Epidemiological research methods

Part IV. Case-control studies

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Randomised controlled trials (RCTs), although regarded as the best method for assessing the efficacy of an intervention,[1] have several shortcomings[2,3] and may be impossible to conduct, for example in the case of harmful risk factors or aetiological factors such as smoking[4] or schistosomes.[5]

Analytical studies such as case-control studies or non-RCT follow-up studies[6] provide alternative approaches for assessing drug or vaccine[7] efficacy, health service[8] interventions, as well as the role of risk factors for disease.[4,5] Using these approaches the relative incidence (for follow-up studies) or relative odds (for case-control studies) of disease is measured in those who have received and not received the intervention, or in those exposed and not exposed to a risk factor. A major limitation is that individuals are being compared in two or more groups (exposed and non-exposed; vaccinated and unvaccinated) not randomly constituted. Their exposure was determined by nature or by themselves. Thus individuals in the two groups may differ not only in their exposure or vaccination status but also with respect to other risk factors. It is often possible to minimise bias introduced by non-random allocation through careful design and analysis of the study.

A second limitation applies mainly to case-control studies, often referred to as retrospective studies because cases and controls are sampled according to outcome, and information about exposure or vaccine status (prior events) evidently relies on the source, availability and quality of this information. Even though newly diagnosed cases may be collected, information about exposure is determined retrospectively from available records or by patient recall.

Case-control studies also depend on the nature of the surveillance system and referral patterns from which cases and controls are obtained. A primary goal of analytical studies (and therefore case-control studies) is to reach the same conclusions as would have been obtained from a controlled trial.[9,10] In general, cases and controls need to be selected in such a way that both groups had the same opportunity for exposure to the intervention or risk factor. The same exclusion criteria for cases and controls need to be applied and a method of obtaining unbiased information about exposure from cases and controls must be devised. In this article we illustrate concepts applicable to all case-control studies by referring to a study[4] of the relationship between tobacco-smoking and lung cancer. The data adapted from that paper, one of the first to demonstrate the relationship, are shown in Table I.

TABLE I. TOBACCO-SMOKING AND CANCER

	Cases*	Controls†	Total
Moderate and heavy smokers = exposed	**106** (*a*)	**255** (*b*)	**361** (*a* + *b*)
Light and non-smokers = unexposed	**48** (*c*)	**267** (*d*)	**315** (*c* + *d*)
Total	**154** (*a* + *c*)	**522** (*b* + *d*)	

*Lung, pharyngeal and laryngeal cancers.
†All other tumours.

Case selection

Cases can be obtained from two general sources.[9] The first is from a population census where all cases are ascertained. Usually this is not feasible because of the costs involved; instead, available lists (cancer registers, admissions to hospital, notifications or registered deaths) are used, but then one cannot be sure that all cases have been assembled — for example a list of hospital admissions for ischaemic heart disease or for traumatic brain injuries would exclude deaths before admission as well as mild episodes either not treated or treated by general practitioners.

To ensure that cases on the list are 'true cases', clear, objective diagnostic criteria for inclusion need to be used.[10] In Schrek *et al.*'s study[4] the 154 cases were defined as all patients diagnosed as having cancer of the larynx, pharynx or lung who presented to the hospital between 1942 and 1944. In 50% of the lung cancer patients and 70% of the laryngeal and pharyngeal cancer patients a histological diagnosis was made. By not using histological diagnoses for all cases the possible relationship between cigarette smoke and only a particular histological type could have been missed. When possible, it is desirable to use a case definition that maximises the number of true positives. However, the more rigorous the diagnostic criteria, the less likely is complete case ascertainment since access to specialised diagnostic centres is limited to specific subgroups; hence there is a trade-off between diagnostic accuracy and complete case ascertainment. Misclassification of case status (because of low diagnostic accuracy) will usually decrease one's chance of finding an association between an exposure and a disease. It is preferable to include only new (incident) cases[10,11] so that uniform diagnostic criteria can be applied. The completeness of case ascertainment affects the potential of cases to be representative for all exposures.[2] For example, a hospital study investigating the relationship between train accidents and head injuries will miss the majority of accident victims who die immediately, and underrepresent trains as a risk factor for head injuries.

