Noel S. Weiss

Clinical Epidemiology

The Study of the Outcome of Illness

Monographs in Epidemiology and Biostatistics
Volume 11

Clinical Epidemiology: The Study of the Outcome of Illness

NOEL S. WEISS

New York Oxford
OXFORD UNIVERSITY PRESS
1986

Oxford University Press
Oxford New York Toronto
Delhi Bombay Calcutta Madras Karachi
Petaling Jaya Singapore Hong Kong Tokyo
Nairobi Dar es Salaam Cape Town
Melbourne Auckland
and associated companies in
Beirut Berlin Ibadan Nicosia

Published by Oxford University Press, Inc.,
200 Madison Avenue, New York, New York 10016

Library of Congress Cataloging-in-Publication Data
Weiss, Noel S., 1943–
Clinical epidemiology.
(Monographs in epidemiology and biostatistics ; v. 11)
Includes bibliographies and index.
1. Epidemiology. 2. Medicine, Clinical. I. Title. II. Series.
[DNLM: 1. Biometry. 2. Epidemiologic Methods. 3. Epidemiology.
W1 MO567LT v.11 / WA 950 W431c]
RA652.W45 1986 614.4 85-15503
ISBN 0-19-503718-9

Printing (last digit): 9 8 7 6 5 4 3 2 1

Printed in the United States of America

Clinical Epidemiology: The Study of the Outcome of Illness

Monographs in Epidemiology and Biostatistics
edited by Abraham M. Lilienfeld

1 THE EPIDEMIOLOGY OF DEMENTIA
James A. Mortimer and Leonard M. Schuman 1981

2 CASE CONTROL STUDIES
Design, Conduct, Analysis
James J. Schlesselman 1982

3 EPIDEMIOLOGY OF MUSCULOSKELETAL DISORDERS
Jennifer L. Kelsey 1982

4 URBANIZATION AND CANCER MORTALITY
The United States Experience, 1950–1975
Michael R. Greenberg 1983

5 AN INTRODUCTION TO EPIDEMIOLOGIC METHODS
Harold A. Kahn 1983

6 THE LEUKEMIAS
Epidemiologic Aspects
Martha S. Linet 1984

7 SCREENING IN CHRONIC DISEASE
Alan S. Morrison 1985

8 CLINICAL TRIALS
Design, Conduct, and Analysis
Curtis L. Meinert 1986

9 VACCINATING AGAINST BRAIN DYSFUNCTION SYNDROME
The Campaign Against Rubella and Measles
Ernest M. Gruenberg 1986

10 OBSERVATIONAL EPIDEMIOLOGIC STUDIES
Jennifer L. Kelsey, W. Douglas Thompson, Alfred S. Evans 1986

11 CLINICAL EPIDEMIOLOGY: THE STUDY
OF THE OUTCOME OF ILLNESS
Noel S. Weiss 1986

Preface

This book intends to pull together a number of areas of research that are devoted to measuring and determining the factors that affect the outcome of illness. It gives these areas of research a collective label: clinical epidemiology. This is a term that has been used to mean various things, the most common being epidemiologic research conducted in the "clinic" (or other institution in which health care is provided) by clinicians. In this book, however, the distinction between epidemiologic and clinical epidemiologic research will be made on the basis of the *subject* of the inquiry, that is, the causes versus the consequences of illness.

My goal in writing the book has been to enhance the skills of persons who are conducting or interpreting research that relates to the impact of diagnostic or therapeutic procedures on illness outcome, whether those persons are physicians, nurses, dentists, veterinarians, or other providers of health care. I have assumed that readers will be familiar with such topics as rates and probability, topics that would be covered in an introductory epidemiology or biostatistics course, so the book also may be of benefit to students of epidemiology or biostatistics who are considering work in the clinical setting.

The book begins with a description of the clinical context into which the research findings ought to fit, hence the discussion of decision analysis. Next, there are chapters on the evaluation of diagnostic tests with respect to both their accuracy and their measurable contribution to illness outcome. The discussion of therapy is in two parts—efficacy and safety. The former is sufficiently lengthy to war-

rant separate chapters for experimental and nonexperimental approaches. The concluding chapter of the book concentrates on the role of studies that measure the natural history of illness. An appendix presents selected statistical methods commonly used in planning and analyzing data from clinical epidemiologic studies.

The book can be read in an armchair, but to get the most out of some sections it would be useful to have a desk, calculator, pencil, and paper. To encourage the active participation of the reader, I have included questions (with answers) at the end of each chapter.

