Chapter V

CASE-CONTROL STUDIES

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We saw in the previous chapter that the cross-sectional study made it possible, inexpensively, to count the clinical events that are of interest to the physician. In other words, it makes it possible to appreciate the scale of a phenomenon, by its common character but also by its repercussions.

It is caricatural, but realistic, to divide the pathologies into two categories, rare and less rare (or frequent). The academic world can confirm the importance of these rare events: it has been estimated that 90% of educational programs deal about 10% of pathology. If 40% of us will die from cardiovascular disease, and 20 to 25% from cancer (only a few of which are common diseases), the prognosis of the remaining 40% will be more or less linked to one of the many rare diseases!

Because they are rare, these events are often described and analyzed by unsophisticated studies, single case reports or case series. The main weakness of these studies is the absence of a control group, and therefore the impossibility of making any comparison.

This is not the situation with the case-control study. It is a more sophisticated study in its design, the advantages, disadvantages and constraints of which are described in the following pages. It clearly has assets, since it enjoys a "love rating" among epidemiologists: 30 to 40% of publications in epidemiology are case-control studies.

The case-control study is usually a retrospective study. Like the cohort study, it is an observational, analytical, non-experimental study.

Case-control studies, like cohort studies, fall into the category of observational studies as opposed to experimental studies represented by randomized trials. Observational studies, because we examine, without intervening on the patient, the possible relationships between one or more risk factors and the occurrence of one or more pathological states.

Unlike cohort studies, where subjects are selected on the criterion of exposure to the risk factor in order to analyze their future and the pathological consequences of the risk factor present in the future, case-control studies are based on the reverse approach: the subjects are selected in the present or the past according to their status vis-à-vis the disease (they will therefore be cases, subjects affected by the disease, or controls, healthy subjects) and one seeks to determine the potential risk factor which, in the present or the past of the subjects, differs between the cases and the controls and could therefore be involved in the genesis of the disease studied.

This approach was developed in part to meet the needs of studying chronic diseases with a long latency period.

The advantages are obvious:

1- A case-control study can be completed quickly: The disease has already been declared and the etiological investigation is usually retrospective. The duration of the study is therefore independent of the incubation period or the latency period.

2- The case-control strategy is particularly interesting for rare diseases: the prospective cohort study of a rare disease would require a very large number of subjects subjected to the presumed exposure and followed up over an indeterminate period of time before seeing a small number of affected subjects appear. The risk, particularly significant if the presumed etiology is not confirmed or if the incriminated risk factor plays only a small role in the pathogenesis of the disease, is to carry out a long, expensive and difficult study for a result negative or non-informative.

Example: the incidence of Horton's disease (Giant Cell Arteritis) in France is around 10/100,000 inhabitants/year. The latency time of the disease is unknown, but it appears only in subjects over 50 years of age, which suggests the need for physiological or pathological aging before the disease can declare itself. It would therefore be necessary in a cohort study, to follow more than a million people to hope to collect, taking into account the obligatory attrition of the cohort, a hundred cases after probably many years. The cohort strategy is not appropriate.

On the other hand, the case-control study will make it possible to gather a sufficient number of sick subjects to compare in a statistically satisfactory manner the distribution of risk factors between patients and healthy subjects.

3- One can analyze in a case-control study a large number of presumed risk factors that one collects in the antecedents of the subjects, while one assembles the populations in a cohort study on the basis of exposure subjects to a specific risk factor whose role we want to understand. By allowing a large number of hypotheses to be explored, the case-control study is particularly useful when knowledge of a given disease is limited and there is no preferential direction of investigation.

4- A case-control study is therefore much less expensive, both in money and in time or employees.

I- STRUCTURE OF THE STUDY:

It is represented in **Figure 1 and 2.** A case-control study in its structure always goes back in time from the present to the past (unlike the cohort study, which follows time in its 'normal' direction from the present to the future , or from the past to the present).

Three steps are particularly important in its construction:
1- The selection of a sample from a population of sick subjects.
2- The selection of a sample from a population of healthy subjects (controls).
3- Measurement of suspected risk factors.

