PRACTICAL 9

21 – 24 APRIL 2020

Lecture 4

Epidemiology – part 2. Types of epidemiological studies. Descriptive studies. Analytical studies – types, design, conducting. Cohort studies.

EPIDEMIOLOGY
COHORT AND CASE-CONTROL STUDIES - TYPES, DESIGN, CONDUCTING, POTENTIAL ERRORS.

OBJECTIVE OF THE PRACTICAL 9:
To enable students to understand the characteristics of the cohort and case-control epidemiological studies; to enable students to analyze the design and the results from cohort and case-control studies as well as to understand the potential errors in them.

Enabling objectives:
At the end of the lesson students should be able to:
1. Define the distinct features of cohort and case-control studies.
2. Describe the basic design of cohort and case-control studies.
3. Distinguish different types of the cohort and case-control studies.
4. Define the indications and potential errors in for cohort and case-control studies.
5. Compare case-control and cohort studies.
6. Enlist advantages and disadvantages of cohort and case-control studies.
7. Analyze the design and the results of concrete examples of cohort and case-control studies.

SYLLABUS OF THE PRACTICAL – *Reference to Lecture 4*

1. Cohort studies – *Reference to Lecture 4*

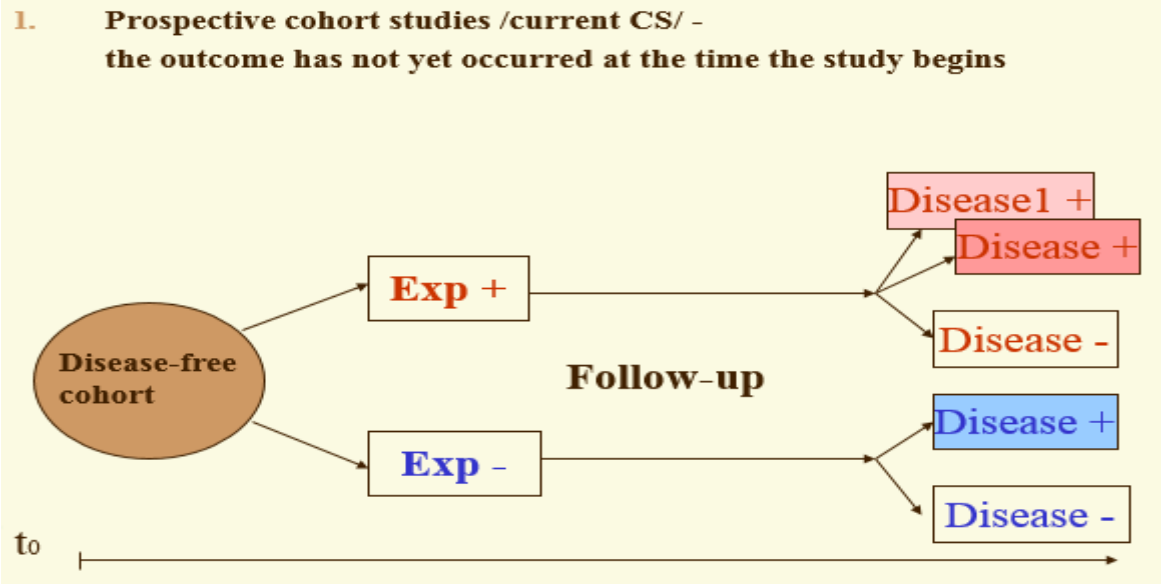
- Definition of cohort studies. Cohort studies, also called follow-up or incidence studies, begin with a group of people who are free of disease, and who are classified into subgroups according to exposure to a potential cause of disease or outcome.
- Study design.
- Elements of cohort study - potential difficulties of conducting

Example 1: *potential difficulties of conducting (**in bold**)*

In 1976, **121 700** married female nurses aged 30–55 years completed the initial Nurses' Health Survey questionnaire. **Every two years**, **self-administered questionnaires** were sent to these nurses, who supplied information on their health behaviors and reproductive and medical histories. The initial cohort was enrolled with the objective of evaluating the health effects of oral contraceptive use. Investigators tested their methods on small subgroups of the larger cohort, and obtained information on disease outcomes from routine data sources. In addition to studying the relationship between oral contraceptive use and the risk of ovarian and breast cancer, they were also able to evaluate other diseases in this cohort – such as heart disease and stroke, and the relationship between smoking and the risk of

stroke. Although stroke is a relatively common cause of death, it is a **rare occurrence in younger women**, and so **a large cohort is necessary**.