Control selection

Selection of controls is more difficult than selection of cases since the total number of possible controls is much larger. Controls can be obtained from several sources, including hospitals, friends, neighbours and the community. Controls need to be similar to cases with regard to their past potential for exposure[10,12] to the intervention or risk factor under study

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and comparable to cases in terms of factors not being studied.[9,10,13] Comparability (and not generalisability) is the key to ensuring that a particular case-control study's results are valid. In selecting controls for comparability, the challenge is to search for denominators (cases and controls from the same population) that gave rise to the numerators (cases).[14] This does not mean that controls must always be disease-free.

In the smoking/lung cancer example,[4] the controls were selected from the same hospital as the cases. They included patients with 'other tumours' who presented during 1942 - 1944. Hospital-based controls are often used as a comparison group for cases, but several potential biases need to be considered. In a study of risk factors for lung cancer, patients with a disease known to be associated with an exposure important to lung cancer should be excluded as controls (for example ischaemic heart disease patients). Similarly, in Schrek *et al.*'s study,[4] inclusion of patients with other tumours probably resulted in an underestimate of the effect of smoking since many other tumours have since been shown to be associated with smoking.

A problem with hospital-based studies is that hospital patients give an overrepresentative impression of the amount of co-morbidity (number of diseases found in a single patient) and chronicity of disease that occurs in the community.[10,15] People suffering from two conditions (for example, measles and malnutrition) are much commoner in hospitals than in the community. Selection of hospital controls for a study of malnutrition as a risk factor for measles would thus be problematic, because cases of both are more likely to be in hospital than cases of either alone. One way of ensuring that appropriate controls are selected in hospital-based studies is to take a range of diagnostic categories or several control groups.[16] In this way any biases introduced by including an inappropriate category would be minimised. This includes biases introduced due to particular hospital referral patterns.

Neighbourhood or family controls are often used to ensure that cases and controls are comparable in terms of socio-economic status. In a study of BCG efficacy in children,[7] an anticipated problem was that cases of tuberculosis could differ from controls not only in terms of vaccine status but in terms of access to vaccination. To ensure comparability in terms of potential for exposure, the controls selected were TB-free household members of the cases.

Defining the exposure (intervention or risk factor)

In an RCT, exposure is under the control of the investigator (known dose, known duration). In a case-control study the exposure is not under such control. For some exposures individuals self-selected into exposure categories are also more likely to have a different overall risk of the disease than the general population. Joggers, for example, tend to lead healthier lifestyles, and any increased survival can therefore not simply be attributed to the exposure (jogging).

Detection of the exposure relies upon obtaining information about exposure concurrent with or at some time before inclusion in the study. The source of the information affects the reliability of classification of a person into an exposed or unexposed group. Questionnaire information obtained from interviewing cases and controls can be biased if cases remember differently (or are prompted to remember more because they have the disease) than the controls. Often the need for equal ascertainment of exposure in cases and controls determines the source of the controls (hospital v. community). Hospital-based patients tend to recall information about past exposure differently from people in the community.[10] Similarly, in studies where subjects have died[17] or have an outcome likely to affect their recall (Alzheimer's disease, for example[18]), surrogates are used to obtain exposure information; surrogate controls should also be used to reduce biased recall.[19]

Attempts should always be made to validate information about prior exposure from objective sources (e.g. clinic cards for vaccination) but these are often not available. For current exposures of interest, objective measures can be used e.g. urinary cotinine for smoking, a scar for BCG vaccination, or a blood test for HBsAg. However, it is often more important to know about the timing, duration and level of exposure (in smokers for example), whether the exposure was continuous or intermittent (in cases of radiation exposure) and whether there was an adequate latent period between exposure and disease (in most patients with chronic diseases). If a latent period is required for onset of disease, separate analyses by time strata should be conducted.

Misclassification of exposure (as with disease) will usually result in a more conservative result, i.e. a real association may be missed or the OR towards unity may be biased.[19]

Analysis of case-control studies

If the results from the tobacco-smoking and cancer study had been from a randomised trial, we would compare the incidence of cases among exposed $(a/a + b)$ to the incidence of cases among non-exposed $(c/c + d)$ and calculate a rate ratio or relative risk. However, Schrek *et al.*'s study[4] had 154 cases $(a + c)$ and 522 controls $(b + d)$, neither of which were random samples of all cases or controls from the population (presumed to be the referral area of the hospital). We therefore cannot obtain a real estimate of incidence rate for exposed or unexposed subjects since the numerators (cases) relate in an unknown way to the denominators (the population at risk). We cannot directly calculate risk ratios or relative risk (or the ratio of the incidence rate of disease in exposed divided by unexposed). We can, however, determine the odds of disease among exposed (a/b) and unexposed (c/d) subjects. The odds are equivalent to the return on a fair bet in racing. They are related to probability (p) by the formula, odds $= p/(1 - p)$. For example, odds of 1 in 4 is equivalent to a probability of 0,2. The ratio of the two odds $(a/b \div c/d$ or $ad/bc)$ is known as the cross-products ratio or odds ratio (OR) and is used as the measure of association in case-control studies.[2,10,13] If the OR equals 1, there is no association between exposure and disease. From our example (Table I):