Fig. 1 - Structure of a case-control study

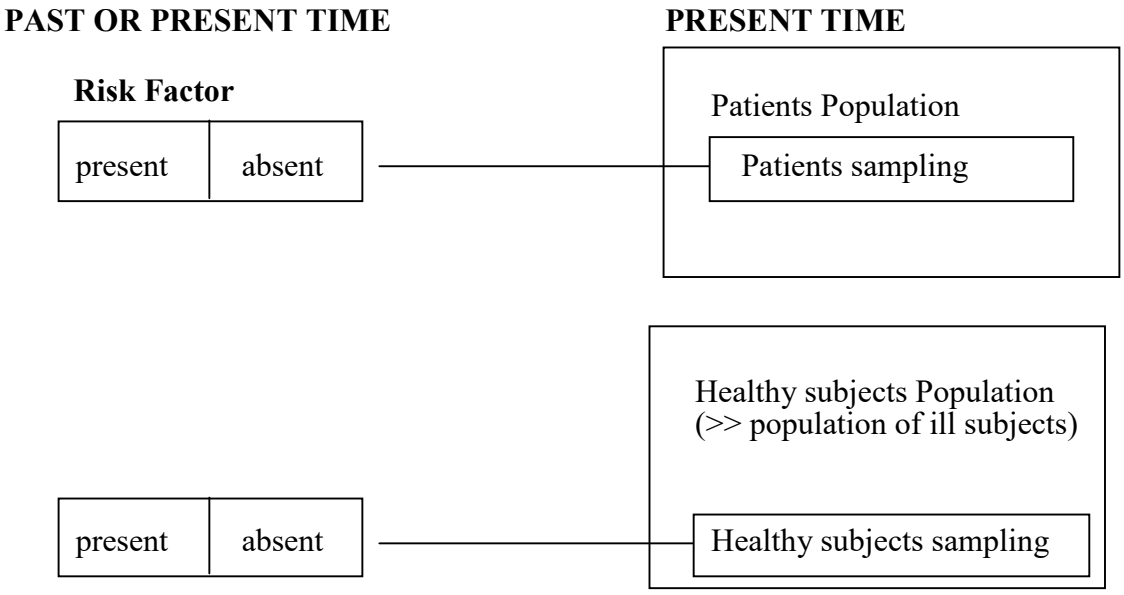
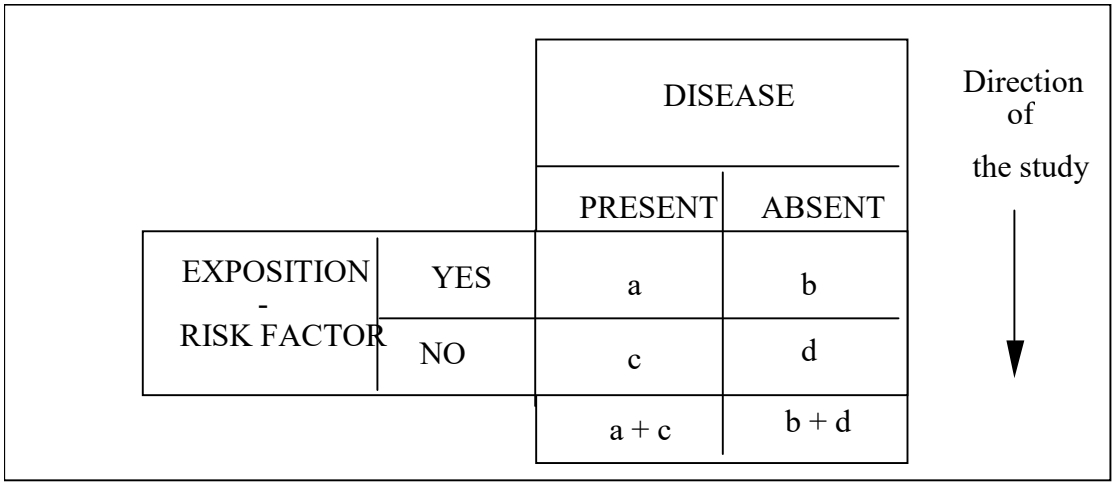
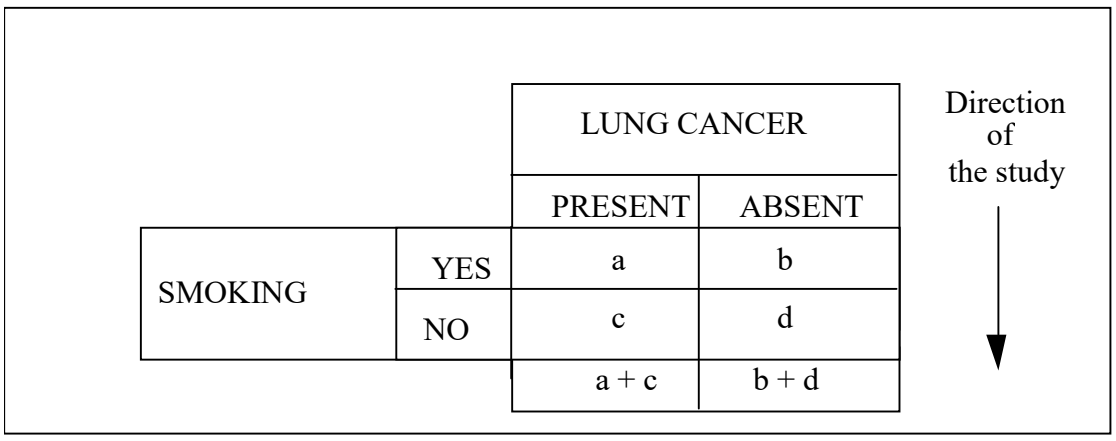


