Review article

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COHORT STUDY AS A METHOD IN ASSESSING ENVIRONMENTAL EXPOSURES AND HEALTH OUTCOMES

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Cohort study has made, and will continue to make, important contributions to the environmental epidemiologic research. The purpose of this article is to discuss the principles of a cohort study design and related methodological issues in environmental epidemiology. Many examples illustrate the value of the cohort study as investigative approach in assessing environmental exposures and health outcomes. Cohort studies have provided fundamental knowledge for prevention strategies. *Acta Medica Medianae 2015;54(4):84-87.*

Key words: *epidemiologic methods, cohort study, environmental exposures, health outcomes*

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Introduction

Epidemiology is one of the core disciplines used to examine the association between environmental hazards and health outcomes. Epidemiologic studies are applied to the control of health problems in populations.

Cohort study is a longitudinal, analytical and observational epidemiological method. The word "cohort" has its origin in the Latin cohors, referring to warriors and the notion of group of persons proceeding together in time. The word "cohort" has been adopted into epidemiology to define a set of people followed over a period of time. The modern epidemiological definition of the word now means a "group of people with defined characteristics who are followed up to determine incidence of, or mortality from, some specific disease, all causes of death, or some other outcome"(1).

Study design and methodological issues

A well-designed cohort study can provide powerful results. In a cohort study, an outcome or disease-free study population is first identified by the exposure or event of interest and followed in time until the disease or outcome of interest occurs. Because exposure is identified before the outcome, cohort studies have a temporal framework to assess causality and thus have the potential to provide the strongest scientific evidence (2).

Cohort studies are particularly advantageous for examining rare exposures because subjects are selected by their exposure status. Additionally, the investigator can examine multiple outcomes simultaneously. Disadvantages include the need for a large sample size and the potentially long follow-up duration of the study design resulting in a costly endeavor.

Cohort studies can be prospective or retrospective. Prospective studies are carried out from the present time into the future. Because prospective studies are designed with specific data collection methods, it has the advantage of being tailored to collect specific exposure data and may be more complete. The disadvantage of a prospective cohort study may be the long follow-up period while waiting for events or diseases to occur. Thus, this study design is inefficient for investigating diseases with long latency periods and is vulnerable to a high loss to follow-up rate.

Instead, retrospective cohort studies are better indicated given the timeliness and inexpensive nature of the study design. Retrospective cohort studies, also known as historical cohort studies, are carried out at the present time and look to the past to examine medical events or outcomes. In other words, a cohort of subjects selected based on exposure status is chosen at the present time, and outcome data (i.e. disease status, event status), which was measured in the past, are reconstructed for analysis. The primary disadvantage of this study design is the limited control the investigator has over data collection. The existing data may be incomplete, inaccurate, or inconsistently measured between subjects (3). However, because of the immediate availability of the data, this study design is comparatively less costly and shorter than prospective cohort studies. Many cohort studies combine both, prospective and retrospective design.

The hallmark of a cohort study is defining the selected group of subjects by exposure status at the start of the investigation. A critical characteristic of subject selection is to have both the exposed and unexposed groups be selected from the same source population (4). Subjects who are not at risk for developing the outcome should be excluded from the study. The source population is determined by practical considerations, such as sampling. Subjects may be effectively sampled from the hospital, be members of a community, or from a doctor's individual practice. A subset of these subjects will be eligible for the study.

Because prospective cohort studies may require long follow-up periods, it is important to minimize loss to follow-up. Loss to follow-up is a situation in which the investigator loses contact with the subject, resulting in missing data. If too many subjects are loss to follow-up, the internal validity of the study is reduced.

Any systematic differences related to the outcome or exposure of risk factors between those who drop out and those who stay in the study must be examined, if possible, by comparing individuals who remain in the study and those who were loss to follow-up or dropped out. It is therefore important to select subjects who can be followed for the entire duration of the cohort study.

The measure of association used in cohort studies is called relative risk (RR), the ratio of the incidence rate of a disease or health outcome in an exposed group to the incidence rate of the disease or condition of the nonexposed group. The RR provides a ratio of two risks-the risk associated with an exposure in comparison with the risk associated with nonexposure.

