View Point

Nuances of Cohort Studies and Risk Ratio

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Abstract

Post-graduate students and faculty usually conduct case-control studies. However, sometimes they conduct cohort studies that are short-duration. Most investigators enroll the participants in two groups according to the exposure. Then, follow the participants for some duration. At the end of the study, relative risk is calculated, and the work is published in some journal. The exposure may be one time, which may or may not be quantified. The follow-up duration may not be participant-specific, and differential follow-up does not exist. The author has given three examples: the first example of consanguineous marriages and congenital disabilities, the second example of the ABO blood group system and childhood asthma, and the third example of insecticide spraying and stillbirth. In the given examples, cumulative or density incidence cannot be calculated in a true sense and, therefore, risk ratio. Even estimating the incidence of outcome variables in some studies is not appropriate. Risk ratio calculation in such scenarios is questionable because exposure quantification, follow-up period, and combination are the limiting factors. In case-control studies, the prevalence ratio is calculated, which is analogous to relative risk. The author suggests that, in such circumstances, prevalence ratio calculation will be more appropriate.

Keywords: Cumulative incidence, density incidence, differential follow-up, exposure quantification, prevalence ratio, relative risk

Introduction

'Epidemiological study designs' is one of the most favorite topics for teachers to impart education to undergraduate and post-doctoral students. The interest and focus on this topic have tremendously increased since the National Medical Council, India, has made the Basic Course in Biomedical Research mandatory for postgraduate students and junior faculty for promotion. In the pyramid of the strength of evidence, cohort studies are rated high. The cohort studies are usually classified as open (dynamic) or closed (fixed); another way of classification may be a prospective or retrospective study.[1-3] Students are contented with its implications, ease of analysis, and particularly the calculation of relative risk. The students easily understand the concept of the exposure and outcome variable. The study revolves around the cause-and-effect relationship. Conduction of cohort studies is a challenging task. Even in clinical trials, modified concepts are used to calculate the benefits. The present inscription is confined to observational studies. Risk ratio and relative risk terms are used frequently and synonymously, as there is no difference conceptually or in calculation. Three hypothetical scenarios (based on experience) are described below, which have driven the students/faculty to jump to calculate the risk ratio. For simplicity of understanding, all three examples are of closed cohort studies.

Examples

1. Several articles show an association or no association between consanguineous marriages and congenital disabilities.[4,5] In a teaching hospital, in the antenatal clinic, the routine history of consanguineous marriages is asked. At the time of delivery, congenital physical birth disabilities are noted. One Obstetrics and Gynecology Department postgraduate student framed a research question, 'Do consanguineous marriages lead to congenital physical birth disabilities?' While taking history during the ante-natal clinic, the student invariably asked about the history of consanguineous marriage. Only one to fourth-degree consanguineous marriages were

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considered. The student enrolled all pregnant women for one year and followed all the registered women till delivery. Both cohorts, exposed to the cause and not exposed to the cause, were followed, and the postgraduate students calculated the risk ratio. The risk ratio of getting congenital physical disabilities among consanguineous marriages was about 1.35.

2. Some articles show differential asthma severity among children belonging to various ABO systems of blood groups.[6,7] The pediatrics department had a research question: Do B blood group children have severe asthma compared to other children? The department enrolled all live births in the hospital, examined their blood groups, and followed them for five years for the occurrence of asthma and its severity. The investigator calculated the relative risk of getting severe asthma among the B blood group children compared to other group children. The relative risk was 2.13.
3. In a district, grape cultivation is widespread. Men and women spray insecticide on grape plants for better yield. Exposure to insecticide during the first or second trimester is known to result in stillbirth primarily due to congenital malformations, but the results are uncertain.[8,9] After antenatal registration and during follow-up visits, one researcher took a detailed history of insecticide spraying in terms of the number of days and hours per day. All the women were observed till delivery. The relative risk of stillbirth among those exposed to insecticide spraying was 1.48.