Fig. 2 - 2x2 table representation of a case-control study: (a + c) cases et (b + d) controls are defined at the study onset





II- DEVELOPMENT OF THE STUDY:

Vocabulary clarification: retrospective and prospective studies. The expression "retrospective study" is synonymous for many authors with a case-control study, and the expression "prospective study" with a cohort study.

The reality, however, is more nuanced. **A cohort study can be retrospective** if the subjects exposure has been accurately determined in the past, and disease states have been duly recorded. It is thus possible to carry out a retrospective cohort study on a population monitored within the framework of occupational medicine, where all the employees of a factory A, subjected to an accidental toxic exposure X which occurred in year Y, will be compared with the employees of a similar factory B where the accident did not take place. Pathologies occurring between year Y and the time of the study will have been noted in the registers of the Occupational Medicine department during the mandatory biannual or annual consultations. Simply, *the time of the study flows in the physiological direction from the past to the present*.

Similarly, the term prospective can apply to case-control studies when the study does not relate to prevalent or diagnosed cases in the past, but to incident cases which will be recruited during a defined period of time from the start of the study, and associated with controls recruited during the same period. From the diagnosis of new cases, the research will focus on the risk factors of the past, *and the study thus goes back in time from the present to the past*.

A- Definition and selection of cases:

This is a major problem, the non-resolution of which can be the source of a certain number of biases, particularly in case-control studies of rare diseases involving multicenter cooperation.

Definition of the disease and selection of patients are the two parts of the question.

1- Definition of the disease:

Establishing objective criteria to arrive at a reproducible diagnosis of the disease can often be quite difficult. Consider, for example, the case of rheumatoid arthritis: this relatively common disease presents with a large number of clinical signs and laboratory tests whose sensitivity and specificity vary according to the laboratory, the age of the patient, the population in which the tests are carried out, the association with more or less specific clinical signs, etc.

Moreover, the variation between different observers in the interpretation of clinical signs and laboratory findings can be significant. Very often, in fact, the diagnosis is based on a bundle of arguments and the feeling of the clinician formed from the evolution of the patient over time, the appearance of the joint inflammation, its location, the response to therapy... The nosological framework admits borderline forms with other systemic diseases, and the differential diagnosis can be difficult to establish. The variability of the criteria and the subjectivity of the clinician necessarily involved in the diagnosis, can make the homogeneity of the diagnosis very uncertain in a multicenter study.

It is therefore necessary to draw up a list of diagnostic criteria, both symptoms and physical signs and laboratory tests, and to try to define their **specificity and sensitivity** for each of them. It is then necessary to define which combination of criteria will be required to admit the diagnosis (Work of the ARA (American Rheumatology Association) for rheumatoid arthritis, of the DSM IV (Diagnostic and Statistical Manual-Revision 4) in Psychiatry, etc.).

The establishment of diagnostic criteria is difficult, including for pathologies that we believe we know well: thus, in 2009, there are no validated diagnostic criteria for bacterial pneumonia (apart from the severity criteria justifying intensive care); the diagnostic criteria for Sjögren syndrome, type 2 diabetes or dysmetabolic syndrome are constantly evolving and come up against differences in conception between the different continents:

Often – and more modestly – we establish *classification* criteria rather than *diagnostic* criteria. A disease that is relatively well defined on the anatomo-pathological level, but very polymorphic on the clinical level, such as sarcoidosis, does not currently have recognized or only sketched out diagnostic or classification criteria.

The last step will consist of testing the reproducibility and validity of the criteria on a sample of investigators participating in the study:

- What is the **inter-observer variability**? Will two observers confronted with the same case respond in the same way?
- What is the **intra-observer variability**? Will the same observer confronted with the same case at a distance in time respond in the same way?
- The **validity -or accuracy-** of the criteria may be more difficult to measure. Do the criteria accurately define or measure what they are intended to define or measure? The answer requires the existence of a standard criterion, or **gold standard**, which allows a reliable diagnosis to which one can refer. Such standards do not always exist, and it is then necessary to refer to the opinion of experts, to the experience of those who use the diagnostic criteria in their daily practice... which implies the appearance of a certain subjectivity from the first stage of the development of the study.

