult to define the control group of the same source population. It is convenient to use hospital-based controls because the response rate is usually high. However, it has been shown that hospitalized controls are more likely to smoke, drink excessive alcohol and use oral contraceptives. Presumably there are other unknown potential confounders as well. These may affect the accuracy of the conclusions drawn from the study if the control group is hospital-based.

Another aspect worth mentioning is the number of controls per case. If the case number is substantial, the best case-control ratio is one to one. If the number of cases is limited, we may increase the case-control

ratio to increase the power of the study. However, the maximum recommended case-control ratio is 1:5.

Bias in case-control study

Selection bias

There are two issues about selection bias in a case-control study. Do the cases represent the population? This will affect the external validity. It means whether the result can be generalized to the whole population. The second issue about selection bias is the selection of controls. Are the controls from the same source population as the cases? This affects the internal validity of the study. In general, internal validity has priority over external validity.

Measurement bias

Measurement of the outcome is usually not a problem in case-control study. It is not difficult to determine cases and healthy controls. The measurement of exposures is the major potential bias. Patients are more motivated to recall exposures than normal controls, for example mothers of abnormal newborns may recall more febrile illnesses during pregnancy than mothers of normal newborns even though the actual number of febrile illnesses is the same.

RANDOMIZED CONTROL TRIAL

When we say a certain treatment modality is effective, we should ask ourselves, "What is the evidence?" The traditional methods of evaluating efficacy of treatments include patho-physiological reasoning, single case reports, personal experience, case series and non-randomized control studies. However, there are drawbacks in these sources. Taking the case series as an example, we should bear in mind that there are many non-specific effects including the natural history of the disease, regression-to-the-mean effect and placebo effect. In assessing the efficacy of a treatment, the randomized control trial is the gold standard.⁴

The basic design of a randomized control study is as follows:

1. Subjects are recruited for the study
2. Informed consents should be obtained
3. The subjects are randomized into the treatment group and placebo group
4. Subject should be blinded for the treatment if

- possible to eliminate placebo effect
5. The assessors (doctors) should also be blinded if possible to eliminate measurement bias
6. Data are collected
7. Some strict studies even blind the personnel who are doing the statistical analysis
8. Outcomes in the two groups are compared to see if there is any statistically significant difference

Why should randomization be done? The reason is that we want to make sure that the treatment group and the placebo group are the same in all aspects except for the treatment. So if there is any difference in the outcome, we can attribute the difference to the treatment.

Intention to treat analysis

When we read articles of randomized control studies, we often encounter the term 'intention to treat'. What does it mean exactly? As mentioned above, in a randomized control trial, the purpose of randomization is to eliminate bias. It can make sure all variables of treatment and control groups are the same except for the treatment. Let us take a hypothetical example. We have a question: "Can annual cervical smear screening reduce the mortality due to carcinoma of cervix?" For this hypothetical study, twenty thousand subjects were recruited; 10000 were in the intervention group and the other 10000 were in the control group. It was found that in the intervention group, 2000 defaulted cervical smear screening. Among the 8000 compliant subjects, 25 died of carcinoma of cervix. Among the 2000 defaulters, 10 died of carcinoma of cervix. In the control group, 50 out of the 10000 died of carcinoma of cervix within the follow up period. When we do the intention to treat analysis, the 2000 defaulters are also taken into account. We analyze the results as if the defaulters are in the intervention group. So the mortality due to carcinoma of cervix in the intervention group is $(25+10)/(8000+2000)$ and it is equal to $35/10000$. In the control group, the mortality due to carcinoma of cervix is $50/10000$.

The intention to treat analysis has the advantage that it preserves the effect of randomization so that there will be no selection bias. Moreover, it is more similar to the real practice; not all patients will be compliant to what is offered. It makes the difference between the intervention and control groups smaller. The result is thus more conservative and any difference so detected is more likely to be genuine.

Ethical issues

While the randomized control trial is the gold standard, there are a number of ethical issues. For example, if we ask, "Will smoking cause lung cancer?" The most 'scientific' way to get the answer is to recruit non-smoking subjects into the randomized control trial. The subjects are randomized into two groups, namely smoking and non-smoking groups. Those subjects in the smoking are forced to smoke every day while the non-smoking group continues the non-smoking status. Then we compare the incidence of lung cancer to see if smoking will increase the chance of lung cancer.

Obviously, the above proposal is unethical. We therefore have to rely on the cohort study and compare the incidence of lung cancers in smoking and non-smoking subjects. However, even though there is a difference in incidence of lung cancer, the conclusion from the cohort study may be attacked. One can argue that there may be a gene which has two effects: making a person more likely to smoke and making a person prone to develop lung cancer. So the apparent association between smoking and lung cancer is not the causal relation. To resolve this issue, one can again perform a randomized control study. This time, we randomize smokers into two groups: one group (control) is advised to quit smoking in the usual environment; the other group (intervention group) is put into an intensive quitting smoking programme. Suppose the rate of quitting smoking is higher in the intervention group than the control. We then compare the outcomes of the intervention and control groups many years later and see whether intensive quit smoking programme will reduce the incidence of lung cancer. If it does, we will have stronger evidence to say that smoking causes lung cancer.

Another ethical issue is that if there is an effective treatment of a certain disease, we should not perform randomized control trials to compare a new drug with a placebo unless there is no harm for a delay in treatment. Instead, we may compare the new drug with the old drug and try to show that the new drug is equivalent or superior to the old drug.

CONCLUSION

The three types of studies mentioned above are commonly used in medical research. Medical personnel who are interested in research should learn these methods thoroughly. Those doctors who are not involved in medical research should also have an idea so that when they read medical journals, they can be more critical in appraising the articles.

Learning Points:

Doctors should familiarize themselves with the inherent strengths and weaknesses of different research study designs so that they can be more critical when appraising published articles.

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Suggested Reading

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