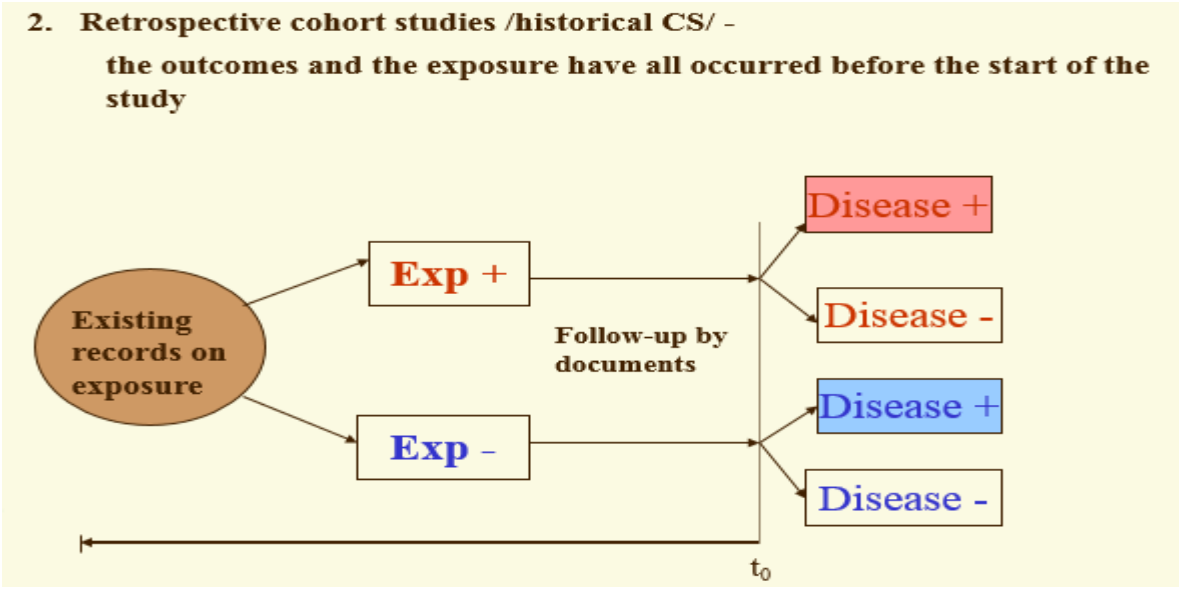
- Types of cohort studies:
  (1) Prospective cohort study – design



Example 2: *Prospective cohort study*

A cohort study of 22 707 Chinese men in Taiwan was set up to investigate the association between the hepatitis B surface antigen (HBsAg) and the development of primary hepatocellular carcinoma. The study was conducted among male government employees who were enrolled through routine health care services. All participants completed a health questionnaire and provided a blood sample at the time of their entry into the study. Participants were then followed up for an average of 3.3 years (Beasley et al., 1981).

(2) Retrospective cohort study – design



Example 2. *Retrospective cohort study*

Male age-specific mortality rates from all causes in the rubber worker cohort and in three other comparison groups: steel workers, Ohio state population and USA national population.