2- Selection of cases:

a- Criteria for inclusion or eligibility of subjects:

The subjects included must of course correspond to the diagnostic criteria previously set, but must also be representative of the entire patient population to which it is desired that the results of the study apply. They may not correspond to the entire population affected by the disease, because patients must have a reasonable probability of being affected by the disease due to the risk factor studied, otherwise the real association between risk factor and disease may be diluted by external factors:

Example : Phlebitis with or without pulmonary embolism can occur in the community in ambulatory subjects, but we know that a significant proportion occurs in hospitals. The study of the association of thromboembolism and taking oral contraceptives should exclude – or at least have separately analyzed – cases of thromboembolism occurring in a hospital setting. Hospitalized patients are more likely to be bedridden, to have undergone thrombogenic surgery (particularly orthopedic), to be suffering from cancer, or simply to have given birth… all important risk factors for venous thrombosis.

On the other hand, these same patients, because of their age, or recent childbirth! are much more likely to not be on oral contraception than ambulatory patients… a study carried out on a sample of patients representative of the entire population affected by venous thrombosis could therefore not highlight the role, however real, of oral contraception (OC), *by dilution*

effect of the group at risk of OC in a group undergoing other more important risk factors, and not taking, or no longer taking, OC.

Finally, a choice must be made between **prevalent cases** -most often already treated- and **incident cases**, for which the measurement of exposure can be done without risk of modification of the latter by the possible treatment or the progression of the disease and without risk of confusion between the suspected exposure and one of the consequences of the pathological process.

Examples:

- marital or conjugal problems as a cause or consequence of a depressive pathology where history taking can be difficult and unreliable.
- Hepatitis B virus: etiological agent of hepatic carcinomas very common in Southeast Asia or simple contaminant of a previously pathological liver? The question had been debated for a very long time before being settled by prospective studies, objectifying the temporal sequence: 1. Infection with the hepatitis B virus, 2. Chronic hepatitis B, and 3. Late onset of cell transformation with appearance of hepatocarcinoma, pleading in favor of the etiological oncogenic role of the virus.

b- Origin of the cases studied:

The study can be limited to **hospitalized case**s. It will then be relatively easy to make and inexpensive. It can also extend to the **entire population** living in a predetermined area. It will then have the advantage of embracing a much broader spectrum of the disease and of avoiding the selection bias inherent in any hospitalized population. On the other hand, it will often be much more difficult and more expensive to achieve.

The main problem is that of the **generalization** of the results:

- Is it reasonable, for the disease in question, to extend the results of the study to the entire patient population if only hospitalized patients were studied?
- Is it useful to carry out a study on hospitalized patients only, if the final goal consists for example of the recognition and the eviction of a risk factor in the general population?
-Is it useful to carry out a study on the whole population if only hospitalized cases, potentially more serious, pose a therapeutic problem or present a severe prognosis?

The problem is not only theoretical: the treatment of patients with viral hepatitis C has been generalized on the basis of the complications observed in the hospital environment and in particular cirrhosis with hepatic insufficiency or portal hypertension and secondary hepatocarcinomas. However, one of the rare population-based studies – double cohort – of patients with post-transfusion hepatitis followed over an average period of 18 years shows that their overall mortality is similar to that of patients without hepatitis, and that the excess hepatic mortality is primarily related to alcohol abuse, which acts as a modifier of the agonist effect, *although all patients with post-transfusion hepatitis have a histology of cirrhosis on liver biopsy.* Should we therefore impose a heavy and difficult to bear treatment or act on the alcohol factor? The question deserves at least to be asked.

B- Selection and definition of controls:

They should be drawn from the **population from which the cases originated** to ensure maximum comparability between cases and controls. Any exclusions or restrictions applied to cases therefore also apply to witnesses. The population from which the cases arise may be

different from the healthy population, and the control subjects are therefore not necessarily representative of the population of healthy subjects.

The choice of the control population is crucial in a case-control study, because the results of the study are based precisely on the comparison between cases and controls: from the choice of controls will therefore depend the conclusions of the study, and the possible biases with which they will be tainted.

In current practice, doctors know how to diagnose a case - with the reservations expressed above on the validity of the diagnostic criteria - but often pay little attention to the controls: as a result, controls may be more important than the cases in explaining the discrepancies between case-control studies.

