EDITORIAL (SEE LIBBY ET AL., P. 1620)

Metformin, Cancer, Alphabet Soup, and the Role of Epidemiology in Etiologic Research

BRUCE B. DUNCAN, MD, PHD
MARIA I. SCHMIDT, MD, PHD

Libby et al. (1), in this issue of *Diabetes Care*, report a lower incidence of a broad range of cancers among diabetic patients treated with metformin. Specifically, by linking data from a population-based diabetes registry with those from a drug use registry and a cancer registry, they effectively followed medication use in over 8,000 diabetic individuals and ascertained over 700 incident cancers. They found, over a 10-year period, that metformin use was associated with a 54% (95% CI 47–60) lower crude and a 37% (25–47) lower adjusted incidence of cancer. From the survival analysis they performed adjusting for age, sex, BMI, smoking status, and a social deprivation index, one can estimate the association in absolute terms: considering the cancer rate of 11.6% for non–metformin users, for every 23 patients receiving metformin in this cohort one fewer developed cancer (number needed to treat = 1/[0.37 × 0.116]). Their findings are internally consistent. In patients with the longest history of metformin use prior to cancer onset, incidence tended to be lowest. Metformin users who developed cancer also had a greater survival postdiagnosis. A protective association of similar degree was documented against lung, bowel, and breast cancer.

Because these findings come from a large cohort study constructed with record linkage rather than from a randomized clinical trial, they require trial confirmation prior to clinical application. Nevertheless, they add to a rapidly growing literature suggesting, on the basis of a plausible mechanism and consistent empirical findings in both laboratory animals and humans, that metformin not only exerts a major protective effect against the development of a wide range of cancers but also improves prognosis in those found to have these cancers.

In addition to a preliminary report based on the same diabetes registry (2), the findings of three other studies are in consonance with that of Libby et al. Bowker et al. (3) performed a cohort study with record linkage involving 12,272 new oral antidiabetes drug users in the Saskatchewan provincial health system from 1991 to 1996. Over a mean follow-up of 5.4 years, sulfonylurea users had adjusted cancer mortality 30% greater than that for metformin users (HR 1.3 [95% CI 1.1–1.6]) and insulin users an adjusted cancer mortality 90% greater (1.9 [1.5–2.4]). Monami et al. (4), in a case-control study comparing 195 incident cancer cases with 195 matched control subjects nested within the follow-up of consecutive diabetic patients attending an Italian university-affiliated outpatient clinic, found odds of 0.28 (0.13 – 0.57) for developing cancer in those with ≥36 months of metformin use. In a hospital-based case-control study of pancreatic cancer that included ~350 diabetic patients, Li et al. (5) found that among those with diabetes, users of metformin had adjusted odds of 0.38 (0.22–0.69) of developing cancer compared with those never using metformin, whereas users of insulin, insulin secretagogues, and glitazones all had increased risk compared with those who never used these drugs.

In terms of cancer prognosis, Jiralerspong et al. (6) reported that among diabetic breast cancer patients receiving neoadjuvant chemotherapy, those who were incidentally receiving metformin experienced a pathologic complete response rate of 24% as opposed to only 8% for those not receiving the drug ($P < 0.001$). In fact, findings such as these have recently led to the development of at least three clinical trials aiming to evaluate metformin as adjuvant therapy in the treatment of cancer (7,8).

In the context of these previous studies, Libby et al., given the size and methodologic quality of the study, provide us with a major step forward in the characterization of the metformin-cancer association and its potential in terms of both reducing risk and improving prognosis of cancer. Certainly other studies will follow that will help estimate where in fact the association's point estimates lie within the CIs Libby et al. present.

Why should a diabetes drug be protective against cancer? A review of metformin's principal mechanism of action, through AMP-activated protein kinase (AMPK), provides at least one plausible answer. AMPK is one of those fascinating orchestrators of our inner workings that have emerged from the battlegrounds of evolution. Molecules similar to mammalian AMPK can be found not just throughout the animal kingdom but also in plants, protists, and fungi (9), and evolving forms of AMPK have accompanied the evolution of higher organisms.

The language of life is composed of many such chemical signals (10), each talking to the others in tongues that little by little we in the scientific community have come to understand. This language evolved through a long series of iterations, advances in each being based on the building blocks at that time present, with molecules frequently being borrowed from their original roles and adapted to perform new ones. Given the resultant redundancy and nonspecificity of the systems that emerged, we should not be surprised to find that a molecule with a major role in metabolism and diabetes might also be a key actor in the etiology of cancer.

Better understanding of these signals and their pathways and our ability to place the mechanisms underlying clinical events such as diabetes or cancer within

From the Graduate Studies Program in Epidemiology, Federal University of Rio Grande do Sul, Porto Alegre, Brazil.
Corresponding author: Bruce B. Duncan, bbduncan@ufrgs.br.
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the resultant mechanistic framework are among the scientific challenges of our day. The pathophysiology of major killers such as diabetes, cardiovascular disease, and cancer lies nested within this framework. The characterization of these diseases as degenerative implies a process of wear and tear, a by-product of the normal workings of the life span. Etiologically, it may be more interesting to characterize them with a different focus, as being the direct product of aberrant signaling—the right signals but at the wrong time or place—as the human body reacts in its time-honored fashion to challenges that it was not selected to meet.

