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Editorial

Cohort and Case-Control Studies in the Evidence-Based Medicine Era

Estudos de Coorte e de Caso-Controle na Era da Medicina Baseada em Evidência

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A cohort study is an observational study where individuals are classified (or selected) according to exposure status (exposed or unexposed), and are followed to evaluate the incidence of disease in a given period of time. Cohort studies can also be used to assess the risks and benefits of using a given medication.

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1. The following are the principal phases of a cohort study: Read phonetically

a. Identify healthy persons at baseline;

b. Assemble groups of subjects exposed and not exposed;

c. Follow-up of the cohort to evaluate the incidence of the disease being studied in two groups;

d. To compare the incidence (risk) in each cohort;

2. Cohort studies have certain advantages:

a) They can discern the temporal relationship between exposure and outcome due to the fact that the exposure precedes the outcome;

b) Can be used to evaluate multiple outcomes;

c) They permit the direct calculation of measures of incidence in cohorts of exposed and unexposed subjects;

d) The status of the outcome does not influence the measurement of exposure status or selection of subjects (concurrent cohort/competing cohort);

e) They are less subject to selection bias than case-control studies;

f) Some studies also allow multiple exposures can be assessed (cohorts of the general population, population groups restricted).

3. Cohort studies have some disadvantages:

a) As with case-control studies, it is an observational study, with all the weaknesses of an observational design (when compared to experimental studies – randomized clinical trials)

b) It may be inefficient for studying rare diseases or those with long latency periods;

c) Generally expensive and difficult to operationalize (in etiological studies);

d) The loss of participants during the follow-up may compromise the validity of results.

Overview of a cohort study:

A cohort study is a specific type of observational study design that has a higher level of evidence than the other observational studies such as case reports and case series, case-control and cross-sectional studies, but a lower level of evidence than experimental studies.

Cohort studies are performed in three basic steps:

1. Assemble or identify groups of individuals exposed and unexposed that are free of the disease being studied;

2. Observe each cohort over time to assess the development of the disease in the groups studied;

3. Compare the risk of developing the disease among groups of exposed and unexposed subjects.

The first step in a cohort study is to identify groups of exposed and unexposed subjects. A cohort is a group of people, taken from the study population, which shares a common experience or condition and whose outcome is unknown at the beginning of the study. In cohort studies, researchers observe exposure status, which occurs "naturally" (i.e., the researcher does not actively interfere). In contrast, in clinical trials, the researchers experimentally apply the exposure to the study participants.

Example: The investigators/researchers want to evaluate whether smoking causes cancer of the cervix. They recruit 2,000 women with an intact uterus. The researchers use a questionnaire to determine the smoking status of all study subjects and then divide the study population into a cohort of smokers and another group of nonsmokers.

They watch each cohort over time and compare the risks of the incidence of cervical cancer between the two groups.

Cohort studies usually focus on the incidence of cases of the disease that occur during the follow-up. To achieve this goal, researchers typically exclude individuals who have the disease present at the beginning of a cohort study (in our example, those who have had cervical cancer would be excluded). The evaluation of the results of the incidence of the disease helps to establish that the exposure of interest precedes the outcome (disease) and, therefore, may represent one cause of the disease.

In the cohort studies, the researchers observe the exposure of interest. As a result, exposed and unexposed individuals may vary depending on other features. In our example, patients who smoke may be more likely to be carriers of HPV, a known risk factor for cervical cancer. The concept that factors other than the exposure may influence the results of the study is called a confounding factor.

Accurately obtaining the study data:

From the moment that the investigators decide what specific variables and outcomes will be used in the study, they should use the most accurate methods possible to measure these characteristic and applying them to all study participants. Important considerations in the measurement of the study data are the validity of measurements, the time between the measurements, and the availability of uniform measures for the population under study.Listen

Validity of measurements:

The validity of a measurement refers to how close the measured data represent the real data. It should be as close to reality as possible.

