EDITORIAL

Why Is Nonadherence to Cancer Screening Associated With Increased Mortality?

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In this issue of *JAMA Internal Medicine*, Pierre-Victor and Pinsky[1] use data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial[2] to demonstrate an association between lack of adherence to cancer screening and increased mortality from causes not related to the screening. Participants in the PLCO Cancer Screening trial were 55 to 74 years of age and generally healthy. At trial entry, participants of both sexes in the screening arm were asked to undergo chest radiographs for lung cancer and flexible sigmoidoscopy for colon cancer, men were asked to undergo prostate-specific antigen tests and digital rectal examinations for prostate cancer, and women were asked to undergo cancer antigen 125 tests and transvaginal ultrasonography for ovarian cancer. Those randomized to the control group received usual care.

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Of the participants randomized to screening, 10.8% did not complete any of the recommended screening tests at baseline and were defined as nonadherents. After 10 years of follow-up, the risk for mortality (excluding mortality due to lung, colon, prostate, and ovarian cancers) was increased about 50% in nonadherents compared with full adherents who underwent all of the recommended tests at baseline. Increased mortality was due to a wide range of causes, including respiratory, digestive, and cardiovascular diseases, as well as cancers unrelated to screening. The comparison of nonadherents with full adherents was not randomized; this is an observational study of mortality rates among participants in the screening arm of the PLCO Cancer Screening trial and, like all observational studies, is susceptible to confounding.

There is no way that nonadherence with cancer screening could cause increased mortality from a range of diseases not associated with screening. The analyses were adjusted for age, race/ethnicity, sex, educational level, cigarette smoking, body mass index, marital status, and major comorbidities, indicating that these health-related variables are unlikely to account for the findings. So, what does account for the increased risk of death? As the authors note, it is most likely that nonadherence with recommended screening is a marker for behaviors that are associated with increased mortality. Previous studies have shown that patients who are adherent to recommended medications are more likely to seek out other preventive services such as screenings and vaccinations, while nonadherence has been associated with increased mortality.[3] This association has been dubbed *adherence bias* or *compliance bias*, but it is really a form of unmeasured confounding.

The findings of the study by Pierre-Victor and Pinsky[1] are interesting, but do the findings have any real clinical effect? It is clear that somehow encouraging or enticing people to be more adherent to cancer screening guidelines will not reduce mortality from unrelated causes. However, compliance bias is important for 2 reasons. First, it highlights the fact that secondary analyses of clinical trial results that compare those who are adherent with the intervention with those who are not adherent with the intervention may markedly overestimate the benefit of the intervention. This problem can be addressed by comparing adherent participants in the intervention group with adherent participants in the control group, if there is an active, placebo, or sham control. In 1 large meta-analysis of observational studies of the association between drug adherence and mortality, a similar mortality benefit was seen among patients with good adherence to both drug treatment and to placebo.[4] Unfortunately, in the PLCO Cancer Screening trial, sham screening was not recommended, so there is no way to compare outcomes among the intervention and control group among nonadherent participants.

Second, compliance bias might explain some of the discrepancies between the findings of observational studies and randomized trials. For example, multiple observational studies of postmenopausal hormone therapy showed marked reductions in the risk of coronary heart disease that later were not confirmed in clinical trials.[5] Similarly, observational studies of the use of beta-carotene suggested reductions in the risk of cancer, but subsequent clinical trials found an increased risk of lung cancer among smokers who took beta-carotene.[6] The observational studies defined a person as a user of hormone therapy or beta-carotene only if he or she was adherent with taking the hormone or vitamin, which may have resulted in lower rates of disease owing to compliance bias. Thus, we should view the findings of observational studies where the risk factor requires adherence to a drug or behavior with some skepticism. This effect is particularly notable in observational studies of preventive interventions in the primary care setting.[7]

ARTICLE INFORMATION

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