Epidemiology for the Nuclear Medicine Technologist

Norman E. Bolus

Nuclear Medicine Technology Program, Division of Medical Imaging and Therapy, School of Health Related Professions, University of Alabama at Birmingham, Birmingham, Alabama

Objective: The purpose of this article is to introduce the nuclear medicine technologist to the field of epidemiology. There are many applications of epidemiology in nuclear medicine, including research studies that deal with the causes of disease or ways to prevent disease from occurring and investigating the possible effects of ionizing radiation on occupational workers and the general public. One use of an epidemiologic study is to suggest ways to reduce the occurrence of a disease. After reading this article, the nuclear medicine technologist will be familiar with: a) the history and underlying assumptions of epidemiology, b) types of epidemiologic studies, c) what is a valid statistical association for an epidemiologic study, d) proper judgment of cause and effect relationships, e) definitions of epidemiologic terms, and f) an example of a nuclear medicine research study.
Key Words: epidemiology; nuclear medicine; radiation studies; valid statistical association; cause and effect relationships; prospective and retrospective studies; biostatistics.

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BRIEF HISTORY AND UNDERLYING ASSUMPTIONS

Epidemiology is the study of the distribution and causes of disease frequency in human populations. It is a Greek word that translates to "the doctrine of what is among or happening to people" (epi = among, demos = people, logos = doctrine). Merriam-Webster defines epidemiology as a branch of medical science that deals with the incidence, distribution, and control of disease in a population. Also, epidemiology is the sum of the factors controlling the presence or absence of a disease or pathogen (*1*). Therefore, epidemiology is a means of predicting disease within a population and a way to make suggestions to prevent the occurrence of disease, thus eliminating any possible effects.

An early example of an epidemiologic study can be seen in the work of John Snow, MD, circa 1854, who postulated that one of the ways cholera was transmitted was by contaminated water through an unknown mechanism within the city of London. Dr. Snow observed that there was a concentration of cholera deaths in one area of downtown London near a city water pump that was used by citizens for drinking water. He hypothesized that there was something in the water causing cholera to occur and the occurrence depended on whether the source of water was coming from downstream or upstream of London on the River Thames. Dr. Snow went door-to-door to determine the source of drinking water for each residence. Once Dr. Snow ascertained where each family got its water, he compared that data to the cases of cholera. The correlation revealed that those that received their water upstream, above the city of London, had fewer cases of cholera than those whose water source was downstream from London. Dr. Snow figured out the problem without knowing the true cause by using a scientific, systematic, observational approach to determining the source of cholera in this group of people. Ultimately, this is what epidemiology is all about (*2*).

In modern epidemiology, statistical analysis of population trends plays a large role in the scientific, systematic, observational approach of understanding the cause and effect relationship associated with disease. There are 2 underlying assumptions upon which the theory of epidemiology depends. The first is that there is always a biologic reason that disease occurs and that there must be biologic plausibility for a disease. In other words, a disease must make sense biologically speaking. If one were to say that radiation makes one glow in the dark, then there must be proof that this can happen. Conversely, if it is said that radiation exposure can cause erythema with a certain 1-time abrupt dose, then there is biologic evidence that this does occur because of radiation-induced dermatitis (*3*). The second underlying assumption is that all human diseases have causal and preventative factors that can be identified by systematic investigation of different populations, or subgroups within a population, in different places or different times. In other words, if the cause of a disease can be found

For correspondence or reprints contact: Norman E. Bolus, Assistant Professor, UAB, LRC Building, Room 371-A, 1714 Ninth Avenue South; Birmingham, Alabama, 35294-1270; Phone: (205) 934-2004; Fax: (205) 975-7302; E-mail: Bolusn@shrp.uab.edu.

and prevention of the disease can be determined for a small group, then everyone can benefit as a whole (*4*).

TYPES OF EPIDEMIOLOGIC STUDIES

There are 3 types of epidemiologic studies that are used: descriptive studies, analytic studies, and experimental studies. Each has certain characteristics that distinguish it from the others.