Time between measurements:

The right time interval between the exposure measurements and the outcome will depend on prior knowledge about the outcome. In some cases, researchers may be interested in the association between recent exposure and disease, particularly if there is concern that exposure may change during the study. For example, non-steroidal anti-inflammatory drugs (NSAIDs) can cause rapid constriction of the renal arteries, leading to an increased risk of acute kidney injury. Researchers studying the relationship between NSAIDs and use of medications and acute kidney injury can concentrate their efforts in obtaining a valid estimate of recent use of NSAIDs in the occurrence of acute kidney injury. The verification of recent use of medication can be obtained by frequently updating the status of each participant during the study. There are other examples where the association of interest is the relationship between long-term exposure and the disease. For example, smoking can cause damage to a kidney transplant by gradual thickening of the intima and media of the arterial wall. The researchers in this study can, therefore, choose to evaluate smoking history over the long term, quantified as the number of pack-years of smoking after transplantation. Cohort studies are not ideal for the study of very recent or very remote exposures. Remote exposures may change over time, obscuring their relationship to the outcome of interest. Very recent exposures can confound the presumed temporal relationship between the exposure and outcome.

Retrospective versus prospective data collection (prospective cohort vs. retrospective cohort):

Cohort studies can be classified as concurrent (prospective, classic) or non-concurrent (retrospective). In non-concurrent studies, all the information about exposure and outcome has occurred before the start of the study. In concurrent studies, the exposure may (or may not) have already occurred, but the outcome has not occurred.

The problems with non-concurrent studies are: information bias and the inability to control confounding variables (lack of information). A prospective study involves collecting new data often for the purpose of addressing a specific issue. The distinction between retrospective and prospective studies is essentially descriptive; in general it does not generate any impact on the plan of analysis or on the results of the study, besides those already mentioned.

A major advantage of cohort studies is the ability to assess multiple outcomes. Researchers of cohorts under study are free to study another outcome, as long as the subjects under study were free of that outcome of interest when the study began. As an example, in a study that evaluated the relationship between smoking and kidney transplants, the investigators could also study whether smoking was associated with the development of kidney or bladder cancer.

One of the largest cohort studies ever conducted was the Nurses Health Study (NHS), which recruited 127,000 nurses, between 30 and 55 years of age. Through questionnaires sent every two years, the NHS evaluated various variables among the nurses such as: health, prescription and nonprescription medication use, social habits, eating and physical activity habits, among others. This open cohort study design allowed the creation of multiple cohort studies that assessed risk factors for a wide range of diseases, including cancer, heart disease and fractures, among various other outcomes. These studies have the ability to discern the temporal relationship between exposure and outcome.

Unlike cross-sectional studies, cohort studies can reveal temporal relationships between the exposure and the outcome, as long as a reasonable time interval has elapsed between measurement of exposure and the occurrence of the outcome. The existence of a temporal relationship strengthens the evidence that the exposure is a possible cause of the disease. Establishing a temporal relationship between exposure and outcome is inherent in the study design and cannot be solved by any statistical methodology.

Disadvantages of cohort studies:

a) Cohort studies are observational studies, and therefore are subject to confounding factors. That is, other factors that are related to the exposure of interest may explain some or all associations that are observed.

b) Inability to examine diseases that are rare or that have a long latency. Cohort studies may be inefficient if the outcome is rare or the disease has a long latency period.

Example 1: Researchers want to investigate whether use of talc in childhood increases the risk of ovarian cancer in adulthood. Using a cohort study design, one approach could be to recruit cohorts of children with and without a history of using of talc and follow these groups for the subsequent development of ovarian cancer. However, many years of follow-up would probably be necessary for the development of cancers in adulthood. In this example, the long latency period between exposure and outcome would make study this very expensive and logistically difficult.

Example 2: The researchers intend to investigate whether sleeping in the prone position is a potential cause of sudden infant death syndrome (SIDS) in babies.

Using a cohort approach, they could identify a cohort of children who sleep in the prone position and a cohort of children who sleep in the supine position and then compare the risks of SIDS between the cohorts. However, SIDS is relatively rare, requiring the recruitment of thousands of newborns to accumulate enough cases of SIDS to be able to draw meaningful conclusions. In this case, a case-control study would be more appropriate. It is possible to overcome the limitations of the cohort studies with rare diseases and high latency using data sources to facilitate the study of large populations.

