Special Contribution

Principles of Radiation Epidemiology

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Epidemiology is the study of the distribution and determinants of diseases or other health-related events. Descriptive epidemiology aims to investigate the distribution of diseases by time, region or in different groups of individuals, while analytical studies are used to study determinants of diseases. The most common analytical approaches are case-control studies and cohort studies. Both study designs are introduced with respect to methods, measures of risk, weaknesses and strengths. Examples for radiation epidemiological studies are the atomic bomb survivors of Hiroshima and Nagasaki, and occupationally, environmentally or medically radiation exposed populations. Generally, the choice of the study design depends on many factors such as the disease (frequency, latency) and the exposure (rare or not) to be studied, the time over which the study can be carried out, the resources available to collect detailed individual data and the potential to minimize bias and confounding. The interpretation of results of epidemiological studies requires consideration of systematic errors (information bias, selection bias), confounding and chance. Finally, the likelihood that an association between radiation exposure and health outcome is causal should be evaluated. Criteria for assessing if an association is causal include temporal relationship, biological plausibility, consistency, strength of the association, exposure-response relationship, reversibility and coherence.

Key words: Epidemiology, case-control study, cohort study, causality, bias, confounding

1. What is epidemiology?

Epidemiology is the study of the distribution of disease in the population and of factors that affect it. It is an important component of public health, and helps to identify risk factors for disease and targets for preventive measures. Epidemiology falls into descriptive and analytical epidemiology. Descriptive epidemiology investigates how frequent the disease in a population or a group of individuals is and how the disease frequency varies over time, in different regions and between specific groups. Descriptive epidemiology is important to note e.g. time trends in disease rates in a defined population. A decrease over time might be a sign for the success of preventive measures some time ago or the reduction of a significant risk factor for this specific disease. The objective of analytical epidemiological studies is to investigate a possible association between a risk factor (here radiation) and a specific disease of interest. In contrast to experimental studies under controlled laboratory conditions, epidemiological studies in humans are mostly observational due to ethical and practical issues.

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2. Types of study designs

In observational epidemiological studies, several methods are used to carry out a study[1]. These include descriptive, hypothesis-generating designs such as ecological studies and cross-sectional studies, and analytical studies that allow inference on causality such as case-control studies and cohort studies. The latter two study designs will be introduced in the following.

Cohort studies

The basic concept of a cohort study is 1) the identification of a group of persons with individual data on the exposure of interest, and 2) the follow-up of the cohort to determine their subsequent disease incidence or mortality. Cohort studies can be prospective, retrospective or a mixture of both. In a prospective study, the follow-up is from the present into the future. In a retrospective study or historic cohort, the follow-up is from the present into the past. The mixed follow-up type is from the past into the future. The choice of an appropriate comparison group for an exposed cohort is essential. The comparison group should be as similar as possible with respect to all risk factors relevant for the health effect of interest except for the exposure of interest, here radiation. To identify such a group is often difficult. Possible choices are external (e.g. general population) or internal sources (e.g. persons in similar locality or occupation). Internal comparison groups are preferable. Choosing for example the general population as external comparison group for a cohort of uranium miners, then bias is inevitable due to the "healthy worker effect" (those who work tend to be healthier than those who do not or cannot work) and differences in many other risk factors than radiation (smoking habits, nutrition, occupational carcinogens). A better comparison group is not or low exposed workers of the same uranium facility (e.g. surface workers, open pit miners), because lifestyle factors relevant for the disease of interest are expected to be comparable.

A follow-up mechanism has to be established. This could be a passive follow-up through linkage with mortality or disease registry – if available and complete - or an active follow-up through personal interviews, self-administered questionnaires or repeated exams or others. The advantage of an active follow-up is the possibility to collect information on all factors potentially related to the disease or the exposure and – if possible to collect biological material (i.e. blood samples). The disadvantage is the time and efforts needed to collect the information and the possibility of high refusal rates or withdrawals during follow-up over time.

