Invited Commentary: Screening as a Nuisance Variable in Cancer Epidemiology: Methodological Considerations

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Received for publication December 9, 2002; accepted for publication January 22, 2003.

A large literature has developed over the last two decades around methods for evaluating the effects and benefits of screening procedures for cancer. In contrast, the role of screening for cancer as a nuisance variable is one that has as yet received little attention. This is unfortunate, because, as Noel Weiss points out in the lead commentary in this issue of the Journal (1), screening procedures can induce distortions in associations between exposures of interest and cancer outcomes and can complicate interpretation of some of these associations. This invited commentary supplements Weiss's treatment of the topic.

STUDIES OF CANCER INCIDENCE

Studies of risk factors for disease have two purposes: understanding and action. Those who seek to understand cancer etiology use epidemiologic studies to discover risk factors for disease and to fit them into a coherent biologic framework. Those who seek to minimize the burden of disease use these studies to determine the impacts of potential interventions that change the levels of these risk factors. Few areas in epidemiology have a larger apparent divide between the two purposes than studies involving screening for cancer.

In the study of cancer etiology, cancer diagnosis may be viewed as a proxy for an underlying biologic process of tumorigenesis and cancer growth that has already occurred. In the more direct examination of the impact of modifying various risk factors, cancer diagnosis may be seen as a surrogate for such later outcomes of greater consequence as mortality. Unfortunately, cancer diagnosis may be a poor proxy for past and a poor surrogate (2) for future outcomes; this is nowhere truer than in studies where cancer screening has an impact. Further, in these settings, cancer incidence may fail to be a proxy for biology in ways different from its failure as a surrogate for mortality. We elaborate on these points below.

In the accompanying paper, Weiss discusses two settings in which screening can distort associations of other factors and cancer: 1) where screening increases the detection of precursors of cancer and so decreases the incidence of cancer, and 2) where screening increases the detection of lesions classified as cancer. In both of these settings, cancer diagnosis becomes a poor proxy for biologic processes: The increase or decrease in diagnosis associated with screening and with risk factors associated with screening is clearly not due to changes in the biologic processes of tumorigenesis and tumor growth, and so etiologic inference becomes more challenging.

Cancer incidence is most obviously a poor surrogate for such clinically important outcomes as death when screening increases the detection of lesions classified as cancer. Here, a screening-induced increase in cancer detection is real, but the increased incidence is a positive thing if earlier detection sometimes leads to cures. In looking at the association between screening-associated factors and cancer, one finds that interpretation of cancer incidence figures becomes problematic, because an increased incidence of cancer associated with a risk factor may be the result of screening and so beneficial or the result of increased tumor growth and so harmful.

ROLES OF SCREENING: CONFOUNDER, INTERMEDIATE VARIABLE, AND EFFECT MODIFIER

For both etiologic and public health purposes, one should seek to control for screening as a nuisance variable. Screening may play the role of confounder in the traditional epidemiologic sense, as pointed out by Weiss. Here, standard methods for controlling confounding are appropriate, possibly supplemented by sensitivity analysis (3, 4) to...
account for incomplete measurement of screening as a potential confounder.

Screening (and related diagnostic methods) may also play the role of intermediate variable or effect modifier; studies of hormone therapy for postmenopausal women illustrate these issues conceptually (5, 6). Hormone therapy may increase performance of screening (or diagnostic) mammography for various reasons; thus, screening may be intermediate on a pathway from the exposure to cancer diagnosis. For etiologic inference, one may be primarily interested in the direct effect of the risk factor on cancer incidence, that is, a comparison of the outcomes that would be seen at different levels of hormone therapy were screening procedures to be physically held fixed or applied equally across those different levels. Appropriate methods for controlling screening as an intermediate variable and so estimating the direct effect of exposure are not necessarily the same as appropriate methods for controlling for it as a confounder (7).

The direct effect of an exposure controlling for screening may be of interest for public health purposes. However, the indirect effect of the exposure (i.e., that part mediated by its effect on the frequency of screening) may also be of public health interest, especially where screening or diagnostic procedures are not easily equalized across groups. In these settings, the overall effect of exposure, including both direct and indirect effects, may more closely measure the impact of the exposure.