Cohort studies to evaluate the use of medications:

Cohort studies can be an important tool to study the risks and benefits of a certain medication. These studies may provide specific information about medications that cannot be obtained from clinical trials. First, cohort studies can assess the risks and benefits of drugs in populations that tend to be excluded from randomized trials such as patients with physical and mental disabilities, people end-stage renal disease (ESRD), or those with liver disease. Second, cohort studies can detect side effects and evaluate clinical outcomes of licensed drugs by the *Study* of medication users' data from very large cohorts of patients who obtain their medications from pharmacies with sophisticated information systems. The main limitation of observational studies of drug use is the difficulty in

separating the effect of a medication from the underlying characteristics of those using the drug. For example, observational studies on hormone therapy (HT) have found that women who used Hormone Replacement Therapy (HRT) have lower risks of cardiovascular events compared with women who did not. Clinical trials have not corroborated these results; rather, they show an increased risk of cardiovascular events in HRT users.

The second disadvantage of pharmaco-epidemiology studies is their tendency to assess chronic users of medication, rather than new users. Despite their limitations, pharmaco-epidemiology studies remain an important tool to evaluate drugs that are used in clinical practice.

Incidence proportion versus incidence rate:

Cohort studies usually involve comparison of two cohorts, but may have only one (which can be compared to other published informal groups or to historical data) or more than two (for example, different groups of serum levels of specific serum marker or different doses of a drug). Regardless of the number of cohorts, one must first calculate the incidence of disease in each group, as an incidence proportion or as an incidence rate. This should be done taking into account the time that each participant was followed in the study, generating for each individual a person-time product. Failing to take the person-time product into consideration can lead to a bias, which constitutes a systematic distortion of the true result. For example, suppose that in certain study of smokers and nonsmokers, smokers leave the study more frequently than non-smokers (smoking could predispose subjects to quit the study) so that smokers end up being followed for less time than non-smokers. In these circumstances, it would be possible to observe a lower incidence of diseases among smokers, simply because they are followed for less time.

The follow-up in the denominator of the incidence rate standardized disease rates temporally, eliminating this potential problem.

Relative Risk:

Once we determine the incidence of disease in each cohort, we can compare these incidences. Many types of comparisons are possible; the most common are the relative risk and attributable risk.

The relative risk is defined as the incidence (proportion or rate) in a cohort divided by the incidence in the reference cohort. For example, in a hypothetical study, the incidence rate of failures of kidney transplants is 82.6 per 1,000 person-years among smokers and 55.3 failures per 1,000 person-years among nonsmokers.

Using non-smokers as the reference cohort, the relative risk would be:

$$\frac{\text{82.6 failures per 1000 person-years}}{\text{55.3 failures per 1000 person-years}}$$

RR = 1.49 (comparison between smokers and nonsmokers)

The relative risk can also be expressed using smokers as the reference cohort:

RR = 0.67 (comparison between the nonsmokers and smokers)

*

Both relative risks are correct. You can choose either group to be the reference group. Note that the relative risk has no units.

The interpretation of the first relative risk of 1.49 would be, "transplanted kidneys in patients who smoke are 49% more likely to develop renal insufficiency relative to non-smokers." We say they are "49% more likely" because 1.49 is 49% greater than 1.0.

An interpretation of the second relative risk was non-smokers with a transplanted kidney are 33% less likely to develop renal insufficiency then smokers. The second calculation of relative risk shows an association with a lower risk of disease, because the value is less than 1.0.

Why is smoking associated with a 49% higher risk of failure of the transplant, but among non-smokers, with only a 33% lower risk of failure? In other words, why aren't the relative risks additively symmetric for the same exposure? Note that relative risks – as with all proportions – can take values ranging from 0 to infinity, while 1.0 defines the value of unity. It is more difficult to obtain the relative risks that are much less than 1.0, because they are limited to 0.

For this reason, the relative risks that are below 1.0 indicate stronger associations than the symmetric associations that are larger than 1.0.