Descriptive Study

This study characterizes person, place, and time by asking who was affected, where the disease first occurred, and when the illness started occurring. These questions can help isolate a disease and find a common causative agent that may have started an outbreak. In many food-borne illnesses, such as salmonella poisoning, a descriptive study is usually able to pinpoint the causative agent by interviewing all those that were afflicted and finding a common food that was contaminated with salmonella bacteria. An investigator would first establish who was afflicted. Factors such as age, race, sex, occupation, social economic status, and level of immunity to disease would all be scrutinized. Did only children get sick? Was it any particular group of children based on any of the above factors? Likewise, the investigator would determine where the illness first appeared. Is there a common eating place for all afflicted: lunch room, cafeteria, restaurant, picnic, or ballpark? Geographically, were all these people at the same place at a particular time? Where do they live, work, go to school, or travel? The investigator would also determine when an illness occurred. Through the descriptive study technique of asking the appropriate questions, the investigator may be able to determine the causative agent of the disease. At the end of the study, the investigator should know where the disease first occurred, what food was contaminated, how it was contaminated, and how to prevent another outbreak (*5*).

Analytic Study

The analytic study technique is probably the most recognizable and comprises the classic case/control and cohort studies. This type of study could be used to determine if occupational radiation exposure causes any long-term health effects. Analytic studies attempt to determine the factors associated with a disease by calculating estimates of risk. The first thing an investigator would look for is any common disease a group of people might have based on exposures they have received. Exposures in nuclear medicine would probably be to radiation, but in other industries, exposures may be to coal dust, harmful vapors, or loud noises. These studies could also investigate any effects from exposure and how the exposures might be reduced or eliminated.

There are 3 types of analytic studies: the case/control study, the retrospective cohort study, and the prospective cohort study. In the case/control study, a "case" is a group of subjects that have a certain, specified disease. This case group is compared to a control group with respect to the exposure of interest. This is an effort to isolate the causative agent by determining what common exposure the case group may have had versus the control group. An example might be if leukemia developed in a group of plant workers. Investigators would try to determine if there was a difference in exposure between workers who had leukemia and workers who did not. The best case/control study tries to eliminate all but one variable between the 2 groups. Although this is usually not possible with human populations, researchers try to control for any factors that are known to be associated with the disease being studied. For example, if cancer is being studied, and it is known that older individuals are more likely to have cancer, then the researchers would want to control for age.

The retrospective cohort study looks at 2 groups of individuals that have similar characteristics. One group is exposed to a factor that is possibly associated with a disease or outcome and the other group is not. Retrospectively, the investigator would determine if any of the subjects presented with disease during their life span and whether the exposure played a part. The study could also be done after the patient has contracted the disease or even has died. An example would be determining if chronic low-dose radiation exposure shortens the life span by comparing age of death of deceased radiation workers with the age of death of workers who were not exposed to radiation.

The prospective cohort study also follows 2 groups of individuals—one that has been exposed and another that has not been exposed to some possible harmful agent—to see if disease occurs in the exposed group versus the unexposed group. This could be an on-going study of subjects who worked in an occupation for an extended period of time. An example would be determining if low-dose radiation exposure was the causative agent for a particular disease (e.g., leukemia) in a certain work force (e.g., nuclear submarine naval shipyard workers). The control group might be workers who did not receive any radiation exposure (e.g., secretaries at the shipyard). Both would be followed for some 20 y with follow-up surveys and exams. This is a very costly type of study and is used sparingly today; however, it is the best study type (*6*).

Experimental Study

An experimental study involves a search for strategies to alter the natural history of a disease. Examples are intervention studies, which are used to detect the early stages of a disease. This information may be used to reduce risk factors. An example would be a study linking cigarette smoking cessation with a reduced chance of getting lung cancer, or using a multigated heart study to stage possible heart damage before and during some types of chemotherapy treatment. This type of study could be used to evaluate different diagnostic tests or therapies to improve the prognosis of the patient. Also, the experimental study would be used to verify that a new radiopharmaceutical is safe to use by comparing the effects from the drug to the effects from a placebo. All investigational new drugs must go through an experimental study of some sort before routine human use is allowed (*7*).

EVALUATION OF A VALID STATISTICAL ASSOCIATION

How does an investigator determine if an epidemiologic study is statistically valid? Three factors can affect any study that is done: chance, systematic error, and confounding factors.

