Journal Club:

Estimating risk for developing epilepsy

A population-based study in Rochester, Minnesota

Victoria S.S. Wong, MD
Lisa M. Bateman, MD,
FRCPC

Address correspondence and
reprint requests to Dr. Victoria
S.S. Wong, Department of
Neurology, UCDMC, 4860 Y
St., Suite 3700, Sacramento, CA
95817
vwongmd@gmail.com

This initial Journal Club article looks at a study from Hesdorffer and colleagues¹ who have calculated the lifetime risk of developing epilepsy. The study provides an elegant example of proper epidemiologic methods and results in data that have important implications for public health.

When addressing public health aspects of epilepsy, it is essential to obtain an unbiased estimate of the lifetime risk of epilepsy. With this assessment, the economic burden of epilepsy, including health care expenditures, productivity loss, intangible costs such as those associated with stigma, and additional costs from medical comorbidities of epilepsy can be extrapolated.^{2,3} Similarly, the patient-perceived burden of epilepsy, including associations between epilepsy and poor health, unemployment, lower annual incomes, lower health-related quality of life, smoking, and obesity, can be better evaluated.⁴ Given this information and the proportion of the aging population that is at risk for epilepsy, the limited number of specialists able to care for epilepsy patients is a growing concern. Nearly 35% of adults with self-reported active epilepsy reported not having seen a neurologist or epileptologist in the previous year⁴ and the Workforce Task Force of the American Academy of Neurology predicts a shortfall of neurologists in the years to come.⁵ With these broad consequences of epilepsy, the questions that Hesdorffer and colleagues pose in their study are relevant to neurologic practice.

HYPOTHESIS AND DESIGN What is the risk of developing epilepsy over the course of a lifetime? How much does this risk increase with age? How does the incidence of epilepsy differ among age groups? To answer these critical epidemiologic questions, Hesdorffer and colleagues performed a population-based retrospective cohort study using medical records from Southeastern Minnesota. The study population was limited to those who developed epilepsy between January 1, 1960, and December 31, 1979, as documented through the Rochester Ep-

idemiologic Project, a medical record linkage system that provides access to nearly all medical records of the residents of Olmsted County, MN, for the purpose of medical research.⁶ Using the data from these medical records, the authors calculated the cumulative incidence and lifetime risk of epilepsy.

There is a J-shaped incidence curve for epilepsy, already described in the literature, that illustrates a high incidence of new epilepsy cases occurring in infants under 1 year of age, a relatively lower number of new cases occurring throughout childhood and adulthood, and the largest number of new cases occurring after the age of 60.⁷ In diseases for which the incidence is high in the older population, the calculation of cumulative incidence is biased by the competing risk of death. A competing risk is defined as "an alternative outcome that is of equal or more significant clinical importance than the primary outcome and alters the probability of the outcome of interest."⁸ In the present study, the data analysis takes the competing risk of death into account in order to obtain an accurate estimate of the lifetime risk of epilepsy. More traditional methods of analysis such as Kaplan-Meier estimates and Cox proportional hazards regression that do not adjust for competing risks would result in bias.⁸

METHODS Using the medical records from the Rochester Epidemiologic Project described above, data from the study population were collected including the age at epilepsy diagnosis, epilepsy etiology (progressive symptomatic, remote symptomatic, or idiopathic/cryptogenic), and deaths in the general population. Using this information, Hesdorffer and colleagues first calculated the cumulative incidence, then adjusted for the competing risk of death to calculate the lifetime risk. Both calculations were done in order to compare the 2 results.

Cumulative incidence is a proportion that measures the number of new cases of a disease relative to the number of people in a population who may develop the disease over a specific period of time. The

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From the Department of Neurology, University of California, Davis Medical Center, Sacramento.
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cumulative incidence makes an assumption that “individuals who die before they can be observed to have the disease are assumed to have developed the disease at the same rate as those who survive.”⁹ To calculate the cumulative incidence, the hazard ratio was first obtained by dividing the total number of epilepsy cases at each age by the total population at risk at that same age. This ratio was used to calculate a survival probability at each age and the age-specific incidence at each age. Cumulative incidence was calculated as the summation of all age-specific incidences. In this calculation, it is apparent that death is not taken into account as a competing risk.

Lifetime risk was then calculated in a similar fashion except with the use of an adjusted hazard ratio that did take into account the competing risk of death. With the lifetime risk calculation, members of the population who die are considered to have zero risk for developing epilepsy. In this case, an adjusted hazard ratio was calculated by adding the total number of epilepsy cases at each age to the number of deaths, then dividing by the total population at risk at that same age. This adjusted hazard ratio was then used to calculate an adjusted survival probability at each age and an adjusted age-specific incidence. The summation of the adjusted age-specific incidences resulted in the lifetime risk.