Attributable Risk (also known as "risk difference" or "excess risk"):

The attributable risk is defined as the incidence (proportion or rate) in a cohort minus the incidence of

the other group. For the example of renal transplant and smoking, the attributable risk of transplant failure comparing smokers with nonsmokers would be: 82.6 transplant failures per 1,000 person- years (smokers) - 55.3 transplant failures per 1,000 person-years (non-smokers) = 27.3 transplant failures per 1,000 person-years.

Note that the attributable risk, unlike the relative risk, retains the same units that are being compared.

If the exposure of interest is a cause of the disease, the attributable risk describes the amount of additional or extra risk which is due to the exposure. For example, if smoking actually causes the failure of a kidney transplant, then the interpretation of attributable risk for smoking would be "there is an additional risk of renal insufficiency in 27.3 kidney transplants for each 1,000 person-years in transplant recipients who smoke."

CASE-CONTROL STUDIES

To introduce the concept of case-control study, we can ask the following question:

Does alcohol consumption increase the incidence of pancreatic cancer? A case-control study published in 1989 showed a significant increase of the disease in those who consumed larger quantities of beer.[1]

Considering this possibility, we can design a hypothetical case-control study, as laid out below.

First let's consider what would be the approach of a cohort study for this research question. The researchers were able to identify a cohort of 1,000 adults who drink alcohol regularly and another cohort of 1,000 adults who do not drink alcohol. After exclusion of adults with problems in the pancreas at the beginning of the study, researchers observed each cohort for the development of pancreatic cancer (PC) during follow-up. The data obtained using this approach are presented in Table 1.

These data, comparing adults who consume alcohol with those who do not consume, do not suggest a difference in the incidence of pancreatic cancer, but there are too few cases of pancreatic cancer in this study to reach a meaningful conclusion. In this example, the cohort study design is inefficient because the outcome (pancreatic cancer) occurs infrequently.

And if the cohort study design were reversed? If instead of starting with exposed cohorts (those who consume alcohol) and unexposed (those who do not consume alcohol), researchers began identifying adults with and without the outcome of interest, i.e., cancer of the pancreas?

We can imagine a study in which researchers identified 1,300 adults with pancreatic cancer in a given country in a good quality electronic database. They used the same database to determine whether the cases were regular consumers of alcohol before they developed pancreatic cancer.

The data in Table 2 show an apparently high proportion (77%) of alcohol consumption in patients suffering from pancreatic cancer. The next step would be to compare this figure with patients matched according to age, gender, etc. but who do not have pancreatic cancer.

The researchers used the same database to obtain the data presented in Table 3. This table shows that the proportion of adults without PC and that consume alcohol (71%) is slightly lower than the group with PC, which speaks in favor of alcohol being a risk factor for pancreatic cancer).

Table 1 – *Beer Consumption and Pancreatic Cancer: a cohort study.*

	Pancreatic Cancer		
Consumes Beer	**Yes**	**No**	**Total**
Yes	5	995	1.000
No	6	994	1.000

Table 2 – *Consumption of alcohol among 1300 patients with Pancreatic Cancer.*

	Alcohol Consumption	
Yes	1000	(77%)
No	300	(23%)
Total	1300	

Table 3 – *Consumption of alcohol among 4500 adults without Pancreatic Cancer.*

	Alcohol Consumption	
Yes	3200	(71%)
No	1300	(29%)
Total	4500	

The study results are best appreciated by presenting the data pertaining to patients and unaffected individuals together. The data in Table 4 illustrate the concept. The case-control study starts with patients and unaffected individuals, and then checks their exposure status prior to the development of the disease. Correctly carried out case-control studies can be used to suggest important causal relationships.

Case-Control Studies

The first step to achieving a successful case-control study is the careful selection of cases and controls.

SELECTION OF CASES

A. Carefully Specify the Disease in question

A very specific definition of the disease is extremely important in case-control studies to ensure that the disease in question is really present among individuals who are being defined as cases. This strategy may require the exclusion of individuals with milder forms of a particular disease (or include them and improve the diagnostic accuracy) in order to concentrate on more advanced cases, which can be diagnosed with greater certainty. On the other hand, it is generally less important to devote extra resources to confirm that the control subjects are truly free of the disease in question. Case-control studies usually investigate rare diseases (low incidence, difficult to study in a cohort), which are unlikely to be present in individuals randomized to the control group.