Hormone therapy may make mammography less sensitive at detecting breast cancer (8). As a result, the effect of hormone therapy on cancer incidence may be larger among subjects who are not screened than among subjects who are. In the presence of such effect modification by screening, the appropriate analysis for etiologic goals may differ from that for public health goals. For etiologic goals, we may be most interested in the effect of hormone therapy in unscreened subjects, because detection probabilities of tumors at the same stage will be similar for subjects on and off hormone therapy. In contrast, among screened subjects, detection probabilities may be higher for subjects not using hormones.

For public health purposes, things are again more complicated. Inasmuch as hormone therapy makes cancer detection by screening more difficult, a reduced incidence of cancer among screened hormone users will be real; however, it will again make diagnosis a poor surrogate for death or other late cancer outcomes.

CANCER MORTALITY

Considering cancer mortality rather than incidence as the endpoint removes some of the problems described above. In particular, the problems with interpreting changes in cancer incidence no longer apply, because any screening-induced changes in mortality have the same interpretation as changes in mortality induced by other variables. Nonetheless, screening can serve as a confounder, effect modifier, and intermediate variable when mortality is the outcome.

Mortality as an outcome can raise new issues. Where the outcome is mortality from a specific cancer, uncertainty about attribution of cause of death can plague investigations. In addition, cancer diagnosis may become a confounder, as it may affect subsequent levels of exposure (as has been the case with hormone therapy) and is strongly associated with cancer mortality. Because mortality is different for subjects diagnosed with cancer who have been screened recently than for diagnosed subjects screened in the more distant past, simple analytic adjustments for diagnosis are not appropriate ways to control for confounding by cancer diagnosis in the presence of imbalances of screening. Further, screening can induce confounding in studies of cancer mortality by affecting diagnosis. Cancer diagnosis may go on to affect subsequent exposure; since it will be a strong predictor of cancer mortality as well, diagnosis will be a confounder.

OTHER ISSUES

Weiss discusses what aspects of screening history should be controlled as a confounder in statistical modeling. He proposes that it is sufficient to control for an indicator of whether screening took place during an interval roughly equal to the average duration of the detectable preclinical phase. There are reasons why this suggestion might not be optimal: The sensitivity of screening examinations presumably increases over the course of the detectable preclinical phase as the tumor grows; alternatively, the length of the detectable preclinical phase varies over subjects, and so dichotomization of time at any cutoff will lead to misclassification of whether a tumor is in that phase. These arguments suggest that it might be productive to control for time since last screen instead, although not necessarily entered as a linear term in a model.

Weiss usefully considers the degree of bias induced by possibly differential misclassification in one setting. There has been little consideration of the degree of bias due to screening-induced confounding and other sources of bias. A previous analysis of screening-related bias in the study of the effect of hormone therapy on breast cancer found that bias related to screening as a confounder and intermediate variable was relatively small (6). In general, determining the magnitude of a bias requires 1) defining an effect of interest, 2) determining its true value, and 3) determining the expected value of the estimated effect. Because screening and many exposures in epidemiologic studies vary over time, these steps require methods appropriate for defining and determining the true exposure (and possibly screening) effect from complex data with time-varying variables. Robins’ application of the potential outcomes approach for causality to time-varying exposures provides an appropriate framework for this (7, 9–11). In this setting, applying these steps can be somewhat involved but is essential for defining treatment effects and characterizing bias. The approach is even required for characterizing bias in case-control studies and their variants, because causal effects are defined not for the case-control study sample but for a group of individuals to whom an intervention or exposure might be applied.

Weiss is to be commended for highlighting an important group of issues in cancer epidemiology and for thinking carefully about those issues. It is to be hoped that the publication of his commentary and this invited commentary will spur more attention for and investigation of a heretofore neglected topic.
In conclusion, screening may distort the associations between an exposure and various cancer outcomes. These distortions may result from the role of screening as a confounder, intermediate variable, or effect modifier. This commentary considered how screening in these roles may affect studies of cancer incidence and mortality and how these considerations may differ depending on whether one is interested primarily in etiologic inference or in public health impact.

ACKNOWLEDGMENTS

This work was funded in part by grant R29 HL59184 from the National Heart, Lung, and Blood Institute.

REFERENCES