Chance

There is always a chance that a random variation in the data may make the inference drawn from a study invalid. This should be familiar to nuclear medicine technologists, because radioactive decay is a random process. Whereas we try to minimize random error in nuclear images by optimizing count rates, we cannot eliminate the random variation that will always be present in dealing with the decay of radioisotopes. Likewise, all epidemiologic studies will have some random error associated with them. The question is whether enough error is introduced to make a conclusion invalid. This is determined by statistical tests, such as χ^2 analysis or t tests. Generally, the result of these tests is a P value, which is assigned a value of 0.05 as the limit of significance. If the P value of a result is ≤ 0.05, there is no more than a 5% probability that this result occurred solely due to chance. If the P value is greater than 0.05, chance cannot be excluded as a likely explanation and the findings are not considered statistically significant. In addition, the relative error (SD divided by the mean) should always be included in a study. If not, it is difficult to determine if the magnitude of the variation is relative to the measured value or mean.

Another factor that can affect random error is the power or sample size of a study. If too few samples or individuals are included in a study, the results could be deemed invalid because there is not enough information to show that the differences seen are statistically significant. The sample size needs to be large enough so that the overlap between the 2 groups being studied will be minimal. A power calculation should be performed that includes the number of subjects and the degree of certainty for the study. The higher the power, the better the validity will be.

Systematic Error

Systematic error is also referred to as bias. There are many types of bias or systematic errors (e.g., selection bias, observational bias, interviewer bias, and recall bias) that could be introduced into a study, thus skewing the results (*8*).

Nuclear medicine technologists should be familiar with these concepts. Each day, we perform quality control on our cameras to ensure that a systematic error will not cause our equipment to run improperly. These errors can be caused by an operator failure, such as leaving the camera set on ^{57}Co when it should be set on ^{99m}Tc. Acquiring data on the wrong photopeak introduces a selection bias.

The way a study is set up can greatly affect the outcome. To rule out selection bias, those reading the final results of a study should ascertain if the study was blind, double blind, or open. This would affect who was eligible to be in the study, how the imaging results were interpreted, and the outcome of the study. For instance, if one were to conduct a study determining the level of professionalism in nuclear medicine technology by sampling only technologists, the results may be biased. It would be better to ask patients at different facilities how they felt they were treated by technologists and to randomize the sample group so that the results would reflect not just one set of patients from one facility.

Another form of bias is recall bias. This is when an event in someone's recent past affects how he or she responds to a question. For instance, an individual who contracts salmonella poisoning and then sees a report on the news that salmonella is spread by eating contaminated chicken may believe that the chicken sandwich he or she had for lunch the previous day caused the illness. If this individual is then included in an investigation of a salmonella outbreak, he or she could bias the investigation if the chicken was not, in fact, responsible for the disease.

Confounding Error

A confounding error is a mix of effects between exposure, disease, and another variable that may also be associated with the disease. For instance, if a study of lung cancer in a group of coal miners does not account for the fact that some of the subjects smoke 3 packs of cigarettes a day, smoking would be the confounding variable. This is a common problem in studying humans. We are all exposed to many outside variables that may affect our health. We cannot be studied in a laboratory, where only one variable can be changed between 2 different study groups. This is one reason why there are so many conflicting studies about what is good or bad for human populations.

Another factor that can confound a study is the comparability of the control group. For instance, in a study of 100 case subjects and 100 control subjects, it would be fairly simple to find control subjects that are well matched to the case subjects. When trying to evaluate small changes in large groups (e.g., 1,000 in each group), it becomes much more difficult to find a control group that is well matched to the case group.

Epidemiologists continue to explore better ways to conduct human studies that will factor in multiple variables through mathematic algorithms. However, the majority of studies done today will inevitably have some confounding factors that could invalidate the results. One should look at how a study is designed to determine if obvious confounding factors are addressed by the investigators (*9*).

JUDGMENT OF CAUSE AND EFFECT RELATIONSHIP

There are many factors to consider when attempting to establish a true cause and effect relationship between a possible causative agent and a disease. Correlation does not always imply causation. The most important factors to examine are strength of the association, biologic plausibility and temporality, and reproducibility.

