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Why Epidemiological Studies of Physical Activity in Prostate Cancer Often Underestimate its Benefits

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Wang et al [1] conducted a rigorous analysis investigating physical activity and survival after prostate cancer diagnosis. Major strengths of this study include a large sample size, almost 20 yr of follow-up, and information on physical activity both before and after prostate cancer diagnosis. Among men later diagnosed with nonmetastatic (Mx/M0) prostate cancer, those with higher levels of prediagnostic physical activity (equivalent to 4.4 h/wk of brisk walking) had a 37% lower risk of progression to prostate cancer–specific mortality compared to sedentary men. Postdiagnostic recreational physical activity was associated with a lower risk of progression to prostate cancer–specific mortality, regardless of tumor stage.

These findings contribute valuable evidence to the growing body of literature supporting the benefits of physical activity on prostate cancer progression. Moreover, because of inevitable methodological challenges inherent to epidemiological studies, it seems likely that these remarkably strong inverse associations between recreational physical activity and prostate cancer are underestimated, for several reasons.

First, there is a substantial measurement error for physical activity assessment, causing an underestimate of the magnitude of the inverse associations. Self-reported (and objectively measured) exposures are always subject to measurement error, but physical activity is particularly difficult to report accurately, as it occurs throughout the day with large within- and between-person variations in type, duration, and intensity. Most of the validated physical activity questionnaires list various types with duration categories for each. Each physical activity item is typically assigned a single standardized metabolic equivalent of task (MET) value to represent the typical intensity and metabolic expenditure per hour. This minimizes both participant and investigator burden and allows for comparison across studies. It is often assumed for physical activity and other exposures alike that a measurement error exists but is nondifferential with respect to the outcome of interest. If this is the case, associations are almost always biased to the null hypothesis. However, in analyses such as the current one, the measurement error is probably differential with respect to the outcome. It is likely that the true intensity and metabolic expenditure for each physical activity item are higher for healthier men and lower for men who are becoming sicker because of their progressing disease. Thus, in epidemiological studies of physical activity, total activity is probably underestimated for healthy men and overestimated for unhealthy men, including those with more aggressive prostate cancer. This underestimation for healthy men and overestimation for men more likely to die of prostate cancer will bias the protective association still further to the null hypothesis. Furthermore, this measurement will not reflect a decrease in physical activity intensity, only a decrease in duration. As a consequence, this may not sufficiently rank people; those with more intensity but shorter duration may be assigned fewer MET-h/wk than those with lower intensity but longer duration. This is a common problem with physical activity assessments in epidemiological studies, particularly when physical activity is self-reported. The problem can be mitigated by asking for further details on intensity within each item (eg, pace for walking, jogging, and running). However, these estimates may be imprecise and increase participant burden on questionnaires that are often already long. Adjusting for

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proxies of healthfulness (eg, stage, age, comorbidities) will also mitigate this bias.

Second, assessing prediagnosis physical activity—or any prediagnosis exposure—in a case-only survival analysis introduces selection bias. This selection bias structure has been discussed primarily in the context of prediagnosis obesity and chronic disease; obesity is often associated with lower mortality among those with chronic disease (the "obesity paradox"). However, such findings do not imply that obesity before diagnosis will improve survival after disease diagnosis [2]. Because obesity increases the risk of chronic disease, nonobese patients with chronic disease must have other risk factors (eg, genetic predispositions) that may also be associated with worse survival after diagnosis. Related to this analysis, evidence suggests that physical activity decreases the risk of many cancers and chronic diseases, including prostate cancer [3]. Thus, when Wang et al examine prediagnosis physical activity and survival after prostate cancer diagnosis among cases only, patients who were diagnosed with prostate cancer despite high physical activity were more likely to have other risk factors (eg, family history of prostate cancer) that may be associated with more aggressive prostate cancer. As a result, the observed inverse association between prediagnosis physical activity and survival after diagnosis is probably underestimated here. In this specific situation, this selection bias structure does not have very detrimental implications; it is only underestimating the benefits of physical activity. However, it should still be avoided. When assessing unhealthy prediagnosis exposures such as obesity among patients with chronic disease, these exposures can deceptively appear to improve survival. Thus, associations between prediagnosis exposures and disease-specific mortality are typically better analyzed within the whole population rather than among cases only.

In their examination of postdiagnosis physical activity and prostate cancer survival, the authors took important steps to mitigate reverse causation. However, in doing so, they probably also concealed some of the true beneficial effects of physical activity on prostate cancer progression. Reverse causation, whereby progressing disease influences risk factors (eg, disease often causes individuals to lose weight, eat less, exercise less, change medications) is a critical issue in many epidemiological analyses, and analytical measures must be taken to address this. Here, the authors applied physical activity exposure from 4–6 yr previous to the current exposure period in case men became less active because they were sick. However, this prevents investigators from analyzing the impact of more recent physical activity, which may also have true benefits independent of reverse causation. Lagging also excludes anyone who died within 4–6 yr after diagnosis, so the authors were less able to assess the effect of postdiagnosis physical activity on men with more aggressive disease.

In summary, it is likely that many analyses, including the current one by Wang et al, arrive at underestimates of the inverse relationship between physical activity and prostate cancer. This further highlights one of the many health benefits of physical activity. Physical activity may often achieve prostate cancer benefits of similar magnitude to many prostate cancer drugs and treatments.

Conflicts of interest: The author has nothing to disclose.

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