In the age-long struggle for survival of species, AMPK early on assumed the role of energy quartermaster—its task to regulate energy supply and utilization to maintain health. Taking stock of intracellular nutrient stores, AMPK acts to conserve current and generate new ATP. In so doing, when necessary, it signals restraint in ATP-expending chores like gluconeogenesis, orders the transformation of intracellular fats and carbohydrates into ATP, and stimulates the uptake of new energy from extracellular sources. In terms of diabetes, this makes it a "good guy," lowering hepatic glucose output, increasing glucose uptake, maintaining insulin sensitivity, and as a result lowering plasma glucose levels (9). As more elaborate life forms evolved, AMPK took on additional tasks. In terms of cancer, its basically antianabolic/procatabolic role appears to have become a pathway through which natural tumor suppressors signal the shutdown, or at least slow down, of aberrant cellular growth (11).

The lower risk of cancer with metformin use reported by Libby et al. should be viewed within the context of the greater risk of cancer associated both with diabetes and with obesity. With respect to diabetes, Barone et al. (12), in a meta-analysis of 23 population- and clinic-based observational studies, found an overall HR for all cancer types of 1.41 (95% CI 1.28–1.55) for those with diabetes when compared with normoglycemic individuals. Though power was limited to test associations with specific cancers, epidemiologically significant positive associations were found for a broad range of cancers including endometrial, breast, prostate, gastric, colorectal, and hepatocellular. Hyperglycemia, in other studies, has additionally been predictive of melanoma and cancers of the kidney and pancreas (8).

Why should diabetes predict greater cancer risk? Is it disease treatment or something related inherently to the disease? Some studies now suggest that insulin and insulin secretagogue use increases cancer risk (3,5). Higher C-peptide and insulin levels have predicted cancer in some studies, and because insulin stimulates growth, a pathophysiologic rationale exists for the risk seen with these treatments (8).

On the other hand, some of the diabetes-cancer association could be explained through confounding by obesity. Most of the studies in the meta-analysis by Barone et al. were not adjusted for obesity, and in another recent meta-analysis by Renehan et al. (13), obesity was shown to increase cancer risk for more than a dozen different cancers, with highest risk (relative risks 1.17 to 1.59 for a 5-unit difference in BMI) for endometrial, esophageal (adenocarcinoma), gall bladder, thyroid, colorectal, liver, pancreatic, and kidney cancers. However, because several studies summarized in the meta-analysis by Barone et al. showed diabetes-cancer associations even after control for adiposity, confounding by obesity is probably only a part of the explanation.

Obesity lowers adiponectin levels and leads to leptin resistance. Diabetes is a disease preceded and accompanied by lower levels of adiponectin (14) and lower effective levels of leptin (15). Both of these molecules have been shown to act, in part, by activating AMPK. A limited number of studies have investigated adiponectin levels as predictors of cancer. About half show decreased risk estimates of a size that could be considered epidemiologically important (8).

Because AMPK is activated by low intracellular energy stores, could weight loss be an additional clinically relevant trigger? Observational studies investigating weight loss and subsequent cancer provide mixed results, perhaps in large part because of the potential for reverse causality given that cancer causes weight loss. Thus, the recent report of a nonrandomized controlled trial by Sjöström et al. (16) on the effect of bariatric surgery on cancer risk in 4,047 obese subjects is of great interest. Bariatric surgery patients had a sustained weight reduction 18.6 kg greater than control subjects over 10 years of follow-up. A major reduction in cancer incidence with bariatric surgery was found in women (HR 0.58 [95% CI 0.44–0.77]) but not men (0.97 [0.26 – 1.52]). As related by Renehan (17) in an accompanying editorial, retrospective analyses of investigations of bariatric surgery outcomes by a few other groups support both the effect seen in women and the absence of such an effect in men.

The amount of weight change during the first year of follow-up, analyzed separately in bariatric surgery and control groups, was not related to cancer risk from the fourth year onward in the study of Sjöström et al. This association, however, is an observational one, and weight loss from latent cancer might be present in spite of the exclusion of early cancers.

Physical activity has also been shown to be a strong activator of AMPK (18). Meta-analyses of observational studies suggest that higher levels of physical activity protect against cancers such as lung and colon. For lung cancer, the summary adjusted odds ratios were 0.87 (95% CI 0.79–0.95) for moderate leisure-time physical activity and 0.70 (0.62–0.79) for high activity (19). For colon cancer, the summary relative risk was 0.79 (95% CI 0.72–0.87) for greater recreational activity for men and 0.71 (0.57–0.88) for women (20).

The role of epidemiology in uncovering the etiology of disease has evolved over the years. Few are the opportunities for epidemiologists, nowadays, to raise new hypotheses such as those which John Snow proposed for cholera and Ignaz Semmelweis for puerperal fever. More frequently, in questions such as those that populate the diabetes journals, ours is the role of validating findings emerging from bench research. In this role, epidemiologists help the scientific community to identify findings of potential clinical and epidemiologic relevance from within the alphabet soup of molecules and pathways reported as important in bench research. In this manner, findings of Libby et al. highlight the potential protective function for AMPK in cancer etiology and the potential role for metformin, our current means of enhancing AMPK activity, in cancer prevention.

In regards to clinical trials, a logical place to start would be investigating cancer outcomes in large, already completed metformin trials such as the United Kingdom Prospective Diabetes Study and the Diabetes Prevention Program. Regarding a better understanding of AMPK and its regulation, both in terms of diabetes and of cancer, better comprehension of the components of the language of life and their responses to today's environmental stimuli provide the groundwork not only

for more effective medications but also for more effective options for a healthy lifestyle and for societal health promotion.

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