$$\text{OR} = \frac{106 \times 267}{48 \times 255} \text{ or } 2{,}3.$$

This means that the odds of developing cancer in moderate and heavy smokers is 2,3 times that among light and non-smokers.

Case-control studies are particularly useful for studying rare diseases (such as cancers). When the disease is rare, the OR approximates the relative risk and can be interpreted similarly.[10] As with other commonly used estimates such as the mean or a proportion, the OR is also subject to sampling variation.[20,21] To take account of such variation, confidence intervals should be used to express a range of plausible values for the population OR.[22] For the OR estimate of 2,3 in our example, the 95% confidence interval lies between 1,6 and 3,4, suggesting that the association is not due to chance (1 is not included in the interval).

The relative risk can be directly calculated from case-control studies when a known proportion of cases and controls are sampled. For example, in a study investigating the relationship between survival and intensive care the cases represent all

deaths and the controls a random sample of 50% of survivors. In this example no rare disease assumption is required for the relative risk to equal the OR.[8]

Confounding

The OR obtained from a case-control study may be biased due to the presence of an undetected factor that wholly or partly accounts for the apparent effect of the study exposure, or masks an underlying true association.[2] Such a factor is often referred to as a confounder — common examples include age (e.g. in lung cancer), socio-economic class (e.g. in tuberculosis) and access to health care (e.g. in intensive care unit survival rates). The possible selection or identification of a factor as a confounder requires knowledge of the subject matter; no simple statistical method will do this.[8] There are several methods of ensuring comparability between cases and controls with respect to factors not being studied.

Control of confounding can be obtained either at the sampling and/or at the analysis stage. Options at the sampling stage include: firstly, excluding certain groups (for example, focusing on children from one particular suburb only, or middle-class female office workers between 20 and 45 years of age); secondly, matching cases to controls on a variable known to be associated with the exposure and a determinant of the outcome (e.g. age, smoking, and lung cancer; socio-economic status, BCG vaccination, tuberculosis). The matching can be carried out for several variables but in general is advised only in small studies when specific hypotheses are being tested. In such studies, matching should only be used for variables known to be strongly associated with the disease and exposure.[12,22] For example, in a study of the relationship between blood group and cervical cancer, it is not necessary to match for sex since exposure (to a particular blood group) and sex are not associated. Matching in larger studies usually results in an increase in costs and time and an inability to examine the effect of the variable used for matching.[23,24] If a matched design is used, failure to conduct a matched analysis will underestimate any real effect of the exposure.[12] Stratification is the third method of controlling for confounding in the sampling phase and is similar to matching except that cases and controls are matched within strata.

In the analysis phase, stratification[10] and multivariate techniques such as the Mantel-Haenszel procedure[13] or logistic regression[10,15] can be used. Post-stratification refers to obtaining separate ORs for all levels or strata of the confounder. Schrek *et al.*[4] stratified their data by race and found that the relationship between smoking and cancer was the same among whites and blacks.

After stratification, ORs are produced for each subgroup of interest. Examination of these ORs is essential, particularly when a dose-response relationship is being sought, but researchers often want to report a single overall OR. The Mantel-Haenszel procedure produces a weighted average of the subgroup-specific ORs. In view of its computational simplicity and efficiency it is the recommended estimate of choice for the non-specialist epidemiologist. A third method of adjustment, logistic regression, is used to assess the individual and joint effects of two or more factors of interest.[24]

Table II illustrates a further use of stratification. Schrek *et al.*'s data have been stratified by occupational status (fictitious example). Among those subjects exposed to the occupational factor the OR for cancer is approximately three times that among those not exposed. This suggests that the effect of smoking on lung cancer is not the same for all occupations. No statement about the relationship between smoking and lung cancer can be made without referring to occupation.

