The Time Is Ripe for a Randomized Trial of Metformin in Clinically Localized Prostate Cancer

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In a population study making excellent use of Ontario’s universal health plan electronic data, Margel et al showed increasing duration of metformin use among diabetic men after a diagnosis of prostate cancer was associated with decreased prostate cancer-specific and all-cause mortality. Prostate cancer–specific mortality decreased by 24% for each additional 6 months of metformin use after diagnosis; use of other antidiabetic medications did not significantly decrease prostate cancer–specific mortality. The authors were thorough in their investigation, performing many sensitivity analyses to attempt to rule out possible biases. As the distribution of clinical characteristics specific to metformin users and nonusers was not provided, it is difficult to assess the possibility of residual confounding; however, the authors appropriately adjusted for many covariates. Also, the specificity of the results for metformin lends further support for causal relation. Interestingly, although postdiagnostic use of metformin was highly significant, the association of cumulative metformin use before prostate cancer diagnosis with prostate cancer death was null. As prostate cancer date of diagnosis is a rather arbitrary point in the progression of the disease, this discrepancy between the impact of pre- and postdiagnostic use is perplexing and warrants further study. Despite these concerns, the authors provide a convincing case for a causal interpretation and for initiating a randomized trial of metformin among men with localized prostate cancer at diagnosis. The potential benefits of metformin could exceed those of existing drug therapies, particularly given its safety profile.

Margel et al wisely chose to focus their analysis on prostate cancer mortality. Of course, this is clinically the most important outcome. In addition, compelling data demonstrate that in the United States and other countries where prostate-specific antigen (PSA) screening has become common, a research focus on overall prostate cancer incidence provides results that, at best, are of minimal interest and, at worst, often misleading. The prevalence of prostate cancer in apparently healthy middle-aged and older men is remarkably high. Autopsy studies of men dying of other causes in the pre-PSA era, during which prostate cancer was unsuspected during life, reveal a prevalence in the range of 15%5 to 34%7 in men ages 60 to 69 years. The randomized Prostate Cancer Prevention Trial of finasteride, conducted in men ages 55 years and older with a baseline PSA ≤ 3, showed in the placebo group a prevalence of prostate cancer of 24.4%8 in routine poststudy biopsies after 7 years of follow-up. Thus, the pool of apparently indolent disease is enormous. PSA screening reveals many of these instances, such that most screen-detected cancers are those that never would result in death of the patient. Contemporary studies of total prostate cancer incidence largely measure the propensity to have a biopsy.

Moreover, mounting evidence shows that lethal prostate cancer has a different etiology from indolent disease, and studies attempting to identify risk factors for overall prostate cancer incidence often produce conflicting results as a consequence of that difference. Several exposures are much more strongly associated with lethal disease than with risk of overall prostate cancer; in screened populations, as described in the previous paragraph, overall prostate cancer is mostly indolent disease.9 One such exposure is statin use, which is related to lower risk of advanced and lethal prostate cancer but not overall incidence.9 Indeed, despite not being the central analysis of this article, Margel et al provide further evidence that statin use is strongly associated with lower prostate cancer mortality. In their article, Margel et al suggest that metformin is another exposure associated mainly with lethal outcomes. Several other examples of important factors associated specifically with lethal but not overall prostate cancer incidence—body-mass index, physical activity, smoking—also have an important influence on metabolic syndrome and insulin resistance.

Margel et al cite several biologic actions of metformin that indicate it may be more beneficial for slowing or stopping the progression of cancer than preventing its initial development. Knowledge of the biologic action of metformin, including both indirect effects through metformin’s effect on insulin and direct effects on tumor cell proliferation and apoptosis, influenced the hypothesis and design of this epidemiologic study. In turn, the results of this study can improve our understanding of the biology of prostate cancer progression. The observation that so many exposures involved in the metabolic syndrome are associated with lethal prostate cancer may help focus further studies of the mechanisms for prostate cancer progression. There may be a role for the global metabolic health of the individual that is reflected in all of their tissues—tumor, normal prostate, bone, and other organs—that could affect prostate cancer progression. In Pollak’s7 recent comprehensive review of metformin and cancer, he describes a proposed hypothesis that metformin induces energetic stress by increasing 5′ adenosine monophosphate-activated protein kinase and thereby decreasing gluconeogenesis. In addition to directly affecting the tumor cells, this can lower glucose and insulin in the host, which in turn could reduce the growth of sensitive tumors.7

Based on the strong evidence of this well-executed study, metformin, a drug widely prescribed to diabetics with over 61 million
prescriptions filled in the United States in 2012, may potentially be a safe and effective secondary prevention strategy for prostate cancer. As this study found that metformin was associated with a decreased risk of prostate cancer-specific mortality regardless of primary cancer treatment, the authors rightly suggest that metformin may further improve survival in conjunction with other standard prostate cancer treatments. In addition, the significant association with prostate cancer-specific mortality was noted for postdiagnostic metformin use, suggesting that metformin prescribed after cancer diagnosis could still be an effective chemopreventive agent. The finding of a benefit for all-cause mortality provides further impetus for a trial. According to the National Institutes of Health Clinical Trials Registry, at least nine ongoing clinical trials are investigating metformin and various aspects of prostate cancer. Several trials are underway to explore the benefits of metformin among men with recurrent, advanced, or metastatic prostate cancer; such trials will be useful, but perhaps this may be too late in the course of the disease to have an influence on progression. Other trials plan to administer metformin to men on active surveillance or before radical prostatectomy and will measure the effects on tumor markers of proliferation; though this approach may yield promising results, it is not directly translatable to prostate cancer clinical progression and mortality. For all these ongoing trials, null results will not preclude the possibility that metformin can slow the progression of early-stage disease and reduce prostate-cancer mortality. We agree with Margel et al 1 that their findings clearly are insufficient to warrant recommendations to institute metformin treatment in men with prostate cancer. However, their results provide a compelling rationale for conducting a large-scale long-term randomized trial of metformin in men with clinically localized disease to reduce prostate-specific mortality as an urgent research priority.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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