Example: hormone replacement therapy (HRT) for menopause began to be prescribed in the 1960s and initially, included only estrogen not counterbalanced by progestin. In 1975, the first case-control study appeared in the New England Journal of Medicine, reporting an excess of endometrial cancer in treated patients. Patients with endometrial cancer and those without were asked about their past or present use of HRT. The resulting odds ratio was 4.5 for the appearance of cancer under HRT, and the difference was statistically significant (3).

Criticism of this study came from the mode of diagnosis of the cancer of the postmenopausal endometrium: for the diagnosis to be made, the patient had to present metrorrhagia motivating the biopsy curettage. However, estrogen promotes metrorrhagia… so metrorrhagic patients were more likely to have taken estrogen (detection bias) than non-metrorrhagic patients (therefore not biopsied). Thus the odds ratio could derive from the fact that the selection of cases had not been made solely on the presence of the disease, but also on the presence of the risk factor (inducing metrorragia, and thereby the diagnosis).

A second study, to compensate for the potential bias of the first, therefore only included patients who came to consult for metrorrhagia, in whom curettage was performed. The metrorrhagia detection bias disappeared. Patients with cancer diagnosed on curettage constituted the case group, patients without cancer, the control group. The odds ratio, this time, was equal to 1, thus exonerating HRT… and proving that the results of the first study stemmed from detection bias (4).

The evidence did not last long: if estrogen induced breakthrough bleeding, then the controls in the second study *were also at greater risk of having taken estrogen*…and therefore were not selected solely on the basis of absence of endometrial cancer, *but also on the basis of the presence of exposure to HRT*... It was therefore no longer possible to highlight a difference with the cases, since cases and controls had been selected, in fact, based on their exposure to THS!

More than 20 well-constructed case-control studies have followed one another on the subject of 'Endometrial cancer and HRT', each trying to compensate for the potential biases of the previous one. The odds ratios varied from 0.5 (protective) to… almost 20, thus demonstrating that they depended above all on the choice of controls.

Finally, a study associating several different control groups, and the cohort studies constructed to settle the question definitively, found odds ratios, and a relative risk, between 2 and 3 and similar to that of… the first study (5).

1- Origin of controls:
Different sources are possible.

Controls recruited from **patients hospitalized** for a reason other than the disease being studied are very frequently used and have many advantages. They are available, easy to contact and therefore the data will be inexpensive to collect. They are subject to the same recruitment biases as cases hospitalized in the same department, and this reduces differential selection biases. They are often, as patients, more inclined to collaborate than healthy subjects selected at random from the general population. They may be more aware of their medical history than subjects interviewed in the general population, which will reduce recall bias. Finally, they can be examined and questioned by the same doctor who will examine and question the cases, and this will reduce the information biases that may arise from an interrogation or examination carried out by two different observers.

However, controls recruited in hospitals have **certain drawbacks**. First of all, they are not or hardly representative of the healthy population, and we know that toxic habits, tobacco or alcohol for example, are very different in hospitalized subjects compared to those observed in the general population.

Although hospitalized in the same hospital or the same service as the cases, the controls can induce a **selection bias** if the hospital is a reference center for the treatment or the diagnosis of the disease studied, but not of the diseases for which the witnesses will be hospitalized. The cases may then come from a much larger population than the controls, and the two groups will no longer be comparable.

Finally, controls can be hospitalized for a condition presenting **common risk factors** with the disease studied: the tobacco-lung cancer association could not be demonstrated in a lung disease department using chronic bronchitis patients as controls.

Selecting controls from the **general population** from which the cases originate ensures the maximum level of **comparability** between cases and controls. Witnesses can be chosen at random from electoral rolls, be contacted by dialing telephone numbers obtained using tables of random numbers, or chosen at random from municipal registers... However, it can be difficult to contact people engaged in working life, responding people contacted may not be representative of the general population (retired elderly people, people on sick leave at home, etc.). Healthy subjects may not have paid attention to such a risk factor in their antecedents, while patients may have thought about it for a long time, and this **disparity in memory** will introduce a bias in the evaluation of exposure in the two groups. Finally, healthy subjects may have very little motivation to participate in the study, and this may introduce a consequent **information bias**.

Controls chosen from **family, friends or neighbors** provide a number of solutions to the problems raised. They share characteristics of the general healthy population, but may be more motivated to participate in the study. They make it possible to avoid selection bias relating to socio-economic level, environment or ethnic characteristics. But members of the same family, close friends are more inclined to share the same exposure to a given risk factor (tobacco for example) than sick subjects, and the **magnitude of an association** between the risk factor and disease may therefore be **underestimated**.