Strength of Association

"Strength of association" refers to the probability that a particular agent or activity is highly correlated with the incidence of a particular disease. For instance, there is a high correlation that cigarette smoking increases the risk for heart disease and lung cancer. The stronger the association, the less likely that the proposed cause and effect is due to some unsuspected or uncontrolled confounding variable. The relative risk of certain exposures may indicate a high strength of association. The higher the relative risk value, the greater the association.

Biologic Plausibility and Temporality

Biologic plausibility requires proof that the cause of a disease can occur biologically. For instance, there is no relationship between the amount of hair on an individual's head and his or her level of intelligence. There must always be a biologic explanation of a causative agent associated with a correlation to make it plausible.

Temporality is the simplest of the cause and effect relationship criteria. An exposure to purported disease-causing agent must always precede the onset of a disease in a logical, biologically sound progression. In other words, you cannot get a disease before an exposure that causes that disease has occurred and the expected latency period has lapsed. When looking at a study, one should be sure that the science behind the question being asked is appropriate and makes sense biologically and temporally.

Reproducibility

Reproducibility is an important factor to determine if a cause and effect relationship is valid. A group of studies must consistently produce similar results. If one study says that smoking causes lung cancer but no one is able to reproduce the study with the same results, then the conclusions inferred from the study would be considered invalid. However, if 30 or 40 studies produce the same results, then a definite cause and effect relationship can be established.

DEFINITIONS OF EPIDEMIOLOGIC TERMS

The following is a list of terms commonly encountered in epidemiology.

- **Cohort:** A group of individuals who share common factors. Nuclear medicine technologists are a cohort of occupationally exposed chronic low-dose radiation workers.
- **Incidence:** The number of new cases of disease in a population in a given period of time.
- **Incidence Rate:** The incidence divided by the number of individuals in the population.
- **Prevalence:** The number of individuals in a population that is affected by a disease at a given point in time.
- **Prevalence Rate:** The prevalence divided by the total population being sampled.
- **Relative Risk:** A generic term that examines incidence when comparing 2 groups. In analytic studies, such as case/control and retrospective and prospective studies, this would be used to determine if the test group has a higher incidence of a disease than the control group.
- **Person-Years:** Product of the number of individuals in a study and the total time they were in the study.

The following terms are related to each other (Table 1) and are primarily used in screening and diagnostic tests.

- **Sensitivity:** The total number of individuals with a given disease that test positive divided by all those that have the disease.
- **Specificity:** The total number of individuals without a given disease that test negative divided by the total without disease.

Positive and negative predictive values indicate how well a particular test detects the presence or absence of a disease.

- **Positive Predictive Value:** The number of individuals with a given disease who test positive divided by the number of individuals who test positive even if they do not have the disease.
- **Negative Predictive Value:** The number of those without a given disease that test negative divided by all who test negative even if they have the disease.

EXAMPLE OF A RESEARCH STUDY USING NUCLEAR MEDICINE

A study analyzed the accuracy of SPECT myocardial perfusion imaging in patients with stints in native coronary arteries. At the defined level of restenosis using angiography of >70% narrowing of a coronary artery as a restenosis event, there was an improved accuracy using SPECT to detect a significant stenosis in a stinted artery. The results were as follows: 32 patients had disease and had a positive

TABLE 1
Standard 2×2 Epidemiology Table

	Proof of disease (i.e., surgery)	
Clinical tests	Disease present	Disease not present
Positive clinical test	TP (32)	FP (4)
Negative clinical test	FN (1)	TN (8)

Sensitivity = TP/TP + FN
Specificity = TN/TN + FP
Positive predicative value = TP/TP + FP
Negative predicative value = TN/TN + FN

SPECT, 1 patient had the disease but had a negative SPECT, 4 patients did not have the disease but tested positive under SPECT, and 8 patients had a negative SPECT and did not have the disease (Table 1). The approximate derived sensitivity, specificity, positive predictive value, and negative predictive values were 95%, 67%, 89%, and 89%, respectively. The positive predictive value of 89% indicated that the study could predict, with good accuracy, a restenosis event (*10*).

CONCLUSION

Epidemiology is a branch of science that affects all of us in some way. We all can benefit from the knowledge that gradually accumulates as more studies are validated through strength of association and reproducibility. Through good research studies, we can also find preventive measures to help avoid disease. Finally, with an understanding of epidemiologic and biostatistical methods, we become better consumers of scientific literature.

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