B. Selecting incident cases

Typically, the goal of case-control studies is to study the development of the disease. Therefore new or incident cases of the disease are usually preferred than the chronic cases of long duration. One reason for focusing on incident cases is to establish whether the exposure of interest (e.g., alcohol consumption) was clearly present before the onset of the disease. For example, the selection of adults with long-standing pancreatic cancer may complicate proof of alcohol consumption before the development of their disease (e.g., they may have started to drink after learning of their disease some years ago but not before – which is more difficult differentiate with the passage of time). A second reason for the choice of incident cases is that the alternative, the selection of chronic cases, may hinder the study of the etiology of the disease if it affects the survival of the individual. To illustrate this concept, consider a case-control study that evaluates whether the serum markers of oxidative stress are related to cerebral vascular accidents (CVA). The researchers start by identifying individuals with stroke (cases) and those without stroke (controls) and then measure the oxidative stress markers in serum samples that were collected 10 years ago.

If the researchers selected as cases individuals with chronic stroke, they would be studying the "survivors of stroke," whose survival could be related to certain healthier characteristics, which would be reflected in lower levels of serum markers of oxidative stress. The result could be an artificial negative association – the higher the levels of the markers, the lower the chances of stroke – between serum markers of oxidative stress and stroke.

SELECTION OF CONTROLS

A. Select controls from the same population base as the cases

Case-control studies compare the frequency of exposure (e.g. alcohol consumption) among individuals who have a disease and individuals who do not have the disease.

Table 4 – *Consumption of alcohol and pancreatic cancer: case-control study.*

Prior Consumption of Alcohol	Pancreatic Cancer		Total
	Yes (N=1300)	No (N=4500)	
Yes	1000 (77%)	3200 (71%)	4.200
No	300 (23%)	1300 (29%)	1.60

The interpretation of the results of a case-control study depends on the assumption that the control group was obtained from a population suitable for estimating the frequency of exposure. The overall objective is to obtain controls that derive from the same population base as the cases.

In the example of the study of pancreatic cancer (PC), the cases in the study could have been selected from the national health system in Sweden, where the database is of high good quality and prevalence of alcohol consumption is relatively high. If researchers, instead of selecting the control group from Sweden, were to select the controls from a different country, say a Muslim countries, where alcohol intake is less common, we would have observed a higher proportion of alcohol consumption among cases (of Sweden, who on average drink more alcohol), leading to the false conclusion that alcohol intake is more common among patients with PC. Listen.

B. The controls should have the same chance of being selected as cases if, instead of healthy, they were or became sick

In the study of PC in Sweden, the controls had the same chance of being diagnosed as cases because they were part of the same health system that captured patients using diagnostic codes. One method to ensure that cases and controls derive from the same underlying population and that will have the same chance of being diagnosed with a disease is to do a nested case-control study. This study design selects cases and controls from a larger cohort study. For example, the Cardiovascular Health Study (CHS) recruited 5,800 elderly from four communities and performed serologic evaluation of renal function among all participantes.[2]

A case-control study nested in the CHS can easily identify cases with renal dysfunction and controls with normal renal function based on laboratory data that were obtained using identical methods. The researchers could then try to estimate the frequency of use of a certain anti-inflammatory drugs (which could impair the kidneys) among the cases and the controls using previously collected data on prescription practices.

C. Pairing

The case-control studies often use pairing to increase the degree of similarity between cases and controls.

In the study of PC, an example of pairing would be to first choose an individual with PC and then identify a control that does not have PC, but that is the same age and sex of that case.

Using appropriate analytical techniques, pairing can reduce the possibility of other factors that disrupt the association between exposure and outcome (called confounding; e.g., in the case of PC, smoking could increase the chance of pancreatic cancer and those who drink alcohol usually smoke more; i.e. the risk factor for PC in those who drink alcohol would actually be smoking, which is more prevalent in those who drink).

