

## CASE DEFINITION IN CASE-CONTROL STUDIES OF THE EFFICACY OF SCREENING

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Evaluation of the efficacy of screening programs involves the comparison of morbidity or mortality rates between screened and unscreened populations. Such comparisons are made most convincingly by means of experiments (1, 2), exemplified by the study of screening for breast cancer carried out by the Health Insurance Plan of Greater New York (HIP) (3). However, there are serious practical difficulties with experimental studies of screening: they are expensive, may require many years to complete, and usually can be done only when new screening procedures are introduced. Once a procedure is established as a part of medical practice, as the Papanicolaou (Pap) smear is, it may be necessary to rely on nonexperimental methods to evaluate it.

Nonexperimental studies are more susceptible than are experimental ones to "confounding." For example, social class (as reflected in education or income) is directly related to frequency of screening with the Pap smear, but is inversely related to cervical cancer rates; relatively low rates of cervical cancer among frequently screened women could be secondary to their relatively high social class. Despite this drawback of the nonexperimental approach, there may be times when it will be able to provide information that cannot be obtained otherwise. (A discussion of the roles of experi-

mental and nonexperimental methods in the evaluation of screening is available elsewhere (1).)

Disease rates in screened and unscreened people can be compared nonexperimentally by means of the follow-up or the case-control approach. The case-control method seems useful since it is relatively economical and rapid, and does not depend on the availability of specialized records. Recently, Clarke and Anderson (4) reported a case-control study of the efficacy of the Pap smear in controlling cancer of the cervix.

Miettinen (5) has described in general the design and analysis of case-control studies. In a study based on newly diagnosed cases, the ratio of the exposure-odds in cases to that in controls drawn from the source population is an estimate of the ratio of the disease rate in exposed compared to nonexposed people. However, screening, unlike most "exposures" in epidemiologic studies, involves the diagnostic process itself. Therefore, the question arises, who should be a "case"?

A case in a study of screening should not be considered eligible primarily on the basis of a new diagnosis. Screening leads to early diagnosis, whether or not early treatment ultimately reduces morbidity or mortality. Consequently, a screened population will have a higher rate of any disease manifestation discovered during the lead-time interval, the period between the time that the disease is detected by screening and the time that diagnosis would have occurred in the absence of screening (1, 6). Thus, if a person is considered to be a case on the basis of a characteristic of disease that comes to attention during the lead-time interval,

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there will be an excess of screen-detected cases, and a beneficial effect of screening could be obscured. The problem of case eligibility cannot be resolved satisfactorily by excluding cases diagnosed initially by screening. This procedure creates a relative deficit of screen-detected cases, which would lead to an apparent favorable effect of screening even if none exists.

If screening and early treatment are beneficial, they reduce morbidity or mortality after the time that diagnosis would occur if there were no screening, that is, after the lead-time interval. Therefore, in a study of the efficacy of screening, case eligibility should be based on disease manifestations that develop only after the lead-time interval. Death from the disease obviously meets this criterion; hence, the emphasis on mortality as an outcome (1, 2).

Consider a case-control study that focuses on mortality. Eligible cases would be deaths from the disease screened for irrespective of the means of initial diagnosis. This group would include deaths from disease diagnosed as a result of screening, as well as deaths from disease that was first diagnosed following the occurrence of symptoms. Eligible controls would include all living members of the source population (5)—people who never had the disease, as well as people who had had the disease, whether or not screen-detected.

It may appear strange that people with the disease should be eligible to be controls. However, in a study that is concerned with whether or not screening reduces *death*, a living person with the disease is a member of the source population, and is not a case. Since screening results in early diagnosis and possibly prolonged life, a living person with known disease is more likely to have been screened than is someone without the disease. Systematic exclusion of diseased people from the control series would thus remove screened subjects preferentially, and could reduce

the apparent size of a true beneficial effect. (This bias would be small if the disease were uncommon.)

As in any case-control study, the actual selection of the case and control series should be made without regard to exposure, that is, screening history. Provided that screening histories of good and comparable quality are available for both series (as might be the case with records from a health maintenance organization), such a study would yield a reasonable estimate of the relation of screening and early treatment to the disease-specific mortality rate. If the control series is found to contain a higher proportion screened than the case series has, this is evidence that screening and early treatment protects against death from the disease.

It may not be possible to obtain satisfactory screening histories from records, and it may be necessary to interview living cases, and controls, to determine screening histories. In this situation, potential cases could be defined as people who develop a manifestation of the disease (other than death) that is sufficiently advanced to ensure diagnosis even without screening, and thus be past the lead-time interval. For example, cases could be defined as people who develop symptomatic metastases of cancer. Such people would include those in whom screening detected early cancer that later recurred and spread as well as people with advanced cancer whose disease was first diagnosed following the occurrence of symptoms. Members of the source population without the defining characteristic of a case—i.e., advanced disease—would be eligible for the control series. Those eligible would include people who had had early disease, whether or not screen-detected, and whose disease had been treated and had not recurred, as well as people who had never had the disease, whether or not they had been screened. The proportions screened in the case and control series

yield an estimate of the ratio of the rate of development of advanced cancer in screened compared to unscreened people (5).

Clarke and Anderson's study (4) provides an example of some of the problems described. In that study, cases had "newly diagnosed invasive carcinoma" of the cervix. This definition of a case has two deficiencies, as explained below.

First, the use of newly discovered cases, if screen-detected, leads to a reduction in the apparent size of a true protective effect of screening and early treatment, as indicated above. Since screening does bring to light some cases of invasive cervical cancer (7), newly diagnosed screen-detected cases may have been included in the study. Clarke and Anderson address this problem by not considering in their analysis screening examinations within the year before diagnosis, examinations that would contribute to the "negative" bias described. However, people tend to be either "participators" or "non-participators" in screening programs. That is, a case diagnosed by screening would be more likely to have had a previous screening examination than would a routinely diagnosed case. Therefore, the approach taken by Clarke and Anderson does not eliminate the "negative" bias from inclusion of cases newly diagnosed by screening, although it reduces it.

Second, Clarke and Anderson appear not to have included cases who developed invasive cancer but who were not newly diagnosed. If the initial diagnosis of some of these people had been the result of screening, these cases represented "failures" of early treatment and their exclu-

sion would artificially elevate the apparent value of screening.

The problem of a proper definition of the occurrence of disease in the evaluation of screening is not limited to case-control studies. If rates in a nonexperimental, or even an experimental, follow-up study reflect disease during the lead-time interval, biased results will be obtained. Compared to a case-control study, however, data-collection procedures in a follow-up study would usually permit easier separation of diagnosis only as a result of screening from the later occurrence of actual illness. Moreover, in a follow-up study it will virtually always be practical to take death as the outcome event, which is the most satisfactory solution. As indicated above, however, use of mortality as the outcome could preclude the determination of screening history in a case-control study.

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