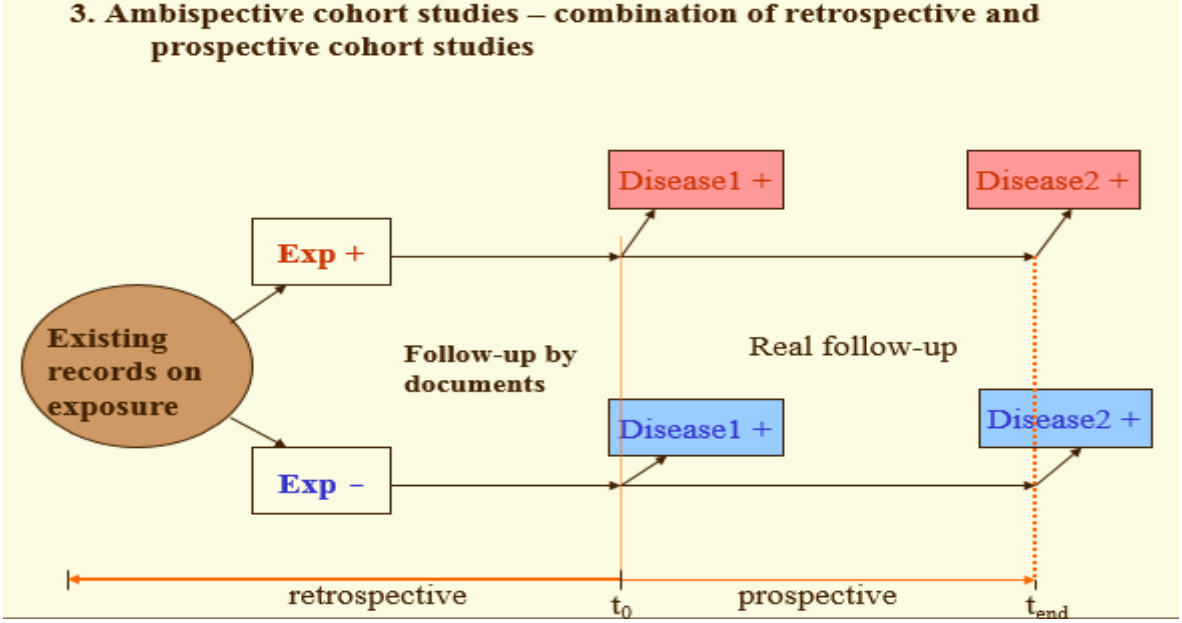
A cohort of workers in a major tyre-manufacturing plant in Akron, Ohio (USA) was set up to examine their overall and cause-specific mortality. A total of 6678 male rubber workers aged 40 to 84 at 1 January 1964 were identified retrospectively from pension, payroll, death claims and other company files. These workers were followed from 1964 to 1972. The age-specific mortality experienced by this cohort was then compared with that experienced by three comparison groups–an industrial cohort of steel workers, the population of the state where the plant is located (Ohio) and the US national population (McMichael et al., 1974).

	Age-specific mortality rate (per 100 000 pyrs)			
Age-group (years)[b]	Rubber worker cohort (1964–72)	Steel worker cohort (1953–61)	Ohio state (1972)	USA (1968)
45–54	852	907	940	980
55–64	2317	2166	2365	2370

[a] Data from McMichael *et al.* (1974).

[b] Only data for these two age-groups were available for all the four populations.

(3) Ambispective cohort study – design



Example 3. An Ambispective Cohort Study

Adverse Events Associated with Treatment of Multidrug-Resistant Tuberculosis in China:

Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis (TB) caused by organisms that are resistant to isoniazid and rifampicin, the 2 most powerful anti-TB drugs. In this study, the aim is to evaluate the incidence of adverse events associated with MDR-TB therapy so as to identify related drugs and to investigate their impact on MDR-TB treatment outcome via a large hospital-based ambispective cohort in China.

Patient's enrollment

An ambispective cohort study was conducted based on hospital medical records from 8 hospitals in 5 provinces (Hebei, Henan, Shandong, Jiangsu, and Guangdong). It included a retrospective study that enrolled 751 MDR-TB patients receiving standardized regimen according to "Regulations on the Prevention and Control of MDR-TB in China" between May 2009 and July 2013, and a follow-up investigation of treatment outcome conducted in Dec 2016 in China. Patients were enrolled in this cohort if they: (1) had been diagnosed as MDR-TB based on a drug susceptibility test; (2) agreed to receive an MDR-TB treatment; (3) had continuously received 6 or more months of MDR-TB therapy.

Data collection

Data were collected through chart review of medical records, including baseline characteristics of adverse events induced by anti-TB treatment, drugs administered in the regimen, and information on adverse events. Adverse events were monitored based on clinical symptoms and signs, as well as laboratory test results.

Follow-up

To obtain the outcomes of patients who received treatment during July 2013, a follow-up investigation was conducted in Dec 2016. This investigation collected the treatment outcome and occurrence time by examining the records of patient registries in the China Program for the Global Fund to Fight TB, based on registry number.

- Indications for cohort studies.
- Advantages and disadvantages of cohort studies.

2. Case-control studies – *Reference to Lecture 4*

- Definition of case-control studies.

Case-control studies provide a relatively simple way to investigate causes of diseases, especially rare diseases. They include people with a disease (or other outcome variable) of interest and a suitable control (comparison or reference) group of people unaffected by the disease or outcome variable. The study compares the occurrence of the possible cause in cases and in controls. The investigators collect data on disease occurrence at one point in time and exposures at a previous point in time.