2- Number of control groups and number of controls per case:

The use of multiple control groups can make it possible to compensate for the biases resulting from the choice of a given control group. If the association between risk factor and disease is found, whether the comparison is made with a group of hospitalized controls, a group of controls drawn at random from the general population or a group of controls made up of direct neighbours, and if the magnitude of the association does not differ significantly from one comparison to another, it will be probable that the association corresponds to a reality and not to an artefact linked to the structure of the study. If, on the contrary, the association differs considerably depending on the comparison group used, the study design may be questionable, and there may be important selection or information biases at the level of one or more control groups explaining the discrepancies.

Independently of the number of control groups, the question arises of the number of controls per case.

When the cost of obtaining information is comparable in the two groups and the number of cases and controls is large enough, the best ratio is 1:1. Statistical analysis of the data will indeed be easier, as will sample size calculations.

When, on the other hand, the number of cases that can be included in the study is low, either because the cost of collecting information is high, or because the disease is rare, increasing the number of checks per case will increase the power of the study and therefore the chances of highlighting an association if it exists.

However, the increase in power is low when 4 controls are exceeded for a control, and it is generally useless to go beyond this ratio.

C- Case and control selection methods. Sampling methods:

Cases and controls come from a population of sick subjects and healthy subjects. The subjects included in the study must be representative of the populations from which they come. They must constitute an **unbiased sample**, that is to say that their selection, conditioned by their status vis-à-vis the disease studied, must not be influenced by their exposure to the suspected risk factor or by any other factor possibly playing a role in the pathophysiology of the disease, otherwise a **selection bias** may be introduced that may influence the results (Cf. the study on lung cancer and smoking conducted in a hospital department for cases and controls) .

1- Random sampling:

This procedure represents the situation where all subjects, case or control, have an equal probability of being selected from their original population by lot or by the use of random number tables.

2- Systematic sampling:

This procedure represents the situation where the subjects are all systematically included in the study for a certain period, and are therefore representative of all the cases occurring during the period considered.

3- Sampling by stratification:

The subjects are randomly selected within previously defined groups: urban population, rural population, men, women... in order to ensure sufficient recruitment in the different interest groups, allowing valid conclusions to be drawn within each of them.

4- Sampling with matching:

Each case is matched to one or more controls on the basis of a **variable that we want to eliminate from the comparison**. For example, one will match by gender or age when studying a disease more frequent in one sex or in one age group, so that the case and the control are comparable with regard to the determining age or sex variable for the onset or course of the disease.

The intuitive purpose of matching is to control for a possible confounder (e.g. sex or age, as natural risk factors for a number of diseases). This goal is fully realized in cohort studies (which include patients on the basis of risk factors, and by matching on a risk factor, eliminate it from the comparison).

On the other hand, in case-control studies, cases like controls must not, if we want to avoid biases, be selected on the basis of a risk factor, even the matching factor, but only on the basis of the absence or presence of disease.

Matching in a case-control study makes it possible to increase the power of the study by providing as many controls as there are cases for the matching characteristic (gender, for example). It does not allow control of the corresponding confounding factor, and can induce a matching bias (6).

Example: Horton's disease (Giant Cell Arteritis) is a vasculitis affecting people over the age of 50, women in 70% of cases. The anatomo-pathological lesion suggests that atherosclerosis can make the bed of the disease. A case-control study studying cardiovascular risk factors was constructed, with matching by age and sex of the controls to the cases: this matching made it possible not to compare a group of 70% women and 30% old men on average aged 75, to a randomly selected group from the general population, which would have been made up of 50% women and 50% men, with an average age of 50 years.