Cohort studies are the core approach in radiation epidemiological studies. The most important cohort study with respect to radiation protection is the Life Span Study of survivors of the atomic bombs of Hiroshima and Nagasaki[2]. It includes 86,572 people with estimated radiation doses. Survivors who were within 2.5 km of the hypocenter at the time of the bombings (exposed group) were compared with a random age and sex matched sample of people 2.5 to 10 km from the hypocenter (non- or low exposed group). The follow-up period for mortality is currently from 1950 to 2003. Follow-up is through the nationwide family registry system (koseki). Information on the underlying and contributing causes of deaths is based on death certificates. Other groups of cohorts include occupational cohorts (nuclear workers, uranium miners, pilots, radiologists, etc.), patients treated for benign or malignant diseases or for diagnostic purposes (e.g. CT) or environmental cohorts (Techa river residents, Tchernobyl residents, etc.).

The frequency of disease is measured by incidence. Incidence is the number of new cases that have been developed during a defined period of time in a defined population. The incidence rate is defined as the number of new cases of a disease divided by the number of person-years at risk for the disease[3]. In a cohort study, the risk ratio is the typical measure of the association between exposure and health effect (outcome). It compares the incidence rate between two groups (radiation exposed to non-exposed).

A comparison of the incidence rates in a cohort with that of an external group such as the general population via indirect standardization for age, gender and calendar year is called Standardized Incidence Ratio (SIR). It calculates the number of observed cases in the cohort divided by the number of expected cases in an external comparison group. A SIR of 1 means that the incidence rate in the cohort is similar to that in the external comparison group. A SIR of greater (or lower) than one means that the incidence is higher (or lower) in the cohort. Usually internal comparisons within the cohort are preferable. Here the risk ratio or relative (RR) is calculated. The RR = 1 if the IR in the exposed and non-exposed group are similar and above or below 1 if the incidence rate in the exposed is higher or lower compared to the non-exposed group. In radiation epidemiology a linear relationship between the exposure and risk is often tested at first in the data analysis. In this case, the excess relative risk per unit of exposure is calculated (ERR). It represents the slope of the linear relationship. An ERR of 0.5 per Gy corresponds to a RR = ERR + 1 = 1.5, i.e. exposure to 1 Gy compared to 0 Gy increases the risk by a factor of 1.5.

Cohort studies allow direct risk estimation due to the calculation of the incidence, and the study of multiple outcomes that might arise after a single exposure rate[4]. They are useful in the study of rare exposures. Cohort studies are the most important study design in order to

assess causality of an association. Potential disadvantages of cohort studies are that they can be very expensive and time consuming, particularly if conducted prospectively. Changes in exposure status and in diagnostic criteria over time can affect the classification of individuals according to exposure and disease status. Losses to follow-up might introduce selection bias.

Case-control studies

In a case-control study, a group of individuals with a given disease (cases) and without disease (controls) is assembled and cases and controls compared with respect to their past exposures. Case-control studies are the preferable study design for rare diseases or with long latency, because cohort studies would not be efficient due to the need of large sizes and very long follow-up in order to identify at least few individuals with the disease of interest. Cases are usually identified through health system such as disease registries or hospitals. A major challenge is the choice of an appropriate control group. Cases and controls should be drawn from the same source population. Each case should have been a potential control if the disease had not developed and each control should have been a case if the disease had developed. Controls are usually randomly selected from the general population or from hospitals and matched by age, gender and other factors. In contrast to cohort studies, the exposure is assessed retrospectively. In case-control studies, it is not possible to calculate an incidence rate. Instead, the odds ratio (OR) is derived from the proportion of individuals exposed in each of the case and control groups. In the case of low incidence rates, the OR is approximately equal to the relative risk (RR).

Examples for case-control studies in radiation epidemiology are the estimation of the lung cancer risk associated with residential radon exposure[5], the risk of brain cancer in relation to mobile phone use[6] or leukemia in young children living in the vicinity of nuclear power plants[7].

Case-control studies allow the investigation of a wide range of potential risk factors. However, in contrast to cohort studies they are restricted to one disease. They are often efficient in time and cost, at least compared to prospective cohort studies. However, it is difficult to select an appropriate control group and to obtain unbiased measure of the past exposure. Case-control studies are not suitable to investigate rare exposures. Generally, case-control studies tend to be more susceptible to bias than cohort studies[8].

3. Interpretation of epidemiological studies

After completion, epidemiological studies provide information on a statistical association between exposure and disease. An important question is whether the observed risk (or association) is a spurious, indirect or causal association. The first step in the interpretation of epidemiological findings is the evaluation of the potential for bias, confounding and chance.