Examples of the environmental epidemiology literature

The first detailed account of the application of the method was given in a report of a study of men employed in the manufacture of coal-gas which demonstrated an approximate doubling of the risk of lung cancer in men who had been specifically employed in the retort houses where the exposure to the products of heated coal would have been highest. The study was undertaken because gas-workers were known to be specially liable to develop cancer of the skin and bladder (5) and Kennaway NM, and Kennaway EL (1947)(6) had noted that, in an analysis of male deaths attributed to cancer of the lung in England and Wales during the period 1921-1938, in seven out of the 56 occupations studied there were different groups of gas-workers and in each case the number observed was greater than the number expected from the experience of the whole, although the number of exposed men could be estimated only approximately.

Very many similar studies have been carried out since then. In the majority the greatest problem has been to quantify the extent to which individual workers were exposed to the suspected carcinogens and hence to provide a dose-response relationship that would permit estimates to be made of the effect of exposure to small amounts of the carcinogen in other situations.

Examples include exposure to white (chrysotile) asbestos (7), and above all the massive study of the risk of a wide range of cancers from exposure to the explosion of the atomic bombs at Hiroshima and Nagasaki undertaken jointly by the American and Japanese at the Radiation Effects Research Institute (8).

The origin of this study is of particular interest, for when concern was raised about long-term impact of the Hiroshima and Nagasaki explosions the Atomic Board Causality Commission organized regular clinical examination of a relatively small selected group. Conclusive evidence that ionizing radiation increased the risk of leukemia, cataracts, and mental retardation in children most heavily exposed in utero was rapidly obtained by a variety of methods, but by 1954 the plan for repeated clinical examination was foundering in the face of negative findings and declining participation and a cohort study was initiated to determine specific mortality rates in a group of some 100,000 people (subsequently increased to about 120,000) selected from nearly three times that number known to have been resident in the two towns at the time of the national census on October 1950 and whose history of exposure was known. This became the basis for the Life Span Study which is continuing, and in conjunction with the evidence from the local cancer registry- has provided the principal evidence on which our current knowledge of the long-term effects of ionizing radiation is based. For many years now the results of this study have provide data for the estimate of risks from different levels of exposure to ionizing radiation that are use routinely for the protection of radiation workers, patients exposed for medical purposes, and the public (8).

In the USA, with the help of volunteer supporters of the American Cancer Society, Hammond and Horn obtained smoking habits for nearly 190000 men aged between 50 and 69 years who were friends of the volunteers and follow-up data were obtained approximately biennially by the same volunteers. Causes of death were obtained from death certificates and the diagnosis of cancer was checked by information obtained from personal doctors, hospitals, and tumor registries.

A preliminary report in 1954 confirmed the predicted association with lung cancer and showed an association between smoking and coronary thrombosis, which was less close but potentially more important because of the large numbers of cases (9). Four years later, after a mean follow-up period of 44 months, a major report was published which gave death rates for each of the four five year age groups studied and the ratio between the number of deaths observed and the number expected from the rate in nonsmokers for 32 di--seases or groups of diseases19. Altogether nearly 12000 deaths were observed and it was possible to compare the ratios of the numbers of deaths observed from many different causes and the numbers expected from the experience of the non-smokers, for cigarette smokers smoking different amounts, for pipe smokers and cigar smokers, and for men who had stopped smoking for different periods. Excess mortality ratios for cigarette smokers were observed for 14 causes of death or groups of causes, with particularly high ratios for lung cancer (10.4 to one) and cancers of the upper respiratory and digestive tracts (5.1 to one). In total, the mortality among cigarette smokers was increased by 57% and over half of this was attributable to the excess of deaths from coronary heart disease, despite the mortality ratio being only 1.7, because the disease was relatively so much more common as a cause o death than any other.

This study was remarkable for two reasons. First, because it was so large; the cohort of nearly 190000 being by far the largest of its type until it was overshadowed by the American Cancer Society's study of a million men and women in the 1960s (10). Secondly, because of the care that was taken to check the diagnoses of the 2350 neoplasms referred to on death certificates, information being obtained about 95% (2242). Only six of the diagnoses of a neoplasm were found to be incorrect and 79% of the cancers said to have caused death were microscopically proven.