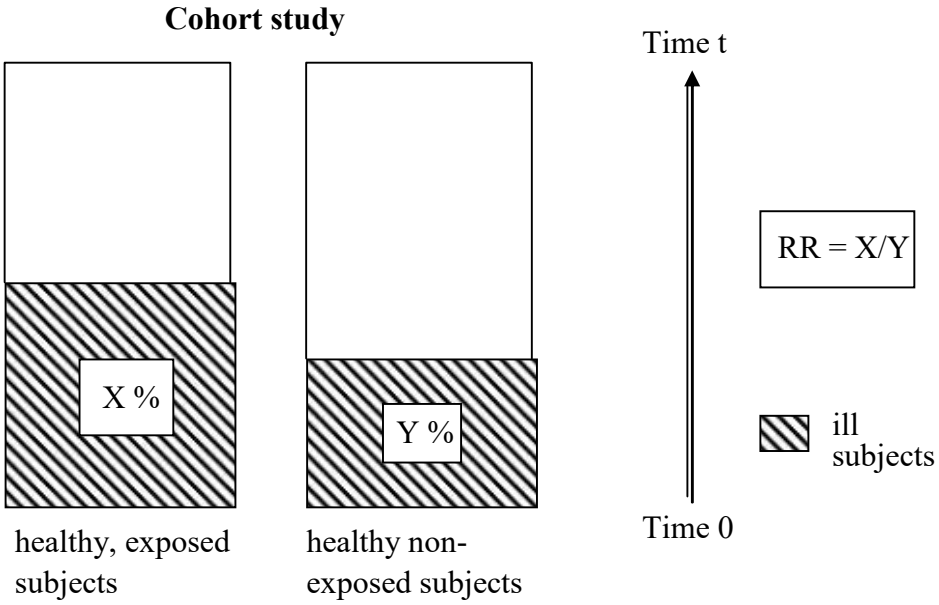
However, cardiovascular risk factors, and smoking in particular, are age and gender dependent. The analysis of the total series only revealed a tendency to the disease in smokers. The separate analysis of men and women highlighted smoking as the most important risk factor in women of this generation, while the risk disappeared diluted in the omni-smoking (70%) of men of this generation on the entire group of patients and controls. *In a case-control study, the matching, by bringing the controls too close to the cases on their exposure factor linked to the matching factor (tobacco in this age group is very linked to the sex, matching factor), can induce a matching bias leading to an artefactual reduction in the odds ratio and bringing it closer to 1. (7)*

III - DATA ANALYSIS

Calculating a risk is easy in a cohort study, since the cohort has been formed on the basis of exposure to the risk factor and the proportion of subjects with the disease among the group of people is then examined. exposed and unexposed.

If this proportion is equal to X% among the exposed subjects, and Y% among the non-exposed subjects, the X/Y ratio gives the relative risk of the exposed persons compared to the non-exposed persons *(fig. 3).*

Fig. 3



In a case-control study, based on knowledge of the status of the subjects with respect to the disease and not the exposure, it is not possible to determine what proportion of exposed subjects will develop the disease because, even if all cases in a given population were registered, the proportion of people exposed in the reference population is not known. The proportion of subjects with exposure to the risk factor is therefore determined among the group of affected subjects on the one hand, and among the group of healthy subjects on the other hand (fig. 4). This is the reverse approach to that followed in a cohort study.

The estimate of the relative risk can however be made under certain assumptions, thanks to the calculation of the odds ratio (table 1).

Odd of exposure among cases:

$$\frac{\text{Proportion of cases exposed}}{\text{Proportion of cases not exposed}} = \frac{a/(a+c)}{c/(a+c)} = ac$$

Exposure odds among controls:

$$\frac{\text{Proportion of controls exposed}}{\text{Proportion of controls not exposed}} = \frac{b/(b+d)}{d/(b+d)} = bd$$

$$\text{Odds ratio} = \frac{\text{Exposure odds among cases}}{\text{Exposure odds among controls}} = \frac{a / c}{b / d} = \frac{ad}{bc}$$

The odds ratio expresses the relative risk when the disease is rare, and is calculated very simply by the ratio of the cross-products of the 2x2 table (table 1).

The logarithmic transformation of the odds ratio gives the coefficients of the different parameters of the variables in a logistic regression equation. A logistic regression equation can therefore integrate multiple variables representing multiple risk factors studied in a case-control study, and determine their respective role and importance in the risk of developing the disease.

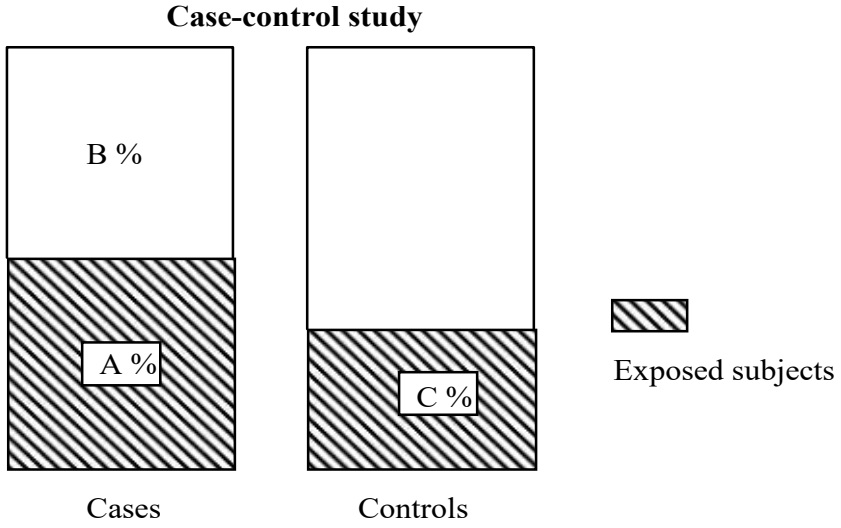


Fig 4

Table 1 - Odds ratio computation in a case-control study: vertical reading of the 2x2 table