Bias

Systematic error or bias tends to lead to an incorrect estimate of the relationship between exposure and the disease of interest. The observed estimate may be either above or below the true value. Two types of bias may occur: selection bias or information bias. Selection bias stems from the absence of comparability between groups being studied. In case-control studies, the participation of cases and/or controls may depend on the exposure of interest. Exposed controls may be more interested to participate than non-exposed. The same holds for cohort studies. Incompleteness of follow-up due to non-response, refusal to participate, withdrawals during follow-up could result in bias if it differs in exposure categories. Also the use of an external comparison group in occupational cohorts may lead to the "healthy worker effect", where persons selected for and retained in employment tend to have better health than the general population.

Information bias occurs when measurements or classification of disease or exposure are not valid, i.e. when they do not measure correctly what they are supposed to measure. Errors may be introduced by the study participants (e.g. recall bias) or by the instruments (questionnaire, dosimeters, etc.). Two types of misclassification error can occur. Differential and non-differential misclassification of exposure or disease. Non-differential bias, where the errors are unrelated to the exposure status or disease status, tends to obscure real differences, i.e. tends to an underestimation of the true risk. Measurement error of dosimeters is an example. Non-differential misclassification occurs if the information is gathered differently for one group than for another, i.e. misclassification of exposure depends on disease status or misclassification of the disease depends on the exposure status. In a case-control study, recall bias is a typical differential bias. Cases may be more motivated to recall and report a potential risk factor for their disease than controls. E.g. brain cancer patients may overestimate the duration of mobile phone use per day compared to controls. In a cohort study, differential bias may occur if e.g. screening for thyroid cancer in children after iodine exposure is performed only or more frequent in exposed compared to low or not exposed children.

Confounding

Confounding occurs when an estimate of the association between an exposure and a disease is mixed up with the real effect of another exposure on the same disease,

the two exposures being correlated[9]. The definition of a confounder is that the variable must be associated with the exposure under study (correlation) and must be an independent risk factor for the disease. An example is the underestimation of the true risk of lung cancer in relation to residential radon without control for tobacco smoke. Tobacco smoke is a strong risk factor for lung cancer and in many studies, the prevalence of smoking is negatively correlated with the radon concentrations in homes[5]. The extent of confounding depends on the magnitude of correlation between exposure and factor and the magnitude of the risk associated with the factor. The direction of confounding depends on the direction of correlation. A negative correlation leads to an underestimation of the true risk and a positive correlation to an overestimation of the true risk. There are several ways to deal with confounding. This could be restriction (e.g. to lifelong non-smokers), matching, stratification and statistical modelling.

Chance

The role of chance is another important point in the interpretation of results of epidemiological studies. Non-statistically significant results do not necessarily mean that there is no relationship. The statistical power to detect an effect might have been too low. The statistical power depends on the study size, magnitude of the risk, prevalence of exposure, length of follow-up and other factors. In addition, the effect could be biased towards zero due to negative confounding or non-differential bias. A statistically significant effect does not mean it is causal. It could be a chance effect due to multiple testing or due to bias and/or confounding.

4. Causality

Even if confounding, bias and chance do not seem to explain an observed positive or negative association between a risk factor and an exposure, the likelihood of a causal association should be assessed, e.g. through the Bradford Hill[10] criteria. They include temporal relationship, biological plausibility, consistency, strength, exposure-response-relationship, specific, reversibility and coherence[9]. Clearly, the exposure should have taken place before the development of the disease and not vice versa.

With regard to biological plausibility, the association is considered more likely to be causal, if a biological mechanism is known or the effect is also demonstrated in animal studies. However, the lack of plausibility may simply reflect the effect of lack of scientific knowledge or the fact that human beings are biologically different from animals. If findings are similar in different studies using different populations and different study designs, the association is more likely to be causal. However, lack of consistency does not exclude a causal association, because studies may differ with respect to levels of exposure or other conditions. The magnitude of the observed association is also a criterion. A strong association is more likely to be causal than a weak association, because the latter could be easily explained by confounding and bias. A clear increase in risk with increasing levels of exposure is also some indicator for causality or reversibility, meaning that removal of the exposure decreases the risk.

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