- Principles of the design of case-control studies.

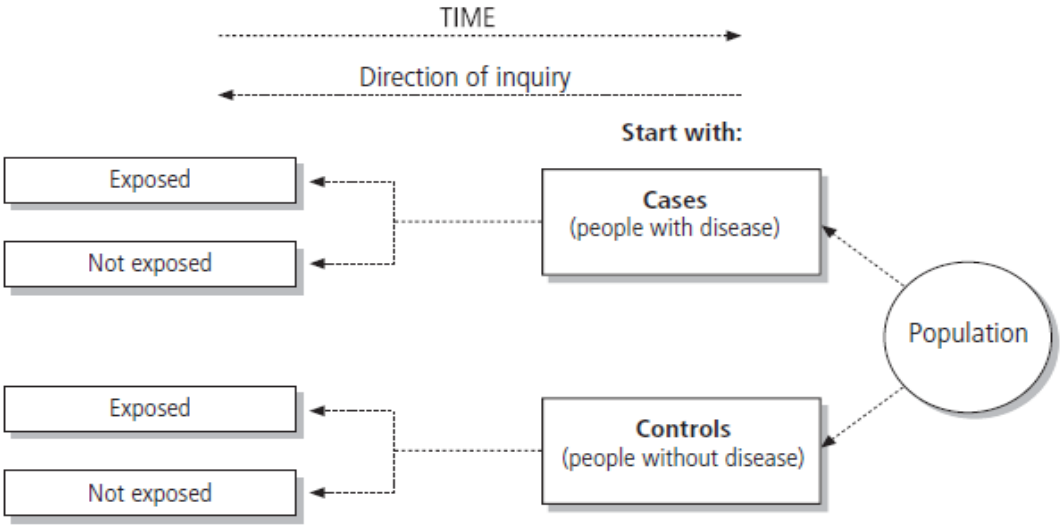


Figure 1. *Design of a case-control study*

- Basic steps of case-control studies.

Example 4. *A case-control study*
Relationship between thalidomide and limb defects in babies born in the Federal Republic of Germany

A classic example of a case-control study was the discovery of the relationship between thalidomide and limb defects in babies born in the Federal Republic of Germany in 1959 and 1960. The study, done in 1961, compared affected children with normal children. Of 46 mothers whose babies had malformations, 41 had been given thalidomide between the fourth and ninth weeks of pregnancy, whereas none of the 300 control mothers, whose children were normal, had taken the drug during pregnancy.10 Accurate timing of the drug intake was crucial for determining relevant exposure.

- Bias in case-control studies.
- Advantages and disadvantages of case-control studies.
- Main differences between case-control and cohort studies.

PRACTICAL WORK:
TASK 1 Fill-in the following table of comparison between the case-control and cohort studies

	CASE-CONTROL STUDY	**COHORT STUDY**
1 Direction of study	Proceeds from effect to cause	Proceeds from cause to effect
2 Starts with		
3 Research question		
5 Number of subjects		
6 Length of study		
7 Suitability for rare diseases		
8 Possibility to study multiple risk factors		
9 Possibility to study multiple diseases		
10 Clear temporal relationship between exposure and disease		
11 Possibility to calculate Incidence rate		
12 Cost		

Discussion of examples of cohort and case-control studies and estimating the risk of developing a disease.

TASK 2 The Nurses' Health Study
The Nurses' Health Study is a cohort study of 121 700 US female registered nurses aged 30–55 years when the cohort was established in mid-1976. A total of 1799 newly diagnosed breast cancer cases were identified during the first 10 years of follow-up from mid-1976 to mid-1986. Analyses were then conducted to investigate the relationship between oral contraceptive use and risk of breast cancer. On the baseline questionnaire in mid-1976, the following question was asked: "If you are now using or have used oral contraceptives, please indicate intervals of oral contraceptive use starting from first use and continuing until the present time. If applicable, please indicate reasons for stopping". The same question was asked on subsequent biennial follow-up questionnaires.

In response to the 1976 questionnaire, 7133 women reported that they were using oral ontraceptives. Responses to the 1978, 1980, and 1982 questionnaires showed that 2399, 1168, and 302 women, respectively, were still using oral contraceptives. In 1984, none of the women were current users.
The information given in the 1976 questionnaire was used to classify nurses according to categories of oral contraceptive use ('non-users', 'past users' and 'current users') and each nurse started contributing person-time at risk to that category. Similarly, for each subsequent two-year interval, women contributed additional person-time of follow-up to each updated report of oral contraceptive use. The follow-up of women who developed breast cancer was truncated at the time their breast cancer was diagnosed (Romieu et al., 1989).

