Case Control Studies

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Introduction to Case-Control Studies

Case-control studies are a type of retrospective, observational study [1]. Clinical research studies commonly look for the relationship between diseases and exposures. In general, observational clinical studies either identify subjects based on their exposure and look forward in time for the outcomes of interest, or identify subjects based on their outcome and look backward in time for the exposures of interest (Fig. 33.1). Identifying subjects based the presence of an outcome of interest (cases) or its absence (controls) is called a *case-control* study. After selection of all cases and controls, the subjects are examined for a prior exposure of interest. Case control studies are powerful tools for assessing rare outcomes and can be inexpensively applied to existing data sets. These studies are limited to dichotomous exposures, more prone to selection and information biases than cohort studies, and can only provide odds ratios as estimates of effect. This chapter will briefly review the uses, indications, limitations, and design of case-control studies.

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Design of Case-Control Studies

Case-control study design begins with case definition and selection of cases. It is common to select all available cases within the source population in order to maximize statistical power, although cases may be randomly sampled for inclusion as long as sampling is independent of exposure [2]. Case definitions should be stated clearly, and whenever possible based on common, published clinical definitions to maximize generalizability. Control selection follows case selection. Controls should be sampled from the same source population that produced the cases, as if they had both been drawn from a designed cohort study. For example, in most chronic pain studies, cases will be drawn from hospital or clinic-based populations, and therefore controls should be drawn from the same group rather than the general population. Controls are sometimes *matched* to cases. The investigator chooses certain matching variables, such as specific demographic factors or comorbidities, and a set of controls are selected for each case that share the same values for these characteristics.

Analysis of Case-Control Studies

Case-control studies allow the investigator to estimate the odds of exposure, given case status, and the odds ratio for case status given exposure can be calculated from these. Multivariable mod-

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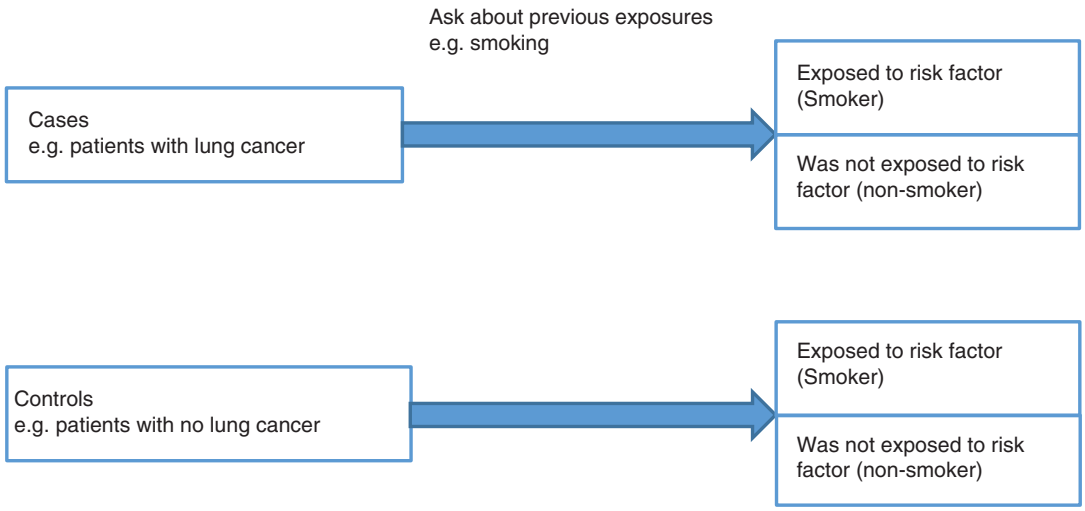

Fig. 33.1 Case control study design

els including multiple risk factors or comorbidities may be constructed using logistic regression (or *conditional logistic regression* in the case of matched case-control studies). Case-control studies cannot estimate relative risks, because the controls are selected by the investigator. If the outcome is relatively rare, however, the odds ratio approaches the relative risk, and the two are taken to be equivalent - the so-called *rare disease assumption.*

Discussion

The primary advantage of case-control studies over cohort studies is that they are more efficient, both statistically and in their cost and ease of execution. This is of particular use when studying rare diseases such as CRPS I, with a reported incidence of 5 per 100,000 persons per year [3]. Matched case-control studies are particularly statistically efficient. Case-control studies require the outcome to already be known, so they are easily performed on existing data sets or registries and require no waiting.

Case-control studies are considered a lower standard of evidence than cohort studies because they are unable to establish cause and effect relationships and are more prone to biases. Case-control studies are nonetheless a powerful tool, and landmark clinical research, such as Doll and Hill's association of cigarette smoking and lung cancer, has been performed using the case-control design [4].

Table 33.1 Analysis of data in case control studies

Exposed	Case	Control	Total
Yes	A	B	A + B
No	C	D	C + D
Total	A + C	B + D	A + B + C + D

Odds of exposure (Cases) = A/C
Odds of exposure (Controls) = B/D
Odds ratio = AD/BC

An Odds ratio of:

- 1.0, means that the odds of exposure among cases is the same as the odds of exposure among controls. Exposure is not associated with development of disease.
- >1.0, means that the odds of exposure among cases is greater than the odds of exposure among controls. Exposure may be a risk factor.
- <1.0, means that the odds of exposure among cases is lower than the odds of exposure among controls. Exposure may be protective.

High Yield Points

- Case control studies enroll based on outcome and look back to identify exposure.
- Case control studies require no waiting, and are simple and inexpensive to conduct.
- Case control studies are suited to diseases with long latency periods or rare outcomes.
- Causality cannot be demonstrated with case-control studies, and they may give a false impression of cause-and-effect relationships.
- Relative risks cannot be calculated from case-control studies, only odds ratios.
- Case control studies are prone to biases, particularly in the section of controls and in systematic differences in information obtained from cases and controls (Table 33.1).

Questions

An epidemiologist wishes to examine the association of CRPS II with childhood psychological trauma using a case-control study. Cases of CRPS II are identified and matched controls selected from a similar population.

1. The relationship between CRPS II and childhood psychological trauma using a case-control study can only be estimated by:
   A. Relative risk
   B. Hazard ratio
   C. Odds ratio
   D. Absolute risk
   Answer: C
2. Controls must be carefully selected for this study to minimize the risk of
   A. Selection bias
   B. Confounding
   C. Type II error
   D. Type I error
   Answer: A
3. Complete childhood records for most patients are not available, so the epidemiologist asks each case and control if they remember any childhood psychological trauma using a validated, structured questionnaire. This method of determining exposure is most prone to which of the following?
   A. Low internal validity
   B. Hawthorne effect
   C. Recall bias
   D. Confounding by indication
   Answer: C

References

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