I am grateful to the University of Washington School of Public Health and Community Medicine for providing me the opportunity to develop a course in clinical epidemiology, and to the University of California at Los Angeles School of Public Health for providing the sheltered environment I needed to begin to put the content of that course into the form of a book. Discussions with Drs. Richard Kronmal and Karen Sherman helped me to sharpen my thinking on several of the issues I have chosen to present. Drs. Thomas Koepsell and Nancy Stevens read the entire manuscript; its clarity has been substantially increased as a result of their efforts. My wife and other members of my family have been an unwavering source of support, from well before the conception of this work through the entire period of its gestation.

Seattle, Washington
May 1985

N.S.W.

Contents

Clinical Epidemiology: The Study of the Outcome of Illness

1 Clinical Epidemiology: What It Is and How It Is Used

Let's say that among your patients is a middle-aged man with intermittent claudication and that his symptoms have been increasing in severity over the last several years. His blood sugar level is normal, but he has a long history of cigarette smoking. The results of the physical examination are normal except for the absence of pulses in the legs. Should he be advised to undergo arteriographic evaluation and an operation for any surgically correctable lesions?

Among the questions that need to be addressed before making such a recommendation are the following: 1. What is the expected progression of symptoms and expected longevity in such a patient in the absence of surgical intervention? 2. To what extent is arteriography capable of (a) identifying remediable lesions, (b) not producing false-positive films, and (c) not producing adverse effects? 3. What is the likelihood (short- and long-term) that surgery can relieve symptoms or prevent progression while at the same time not cause complications? The area of research that attempts to provide answers to these sorts of questions is clinical epidemiology.

Epidemiology per se is the study of variation in the occurrence of disease, and of the reasons for that variation. It first entails making *observations* of individuals (or of populations), for instance, who develops disease and what are the characteristics of the ill or injured individuals that distinguish them from other persons. This process is followed by the formation of *inferences* as to which of these characteristics, or other unmeasured ones, played a role in causing the disease.

Clinical epidemiology is defined here in a parallel way: It is the

study of variation in the *outcome* of illness and of the reasons for that variation. The modus operandi is similar as well. First, observations are made as to the fate of ill persons—who recovers, worsens, develops complications, and what characterizes those who have different fates. Second, inferences are made as to the particular characteristics of the patient or his or her care that were responsible for these differences in outcome.

For many conditions, the most important determinants of outcome are diagnostic and therapeutic interventions. Because research in clinical epidemiology attempts to quantify the importance of these interventions relative to others possible or to none at all, the results obtained have direct applications for providers of health care.

To illustrate the questions that epidemiology and clinical epidemiology try to answer, let's return to our patient with claudication. Epidemiologic studies would make observations pertinent to the etiology of the symptom and its underlying pathology: Cigarette smokers and nonsmokers might be contrasted regarding the prevalence of claudication. If this study and others indicated a strong relationship, perhaps one that increased with the amount and recency of smoking, and if nonepidemiologic evidence were compatible with a deleterious effect of cigarette smoking on the peripheral arteries, then an inference of cause and effect could be drawn.

Clinical epidemiology, however, focuses on the consequences of the condition and the care given for it. Thus, observations might be made of untreated patients with claudication regarding the rate of change in symptoms, of other patients undergoing arteriography to determine the prevalence of surgically correctable lesions, and of still others who undergo surgery to assess the change in symptoms and/or physical signs. These studies would lead to inferences as to the role of surgery in achieving the intended purpose: To what extent was there improvement of symptoms and signs in patients who underwent these procedures? To what extent could any favorable outcomes be attributed to spontaneous regression of disease, or to selection for surgical therapy of patients destined to have favorable outcomes? If arteriography/surgery did produce improvements, what proportion of the patients undergoing arteriography was helped? By how much? Quantitative answers are necessary, for they will have to be balanced against the costs and hazards of arteriography and surgery (see below).

Though the term illness is part of the definition of clinical epi-

demiology, no attempt will be made to define it in any precise way. "Illness" is used here in a far broader sense than is "disease," which often refers to a particular set of anatomic or physiologic abnormalities. Illness may, for example, denote only a symptom that causes a patient to seek care, or to a physical sign detected by a provider of care. Since a large part of the utility of research in clinical epidemiology lies in its evaluation of the work of providers of health care, illness here will refer to any reason people have for seeking the services of such a provider. The methods of clinical epidemiology operate in the same fashion, whether they are applied to persons seeking care for health maintenance, for a specific symptom or sign, or for a disease.

WAYS IN WHICH CLINICAL EPIDEMIOLOGY IS PUT TO USE: DECISION MAKING

Virtually everything we can do for a patient has a "cost" attached to it. Costs can be measured in terms of labor and/or materials expended for the patient's care, such as those involved in taking a medical history, administering diagnostic roentgenography, or synthesizing and marketing a drug. A second cost relates to the deleterious effects on the patient's well-being of some aspects of the care provided. A barium enema will result in radiation exposure in all patients, cause temporary discomfort in most of them, and in rare instances lead to more serious consequences (e.g., bowel perforation). Digitalis will cause side effects in many patients, some minor (e.g., nausea) and some potentially severe (e.g., cardiac arrhythmias).