TABLE II. SMOKING IN RELATION TO DISEASE STRATIFIED BY OCCUPATIONAL STATUS (TO DETECT INTERACTION)

	Occupational factor +		Occupational factor —	
	Cases	Controls	Cases	Controls
Moderate and heavy smokers	**80**	**155**	**26**	**100**
Light and non-smokers	**14**	**100**	**34**	**167**
	OR = 3,7		**OR = 1,3**	

Applications of case-control studies

Relative to RCTs, case-control studies are fraught with potential biases which, if not carefully considered, could distort results. Catalogues of biases have been published as guides to would-be case-control researchers,[16] but the length of the list could deter many. However, it is important not merely to state that a bias is theoretically possible but to find ways of determining its magnitude and the direction of its effect on the resulting OR.

Case-control studies are particularly useful when studying risk factors for rare diseases and diseases of long latency. The tobacco and cancer study[4] is an example of using such studies for aetiological research. This approach has traditionally been applied to chronic diseases (cancer of the lung[4] or liver, for example[5]) but more recently has been shown to be useful in developing countries for investigating the role of risk factors for common diseases (such as typhoid[25] and gastro-enteritis[26]).

The cost and relative speed of completion of case-control studies make them particularly attractive in areas with limited research resources, where they can be used to study health services and vaccine efficacy. The neonatal intensive care study[8] is an example of using case-control studies for health services research. In this setting the case-control technique loses many of its drawbacks: there is no possible recall bias, case ascertainment is complete, and generalisation is limited to the service being investigated. The World Health Organisation suggested the possibility of evaluating vaccine efficacy with case-control studies. There would be major costs savings as a result of using such studies rather than RCTs. The BCG efficacy study[7] mentioned in this article is one of the first such studies to be published.

Although causation cannot be established from a single case-control study, case-control and prospective studies contribute to the weight of evidence[27] used to make a decision on causality. Consistency of findings, high ORs and demonstration of dose-response relationships, are guidelines in the decision on causality.

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Labour after caesarean section — the problem of scar dehiscence

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Summary

Conventional criteria for the prediction and diagnosis of dehiscence of a caesarean section scar during labour were prospectively evaluated. Of 70 patients selected to undergo trial of labour, scar dehiscence occurred in 2 of 35 mothers delivered vaginally and in 4 delivered by caesarean section. Conventional predictive and diagnostic criteria correlated poorly with the occurrence of scar dehiscence. These limitations should be recognised and, during trial of labour after caesarean section, emphasis should be placed on careful monitoring of maternal and fetal condition.

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Vaginal delivery after caesarean section is a controversial practice. The risk of rupture of a lower-segment caesarean section scar during labour has in various studies been reported to be 0,5%,[1] 0,7%,[2] 1,1%,[3] 1,5%,[4] and 2 - 3%.[5] To avoid this risk many obstetricians follow the dictum proposed by Cragin:[6] 'Once a caesarean section, always a caesarean section'.

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Peel and Chamberlain[7] found the perinatal mortality rate to decrease from 71 to 16/1 000 when the proportion of patients who were allowed vaginal delivery after a caesarean section was reduced from 45% to 33%. The trend towards repeat caesarean section is also favoured by the increasing fear of litigation.[8]

In recent years, however, both evidence in favour of and consumer interest in vaginal delivery after caesarean section has increased.[9] Avoidance of repeat caesarean section has particular value in communities in which first deliveries tend to occur at a young age, continued fertility is socially important, and women frequently fail to return to hospital for subsequent deliveries. Routine delivery by repeat caesarean section may result in curtailment of desired fertility and increase the chance of women labouring outside the hospital environment after multiple caesarean section deliveries.

With this in mind, a prospective study of trial labour after caesarean section was undertaken at King Edward VIII Hospital, Durban, a high-risk referral centre serving an urban and rural black community.

The aims of the trial were to ascertain: (*i*) which obstetric factors predict scar dehiscence; (*ii*) which factors contribute to dehiscence; (*iii*) which signs and symptoms are of value in the diagnosis of dehiscence; and (*iv*) the risk to mother and fetus if dehiscence occurs.

Patients and methods

During an 11-month period, all patients who had had a previous caesarean section were assessed antenatally or when in labour for suitability to enter the trial. The following exclusion criteria were used: (*i*) more than one previous caesarean section; (*ii*) any abnormal presentation, such as brow, face or breech presentation or transverse or oblique lie; (*iii*) multiple pregnancy; (*iv*) cardiac disease; (*v*) a known previous vertical uterine incision; (*vi*) a small pelvis (the pelvic size of all patients was assessed clinically —