D. Number of controls

In a case-control study, the disease of interest is usually rare, so finding cases is often the limiting step of the process. There are no specific rules about the number of controls that are needed in each study; however, more controls generally provide a more accurate estimate of the frequency of exposure in the control group and can increase the power of analysis (the ability to detect an association if it is actually present). Financial resources usually determine the number of controls that can be selected for each case. There is a sharp increase in the power of the study when more controls are added, until about three to four controls per case, the point at which adding more controls has little effect on the power of the study.

ADVANTAGES OF CASE-CONTROL STUDIES

A. Case-control studies may be ideal for studying rare diseases or diseases with long latency period.

Cohort studies and randomized clinical trials can be difficult to execute when the outcome of interest is rare or the latency period between exposure and outcome is long (e.g., it may take years between alcohol intake and the appearance of pancreatic cancer).

Case-control studies can be useful to study the processes in which the period of time observed between exposure and the development of the disease is particularly long and if the previous data on exposure are available or can be easily obtained.

For example, it may take years for certain dietary factors, such as fish oil, to produce cardiovascular benefits. A case-control study could

identify individuals with and without coronary heart disease and then question them regarding the frequency and amount of prior consumption of fish oil (obviously controlling for confounding factors).

B. Case control studies allow the study of multiple exposures

Cohort studies identify individuals based on their exposure status, and subsequently follow the cohorts to observe the outcome of interest. In contrast, case-control studies identify individuals based on their disease status, allowing the study of multiple exposures within a pre-defined group of cases and controls. For example, since PC cases and controls without PC are identified, the study investigators could explore other risk factors for PC.

DISADVANTAGES OF CASE-CONTROL STUDIES

A. Observational study design

As in cohort studies, case-control studies are observational studies designs and are subject to confounding. The cases may differ from the controls with regard to factors other than the exposure of interest. The confounding occurs when another factor, other than the exposure of interest, distorts the association between exposure and outcome, thus limiting the inference that the exposure causes the disease.

B. Recall bias

As in cohort studies, case-control studies can obtain the study data using a variety of sources including medical records, questionnaires, interviews and laboratory tests. As in cohort studies, case-control studies seek measurements that are valid, accurate and uniform for the exposure and for the outcome. An important consideration for the measurements in case-control study is the use of interviews or questionnaires to check the status of prior exposure, because these procedures can lead to a specific type of bias known as recall bias. Recall bias occurs when cases and controls remember their exposure status differently. With the PC study, cases with pancreatic cancer might remember having drunk more alcohol than the healthy controls (because those who are ill end up looking harder for something to blame).

The best solution for minimizing the recall bias in case-control studies is the use of data that were collected in a systematic manner, before the development of disease (e.g., organized and complete medical records used in an efficient healthcare system).

C. Case-control studies only provide information about the relative risk (odds ratio) of the disease

Cohort studies can determine the incidence of disease among exposed and unexposed individuals and then compare the incidence between the two groups using a ratio (relative risk) or a difference (attributable risk). Case-control studies can provide only an estimate (approximation) of relative risk. They cannot be used to calculate attributable risk, nor can be used to calculate the specific incidence of the disease in any group.

ANALYSIS OF DATA IN CASE-CONTROL STUDIES

A. Theory of the odds ratio (OR)

The data from the case-control study of PC showed that 77% of adults with PC have a history of alcohol intake and that 71% of adults without PC possessed this same history. Usually we are interested in the question "what is the risk of pancreatic cancer comparing adults who drink alcohol to those who don't?" We can estimate this information based on data from case-control studies using the odds ratio. To develop the concept of odds ratio, imagine that we have an unlimited funding and resources for studying the adults in the Swedish health system.

We carried out a huge cohort study on alcohol consumption and pancreatic cancer.

Hypothetical data are presented in Table 5.