RESULTS The cumulative incidence of epilepsy was found to be 0.9% to age 20, 1.7% to age 50, and 3.4% to age 80. The lifetime risk of epilepsy was found to be 0.9% to age 20, 1.6% to age 50, and 3.0% to age 80. In other words, the cumulative risk of developing epilepsy by the age of 80 would be 3.0%. Most notable is the fact that at younger ages, the cumulative incidence and lifetime risk are similar, whereas beginning at approximately age 70, when mortality increases, the cumulative incidence is larger than the lifetime risk. By ages 80–84, the cumulative incidence was 17.8% higher than the lifetime risk. This occurs because death becomes a larger competing risk, and as a result, the cumulative incidence is an overestimate of lifetime risk.

Interpretation. Hesdorffer and colleagues have brought to attention the lifetime risk of developing epilepsy and some of the implications of this data. They also emphasize the importance of calculating lifetime risk rather than cumulative incidence in order to prevent bias from the competing risk of death.

The strength of the study is that the calculation of lifetime risk is valid based on the methodology used. This method of adjustment for the competing risk of death has been cited in numerous articles, most notably in the geriatric and oncology literature.^{8,10} For example, if one were calculating the incidence of a

second hip fracture, the competing risk of mortality following the first hip fracture would be present. If this competing risk were not taken into account, then there would be an overestimated incidence of second hip fracture.⁸ When such a competing risk is present, the options are to analyze the event of interest while ignoring the competing risk, combine the events (e.g., epilepsy and death) as a single endpoint, or analyze the competing risk.¹⁰ The latter option has been done in this study to obtain the least biased lifetime risk value possible, and it was confirmed that the cumulative incidence was an overestimate of the lifetime risk.

Weaknesses of the study are as follows:

1. With the use of 30-year-old data, there are multiple issues of concern.
 - a) While the clinical definitions of epilepsy as “2 or more unprovoked seizures” and unprovoked seizures as “seizures without an identified proximate precipitant” used in this study are still widely accepted, the study divided the etiology of epilepsy into categories of progressive symptomatic, remote symptomatic, or idiopathic/cryptogenic. These categories do not figure prominently in the analysis, with just a note that the incidence of progressive symptomatic epilepsy increased most among the elderly, but it is still notable that these data were collected before the current system for classification of seizures and syndromes was established.
 - b) As the population of the United States has become more diverse over the past 30 years, the calculated lifetime risk of the Rochester, MN, population between 1960 and 1979 may not be generally applicable today. Although the data are limited, some US studies suggest a higher prevalence of epilepsy among African Americans as compared to whites.¹¹ Increased immigration may also alter the distribution of epilepsy subtypes (e.g., an increase in symptomatic epilepsy from additional neurocysticercosis cases). In addition, life expectancy has changed over time, resulting in a larger elderly population, such that the calculated lifetime risk may be an underestimate.
 - c) The potential causes of symptomatic epilepsy may change over time, with a notable example of HIV, a known risk factor for epilepsy that was not diagnosed 30 years ago.
2. The accuracy of the epilepsy diagnosis may be called into question when performing a broad medical record review. The authors reviewed medical records with a diagnosis of “seizure, convulsion, epilepsy, or conditions known to be re-

lated to seizures.” Given that the term “epilepsy” may be used loosely as a chart diagnosis, particularly by non-neurologists, it is possible that other conditions, such as psychogenic nonepileptic attacks or syncope, could have been misdiagnosed as epilepsy.

Given these concerns, is the calculated lifetime risk still relevant to current neurologic practice? Although the population demographics and the etiologies of symptomatic epilepsy may have changed over time, the only way to establish a current estimate of epilepsy risk is to do a retrospective cohort study.¹² As public health resources are limited, having an estimate of lifetime risk is important to determine the allocation of resources. An estimate of lifetime risk is also key knowledge for the practicing clinical neurologist, who should have an idea of the risk of epilepsy as patients age.

With their article, Hesdorffer and colleagues have emphasized the importance of using the appropriate methodology for obtaining the lifetime risk of epilepsy. Cumulative incidence is a commonly used measure of risk, yet this study shows that in a disease such as epilepsy, with a high incidence in the elderly population where mortality is a competing risk, the cumulative incidence largely overestimates the lifetime risk. At age 80, the cumulative incidence of epilepsy was calculated as 3.4%, which is 13% higher than the lifetime risk of 3.0%. Above age 80, the cumulative incidence was 17.8% higher than the lifetime risk. Although the absolute differences between cumulative incidence and lifetime risk appear small (i.e., 3.4% vs 3.0%), the overestimation of cumulative incidence is essential to take into consideration when interpreted on a larger scale in the context of public health. Beyond epilepsy, the article notes that lifetime risk has been measured for other diseases with high incidence in the elderly such as stroke and AD.¹ With the current aging population and the associated disease burden, it is essential that future epidemiologic geriatric studies make adjustments for the competing risk of death to maximize the accuracy of such estimates.

AUTHOR CONTRIBUTIONS

Dr. Wong: drafting/revising the manuscript, analysis or interpretation of data. Dr. Bateman: drafting/revising the manuscript, analysis or interpretation of data.

DISCLOSURE

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