Questions:
1. What is the association under study? What is the research question?
2. How the participants were classified according to their exposure status?
3. Do you expect any potential systematic errors (bias) in this study? Please explain.

TASK 3 The Nurses' Health Study. Distribution of breast cancer cases and person-years at risk among US female nurses aged 45–49 years at the time of their entry into the cohort according to oral contraceptive use

	Oral contraceptive use		Total
	Ever (current or past use)	Never	
Cases	204	240	244
Person-years at risk	94 029	128 528	222 557

Questions:
1. Calculate an appropriate measure of association between oral contraceptive use and breast cancer.
2. Write in one sentence an interpretation of the calculated measure.

TASK 4 The relationship between artificial sweeteners and bladder cancer

A case–control study was carried out in Canada to assess whether artificial sweeteners, particularly saccharin, increased the risk of bladder cancer. Newly diagnosed cases of bladder cancer that occurred among residents in the provinces of British Columbia, Nova Scotia and Newfoundland between April 1974 and June 1976 were identified through provincial cancer registries and cooperative pathologists and urologists. A total of 821 eligible cases were ascertained, and 632 of these were personally interviewed in their homes using a structured questionnaire. Reasons for failure to interview included death (56), refusal (65), too ill to be interviewed (25), and refusal of permission by the attending physician (34). Most interviews were done within three months of diagnosis, and all within six months. For each case, an individual matched on sex, age (within 5 years), and neighborhood residence was interviewed (Howe et al., 1977).

Questions:
1. What is the association under study? What is the research question?
2. How have the cases been selected?
3. How have the controls been selected?

4. Is it possible to investigate the effect of sex, age and neighborhood residence in this study? Please explain.
5. Do you expect any potential systematic errors (bias) in this study? Please explain.

TASK 5 The relationship between lifetime number of sexual partners and cervical cancer

A population-based case–control study was carried out in Spain and Colombia to assess the relationship between cervical cancer and exposure to human papillomavirus (HPV), selected aspects of sexual and reproductive behavior, use of oral contraceptives, screening practices, smoking, and possible interactions between them. The study included 436 incident cases of histologically confirmed invasive squamous-cell carcinoma of the cervix and 387 controls of similar age randomly selected from the general population that generated the cases (Muñoz et al., 1992a).

The risk of developing cervical cancer was examined in relation to the lifetime number of sexual partners (Bosch et al., 1992).

Example A

Number of sexual partners	Cases	Controls
0 – 1	125	74
2 – 5	265	305

Questions:

1. Calculate an appropriate measure of association between oral contraceptive use and breast cancer.
2. Write in one sentence an interpretation of the calculated measure.

Example B

Number of sexual partners	Cases	Controls
0 – 1	46	8
6+	265	305

Questions:

1. Calculate an appropriate measure of association between oral contraceptive use and breast cancer.
2. Write in one sentence an interpretation of the calculated measure.

TASKS should be submitted by mail to your group assistant as follows:

Assistant	Groups	E-mail for submission of the tasks
Assoc. prof. Mariela Kamburova	2, 6, 8, 10, 12, 13, 17, 18	mariela_kamburova@yahoo.com
Assoc. prof. Stela Georgieva	7, 9, 11, 14, 19, 20	georgieva_sl@yahoo.com
Assist. prof. Dima Tsanova	1, 3, 4, 5, 15, 16	d_krumova@abv.bg

The deadline for submission is 7 days after the date of regular class (27 April – 1 May 2020).

TEST FOR SELF-ASSESSMENT

Determine the type of study in questions 1 to 7:

A. Cohort study
B. Case – control study

1. Proceeds from effect to cause.
2. Tests whether disease occurs more frequently in those exposed than in those non-exposed.
3. Usually the first approach to the testing of a hypothesis.
4. Suitable for the study of rare diseases.
5. Can examine multiple effects of a single exposure.
6. Can show temporal relationship between exposure and disease.
7. Cannot directly compute incidence rates.

Correct answers:
1-B/ 2-A/ 3-B/ 4-B/ 5-A/ 6-A/ 7-B