After recruiting more than 200,000 individuals in the hypothetical cohort study, we can calculate the incidence (proportion) of PC in each group:

Incidence in the group that consumes alcohol = 1000/150,000 = 0.66%

Incidence in the group without alcohol consumption = 300/55,300 = 0.54%

As we are analyzing a hypothetical cohort study, we can use the incidence (proportion) to calculate the relative risk of pancreatic cancer in those who drink alcohol = (0.66/0.54) = 1.22. An interpretation of the relative risk would be "alcohol intake is associated with an increased risk for

Table 5 - *Alcohol consumption and pancreatic cancer: a cohort study.*

Prior Alcohol Consumption	Pancreatic Cancer		Total
	Yes (N=1300)	No (N=4500)	
Yes	1000	150.000	151.000
No	300	55.000	55.300
Total	1300	205.000	206.300

pancreatic cancer of 22%." Comparing data from cohort and from case-control studies, we see that the 4,500 controls represent only a fraction of 205,000 individuals who have PC. In the case-control study, researchers selected the 4,500 individuals of the control group based on the resources available, the study power they were seeking, and what was practical for them to execute. This "arbitrary" selection of 4,500 controls made it impossible to calculate the true incidence of pancreatic cancer among those exposed or not to the ingestion/ consumption of alcohol.

We cannot affirm that the incidence of pancreatic cancer in those who drank alcohol is 1000 / 4200 = 23.8% (see Table 4). This incidence is much higher than the actual incidence of 0.66%, and it would be different depending on the number of controls chosen by the investigator. Likewise, we cannot say that the incidence of pancreatic cancer among adults who do not drink alcohol is 300 / 1600 = 18.7%, for the same reason. Since the error in estimating the incidence is similar in the exposed and unexposed, the ratio of these (false) incidences approximates the relative risk for the disease. This ratio of (false) incidences is not exactly a relative risk, and instead has a different name, the odds ratio. The odds ratio is the principal measure of risk in a case-control study.

B. Practical calculation of the odds ratio (OR)

In fact, the odds ratio is calculated using the number of controls (people without disease) as the denominator. Considering the data from case-control study of pancreatic cancer (Table 6):

Equally correct interpretations of the odds ratio include:

1. Alcohol consumption is associated with a 35% greater chance of PC.

2. The chances of PC are 35% higher among those who drink alcohol compared with those who do not.

3. The odds ratio of PC is 1.35, comparing those who drink alcohol with those who do not drink alcohol.

There is a simple method for calculating the odds ratio for data obtained from case-control studies. First, there should be a contingency table with "with the disease / without the disease" headings at the top and "exposed / not exposed" on the left side. Given this configuration, the table cells are referred to as a, b, c, and d, as shown in the table below (Table 7).

The odds ratio is calculated from this table as (a x d) / (b x c).

Note that no adjustment was made for other factors in this study such as age, race or sex.

As a result, this odds ratio is also called the "gross odds ratio" or "unadjusted odds ratio".

Table 6

Prior Alcohol Consumption	Pancreatic Cancer		Total
	Yes (N=1300)	No (N=4500)	
Yes	1000 (77%)	3200 (71%)	4.200
No	300 (23%)	1300 (29%)	1.600

The odds ratio is calculated as (1.000 / 3.200) / (300/1300) = 1.35.

Table 7

Prior Alcohol Consumption	Pancreatic Cancer		Total
	Yes (N=1300)	No (N=4500)	
Yes	a. 1000	b. 3200	4.200
No	c. 300	d. 1300	1.600

The odds ratio is calculated as (1000 x 1300) / (3200 x 300) = 1.35.

C. Odds ratio and Relative Risk

Using the approach of the cohort study, it was found that the relative risk (RR) of PC, comparing those who drink alcohol with those who do not, was 1.22. Using a case-control approach, it was observed that the odds ratio of PC, comparing with those who drink alcohol with those who do not, was 1.35. These estimates are similar, but not exactly the same. The main factor that determines the agreement between relative risk and odds ratio is the rarity of the outcome in question. The lower the prevalence in the population, the greater the agreement between OR and RR. In the example of alcohol consumption, pancreatic cancer is relatively rare in the population, as there are only 1,300 cases among 206,300 individuals (prevalence = 0.63%). There is no specific cutoff value to define "rare," but generally case-control studies with the prevalence of disease <5% will provide an odds ratio that closely approximates the relative risk.

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