	Cases	Controls	
Exposed	a	b	a + b
Non exposed	c	d	c + d
	a + c	b + d	a + b + c + d

IV - DATA INTERPRETATION

We have seen that special attention should be given of potential biases when designing a case-control study. This type of study is, in fact, by its structure, more subject to the existence of multiple biases than a cohort study and, a fortiori, a randomized study.

Selection bias arises when the inclusion of cases or controls depends in some way on the exposure one proposes to study. The selection of patients is no longer made solely on the disease, but is also influenced by exposure to the risk factor, which therefore can no longer be studied without error. A study of the association between chronic bronchitis and tobacco where all the patients would be recruited at the anti-smoking consultation would highlight a stronger association than the real association (since all the patients are smokers) and would undoubtedly fail to highlighting other risk factors (climate, history of chronic asthma, certain occupational diseases, etc.).

Detection biases are biases relating to abnormalities in the diagnosis of the disease, and may be of a multiple nature: the disease may not be detected because it evolves for a long time at a sub-clinical stage, because the diagnostic tests which we have are not sensitive enough, because the diagnostic criteria chosen for the study are questionable. On the contrary, it can be too easily detected at an asymptomatic stage, when it would perhaps never have been talked about, and the group of patients will then be enriched with patients with potentially risk factors and prognostic factors. different from those of symptomatic patients (example: chronic lymphocytic leukemia in the elderly detected on a systematic blood count; stage 1 myeloma detected on routine protein electrophoresis, etc.). Undetected patients may be different from detected patients, and then, the isolated risk factor may not be generalizable to all the patients for whom the disease will one day be diagnosed. If we use the annual chest X-ray for screening for lung cancer, do we preferentially detect cases with slow progression and a better prognosis than cases that can appear and become symptomatic in less than 12 months?

Observational biases are subdivided into recall bias and misclassification bias:

- Recall biases are particularly frequent in case-control studies, because exposure to the risk factor is determined a posteriori. The patient who has reflected on his illness is more likely to remember such and such a risk factor than the healthy subject in the control group. If the memories are not of equivalent quality in the two groups, the comparison is necessarily distorted and results in a distorted, generally exaggerated, value of the odds ratio. Some diseases, on the other hand, can lead to memory or behavioral disorders, and data collection is then less good in the sick group. The odds ratio is falsely lowered.

- Misclassification bias occurs when exposure or disease status has been misreported. Healthy subjects can then be classified in the group of sick subjects, and vice versa. Unexposed subjects may be classified as exposed subjects. This "mixing" of groups results in a dilution of cause and effect in each group studied. If this took place without a preferential direction, there is a weakening of the odds ratio which approaches 1. If the confusion has always operated in the same direction and if, for example, all the exposed subjects are mistakenly classified among the sick subjects, the odds ratio is abnormally increased. Conversely, the odds ratio is abnormally lowered in the event of unidirectional misclassification when the exposed subjects are preferentially classified among the control subjects. We can even in extreme cases arrive at an inversion of the real association!

Matching can itself be the source of new biases in a case-control study. This occurs when the matching factor is associated with the exposure factor that one wishes to study, without there being a cause and effect relationship between them. It is then necessary, in the analysis of the data, to take into account the matching factor and to calculate the odds ratios separately in each subgroup (for example, in the male group and in the female group if the gender was the matching factor).

IV - ADVANTAGES AND WEAKNESSES OF CASE-CONTROL STUDIES

A- Advantages

- They can be carried out quickly and inexpensively compared to cohort studies.
- They are particularly suited to the study of diseases with a long latency period.
- They are particularly suitablein the study of rare diseases.
- They can examine several risk factors for the same disease.

B - Weaknesses

- They are not profitable for the evaluation of rare risk factors, except if the risk is very high.
- They cannot directly calculate the incidence of the disease in the exposed and unexposed populations, unless all the cases in the population considered are recorded.
- The causal relationship and the temporal sequence between presumed risk factor and disease are sometimes difficult to establish, because the data concerning the exposure are collected at the same time as the data concerning the disease.
- They are particularly prone to bias (essentially selection bias and recall bias).

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