Ideally, no diagnostic or therapeutic measure should be undertaken unless its expected benefits to the patient exceed its expected costs. In most situations, an estimate of the relative magnitude of benefits and costs is easily made. In a patient with pneumococcal pneumonia, the therapeutic benefit of penicillin clearly outweighs the possibility of anaphylaxis (or other adverse effect) and the dollar cost of the drug. In an 85-year-old patient with angina, the various costs of coronary angiography and coronary artery bypass surgery almost always will outweigh the expected benefits in terms of symptom relief or (perhaps) increased longevity.

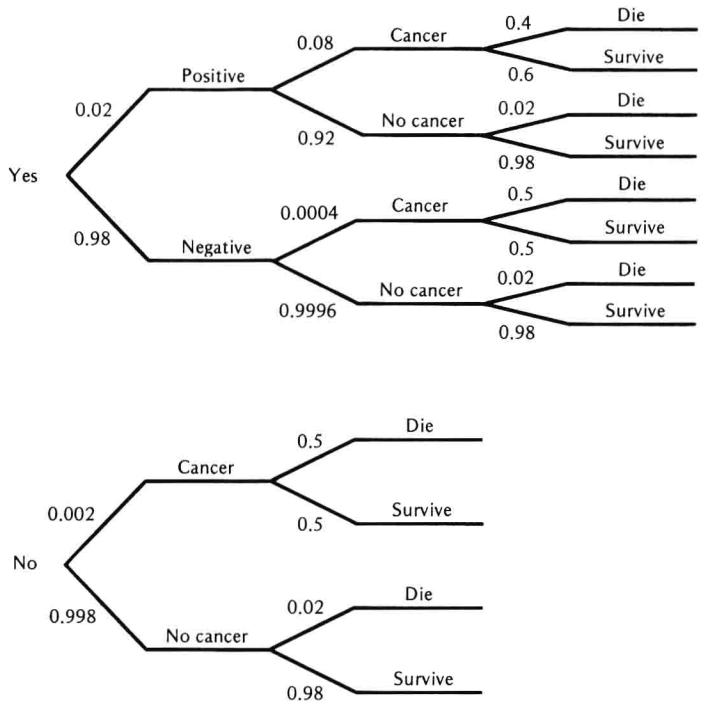
However, a number of situations confront the provider of care in which there appears to exist a near balance of benefits and costs.

For example, at present it is not clear to many providers whether, in order to detect cancer of the large bowel at an early stage, they should examine feces for occult blood using the Hemoccult test in asymptomatic, previously unscreened adult patients. In favor of the decision to use the test is the fact that some patients with undiagnosed cancer of this type who would have died of it will, instead, through treatment of tumors found at an early stage, be cured. Arguing against the use of the Hemoccult test in these patients is the cost of the test itself and the cost of evaluating further persons whose tests are positive but who do not have cancer.

In situations like this, one means of structuring the available information in order to guide the provider's use of diagnostic and therapeutic measures is *decision analysis.* The way in which decision analysis proceeds is illustrated in Figure 1-1. For purposes of this example it will be assumed that (a) the prevalence of cancer of the large bowel in this patient group is 2 per 1,000 and that, in the absence of Hemoccult testing, one-half of those with the cancer will die within the next 3 years; (b) 2% of those tested will be "positive," but among them 92% will be falsely positive (in most asymptomatic persons with blood in their stool, the source of the blood is not a malignancy of the large bowel); (c) a few people (0.04%) will test negative but will actually have the cancer; (d) the 3-year mortality in screened persons with cancer is only 40%, and that of persons without cancer is 2% (with or without screening); (e) other than cost, there are no negative attributes of Hemoccult testing (this will not necessarily be the case for other screening and diagnostic tests, the morbidity of which would have to be incorporated into the "decision tree").

The process of weighing the two alternatives (screen or not screen) begins by enumerating every possible category of patient, first of those who undergo testing and then of patients who do not. (For simplicity, the example described in Figure 1-1 ignores many important outcomes, primarily those relating to morbidity from colorectal cancer and its treatment.) Thus, the top "branch" in Figure 1-1 refers to patients who were screened, had a positive Hemoccult test, were found on further testing to have colorectal cancer, and who, despite the screening, died during the next 3 years.