Cohort studies are applied widely in environmental health. For example, they have been used to examine the effects of environmental and work-related exposures to potentially toxic agents. One concern of cohort studies has been exposure of female workers to occupationally related reproductive hazards and adverse pregnancy outcomes (11). In this review, studies have been conducted on hormonal changes, semen quality, fertility, and various outcomes of pregnancy, e.g., spontaneous abortion, congenital malformations, perinatal mortality, birth weight, and health and development of the children. Also, sex distribution of children has been investigated as a possible risk indicator in some studies. In epidemiological studies, retrospective or prospective cohort design, case referent and nested case referent designs have been used. The validity of epidemiological studies depends on reliable data on the health effect and the exposure. The registers on congenital malformations and on births and other outcomes of pregnancy are useful sources of data for epidemio-logical studies. The coverage of the register and the accuracy of its contents should be known if the register is used for research. Personal interview of the worker is an important source of information, although recall problems may weaken the quality of the data. The reliability of the answers may be increased by using a few complementary questions on possible medical confirmation of the event. If both the interview and register data are available, the reliability of the information increases, the same concerns exposure information also.

Another example is an Australian study that examined the health impacts of occupational exposure to insecticides (12). The investigators compared mortality of 1,999 outdoor staff working as part of an insecticide application program during 1935-1996 with that of 1,984 outdoor workers not occupationally exposed to insecticides, and with the Australian population. Surviving subjects also completed a morbidity questionnaire. Mortality was significantly higher in both exposed and control subjects compared with the Australian population. The major cause was mortality from smoking-related diseases. Mortality was also significantly increased in exposed subjects for a number of conditions that do not appear to be the result of smoking patterns. Compared with the general Australian population, mortality over the total study period was increased for asthma [standardized mortality ratio (SMR) =3.45; 95% confidence interval (CI), 1.39-7.10] and for diabetes (SMR=3.57; 95% CI, 1.16-8.32 for subjects working <5 years). Mortality from pancreatic can-cer was more frequent in subjects exposed to 1,1,1-trichloro-2,2-bis (p-chlorophenyl)ethane (SMR = 5.27; 95% CI, 1.09-15.40 for subjects working <3 years). Compared with the control population, mortality from leukemia was increased in subjects working with more modern chemicals (standardized incidence ratio =20.90; 95% CI, 1.54-284.41 for myeloid leukemia in the highest exposure group). There was also an increase in self-reported chronic illness and asthma, and lower neuropsychological functioning scores among surviving exposed subjects when compared with controls. Diabetes was reported more commonly by subjects reporting occupational use of herbicides. These findings lend weight to other studies suggesting an association between adverse health effects and exposure to pesticides.

Conclusion

Cohort studies are applied widely in environmental health. The major strengths of this design derive from the fact that disease occurs and is detected after subjects are selected and after exposure status is measured. Thus, we can usually be confident that the exposure preceded the disease. Cohort studies have provided fundamental knowledge for prevention strategies.

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Pregledni rad

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KOHORTNA STUDIJA KAO METOD ZA SAGLEDAVANJE IZLOŽENOSTI U ŽIVOTNOJ SREDINI I ZDRAVSTVENIH ISHODA

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Kohortna studija je doprinela i nastaviće značajno da doprinosi istraživanju u oblasti zaštite zdravlja i izloženosti noksama u životnoj sredini. Cij rada bio je da sagleda karakteristike dizajna kohortne studije i razmotri metodološke principe na primerima izloženosti u životnoj i radnoj sredini i zdravstvenih ishoda. Mnogobrojni primeri iz literature ukazuju na značaj kohotnih istraživanja u ovoj oblasti. Rezultati kohortnih studija predstavljaju osnovu za preventivne strategije. *Acta Medica Medianae 2015;54(4):84-87.*

Ključne reči: *epidemiološke metode, kohortna studija, izloženosti u životnoj sredini, zdravstveni ishodi*