Discussion

Most students and faculty know that the more the relative risk, the stronger the association between the exposure and outcome. They also know that a relative risk <1 means exposure offers protection against the outcome. Although most of the standard journals insist on mentioning confidence intervals, several articles in some journals do not mention confidence intervals. The risk is not statistically significant if the 95% confidence intervals encompass zero. Further analysis is also equally important. The risk may be due to confounding factors, so multiple logistic regression is essential, which many investigators do not carry out.

The classical nine criteria of cause and effect relationship described by Sir Bradford Hill[10] include the strength of association and biological gradient or the dose-response curve. The relative risk measures the strength of the association. The dose-response curve is not possible when the exposure is difficult to quantify. Although we may dichotomize the exposure to 'yes' or 'no'; theoretically, there should be a possibility of quantifying the exposure. Categorizing the participants into being exposed to independent variables and not being exposed is the first step. Then, the intensity of exposure calculation is the next essential step.[3] The higher the exposure, the earlier or more severe the outcome. The greatest challenge in cohort studies is quantifying the cumulative exposure; among those exposed, many may evade the exposure entirely or partially whereas several may get exposed after starting the study. Such a phenomenon mainly occurs when the induction period of development of outcome is long. In the first and second examples, there seems to be no possibility of quantifying the exposure. One-time exposures can also be graded. The 1984 Bhopal tragedy of methyl isocyanate gas leaking was a one-time exposure, but the distance from the factory served as the proxy for grading of exposure to the gas. After the Hiroshima and Nagasaki bombings, a similar extent of the dose of radiation exposure was calculated by measuring the distance from the bombing site.[11]

The core component of the cohort study is the follow-up and calculation of incidence among both groups. Some participants may develop the outcome earlier, some develop it later, and others may not. The follow-up period from the initiation of the study and the development of the outcome should be precisely noted. In the first and third examples, all pregnant women who participated will have outcomes at the 'seven to nine months' follow-up period. Scientifically, stillbirths and congenital anomalies are measured as per 100 or 1,000.[12,13] Hence, measuring incidence and calculating relative risk or risk ratio will be inappropriate.

In examples one and three, even if the women are followed for some months later, the actual number of outcome variables will undoubtedly remain the same. The whole concept of follow-up and incidence calculation is annihilated. For the correct relative risk calculation, one must understand the difference between density incidence and cumulative incidence.[1] Density incidence is more relevant in open cohort studies where new participants enter; some leave the cohort before the study ends. The denominator consists of a-summation of time contributed by each participant (person-year follow-up). In comparison, the 'cumulative incidence' is more appropriate in closed cohort studies where new participants do not enter. The calculating cumulative incidence for the study period will have a population as the denominator and the numerator will be the summation of the outcomes that occurred at various points in time. In the examples given above, cumulative incidence can only be calculated in the second example. Some participants are permanently lost to follow-up in cohort studies; however, many studies are not censored, although the best censoring is when the loss to follow-up occurs.[14] Censoring in the above examples was not carried out, and censoring was unnecessary.

All three examples are seemingly cohort studies, but calculating relative risk is not advisable for these studies for the reasons discussed. Many investigators (including the author) have calculated relative risk in such studies.

In circumstances when quantifying the exposure variable and differential follow-up of participants to record a few additional events is not possible, what statistic can be used to study the effect of exposure?

In cross-sectional studies, prevalence odds ratio and prevalence ratio are frequently used and described, and usually, prevalence

ratio for various reasons is favored over prevalence odds ratio.[15-18] The prevalence ratio is analogous to relative risk in cohort studies.[18] The prevalence and risk ratios are similar when the outcome occurs comparatively in a shorter period.[18] The calculation of the prevalence ratio is identical to the calculation of relative risk. Even the calculation of confidence intervals and adjusted prevalence ratio is like the risk ratio calculation.

One may come across several examples similar to the ones mentioned above. The author suggests that when the quantification of the independent variable is next to impossible conceptually, differential follow-up for the outcome variable cannot happen; calculating the prevalence ratio may be more relevant than calculating unscientific relative risk. The author also suggests that reassessing exposure and making further modifications before calculations are prudent.

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Conflicts of interest

There are no conflicts of interest.

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