Second, the proportion of patients in each category is estimated by multiplying together all of the probabilities of the "steps" that define the category. For example, the proportion of screened individuals found to be positive, who have colorectal cancer, and who



Components of cost (dysutility)	Probability	Average dysutility expected	
S, D, C, M	0.00064	(S + D + C + M)	X 0.00064
S, D, C	0.00096	(S + D + C)	X 0.00096
S, D, M	0.00037	(S + D + M)	X 0.00037
S, D	0.01803	(S + D)	X 0.01803
S, D, C, M	0.00020	(S + D + C + M)	X 0.00020
S, D, C	0.00020	(S + D + C)	X 0.00020
S, M	0.01959	(S + M)	X 0.01959
S	0.96001	(S)	X 0.96001
	1.0		X
D, C, M	0.001	(D + C + M)	X 0.001
D, C	0.001	(D + C)	X 0.001
M	0.01996	(M)	X 0.01996
0	0.97804		0
	1.0		Y

Costs:
S = screening
D = diagnosis
C = cancer
M = mortality

Decision: Perform Hemoccult test only if $X < Y$

Figure 1-1. Decision tree for performing the Hemoccult test in asymptomatic patients.

die of the cancer within 3 years is equal to:

0.02	(proportion screened as positive)
× 0.08	(proportion of these patients who have cancer)
× 0.4	(proportion of cancer patients screened as positive
0.0064	who die within 3 years)

Third, a weight or value is assigned to each possible category. These values are the sums of the costs—monetary, physical, and emotional—of the disease and the testing and treatment of it. These values are all negative, for the occurrence of cancer of the large bowel exerts a negative influence on the population's health; hence the terms costs and dysutilities used in Figure 1-1 and hereafter. In question is whether or not the expenditure of some of the population's resources, for instance, on screening, will diminish this negative influence.

Fourth, the proportion of patients in each category is multiplied by the negative value attached to that category. Finally, the sum of these products ("average dysutility expected") for persons undergoing Hemoccult testing (X) is compared with the corresponding sum for persons not tested (Y). If $X < Y$, then testing should be recommended.

Often there is uncertainty as to the probability with which some of the events occur, for instance, the probability of death among screened and unscreened persons with colorectal cancer, or as to the size of the dysutility associated with a particular category of patient (see below). A useful feature of decision analysis is that, once the structures of the decision trees have been developed, the extent to which the decision is affected by changes in the probabilities of the various outcomes or in the particular set of dysutilities chosen can be determined. This process of determining if the decision is influenced by changes in the input information is called "sensitivity analysis." It allows the decision-maker to determine how solid his or her choice is, despite imprecise knowledge.

This book is devoted to describing the means by which one measures the probability of occurrence of the steps that define each category of patient outcome, but as for the measurement of the dysutilities, a few paragraphs here must do. Certainly, some of the dysutilities are easy to estimate accurately, for example, the dollar cost of the Hemoccult test and of the procedures needed to secure a diagnosis. The impact of having the cancer is harder to quantify.

The average cost of treatment can be determined, but what of the physical and psychological effects? And what is the "cost" of death? And, if we are to complete the decision analysis, how can we put these dollar, illness, and death dysutilities in the same units?

As difficult as the task is, in order for providers to make rational decisions regarding the delivery of health care—whether or not they employ decision analysis in a formal way—it is necessary that they weigh the various negative events on a common scale. Most often, the scale is a monetary one. The idea of assigning a certain monetary value to health or to a human life is an unappealing one to most of us, and rarely is anyone in a position to knowingly cause loss of health or life in a specific individual by failing to make a dollar expenditure. Nonetheless, society chooses to allocate only so many of its dollars for reducing the probability of illness and death among its members. We are willing to pay so much, but not more, for road safety, for example. It is probable that additional highway dividers or railroad bridges would prevent some injuries and an occasional accidental traffic death, but in many instances we are unable to "afford" them. Or, perhaps, we may believe that installation of a highly trained, rapid-response, emergency medical service in a town of 10,000 persons could lead to the survival of one person who develops cardiac arrest each year, but it is likely that in many towns of this size, the expense of operating such a program is beyond what the populace is willing to pay.

Since society is responsible for the overwhelming majority of expenditures for health care, the wishes of society should play the major role in determining whether or not individual health care expenses are met as well. Though a provider of health care is committed to doing everything possible to promote a patient's health, the range of what is possible should be delineated by those who will pay the bill. Thus, there are instances in which a health care provider, conscious of society's needs, actually will make recommendations or take actions that fall short of those that he or she would implement if resources for health care were unlimited. Such a provider realizes that these resources *are* limited—what is consumed for one purpose is not available for others. The goal of the health care provider, then, is to use these finite resources in the most efficient way. For example, a provider might be willing to do a Pap smear every 3 years rather than more frequently in women already screened several times as negative, not because this approach is adequate to prevent all mortality from cervical cancer in such patients but because it is a reasonably inexpensive way to prevent *most* of it.