Diabetes, Insulin Use, and Cancer Risk: Are Observational Studies Part of the Solution–or Part of the Problem?

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Cancer has overtaken cardiovascular disease as the leading cause of death in individuals under the age of 65 in the general population, but it is still overshadowed by cardiovascular disease in those with diabetes. People with type 2 diabetes are nonetheless more likely to develop cancer—and to die from it—than members of the general population, so cancer should be numbered among the complications of diabetes (1). Furthermore, the number of cancer victims with diabetes will inevitably rise in proportion to our success in combating vascular disease in the diabetic population.

How can the increased cancer risk in diabetes be explained? To begin with, it should be noted that obesity, insulin resistance, and/or increased levels of IGF-1 and insulin are strongly associated with most (but not all) of the diabetes-related cancers in the nondiabetic population (1). This suggests that hyperglycemia does not play an essential role in the pathogenesis of these tumors, but does not exclude the possibility that it might have secondary effects such as enhanced tumor growth or resistance to anti-tumor therapy. IGF-1 and insulin offer a more plausible mechanistic explanation for the overlapping risk of cancer in the nondiabetic and diabetic populations. Both hormones are mitogenic (but not mutagenic), both are present at high levels in insulin-resistant states, and their receptors are overexpressed on the surface of cancer cells associated with diabetes. They thus have the potential to act as tumor growth factors in vivo as well as in vitro (2,3). On this argument, which we will refer to as the insulin supply hypothesis, drugs used to treat diabetes might influence the risk of cancer by modulating the insulin/IGF axis (1).

There is, however, a possible alternative explanation for the increased risk of cancer in diabetes, which we refer to as the glucose supply hypothesis. Although hyperglycemia clearly cannot account for epidemiologic associations seen in the nondiabetic population, as noted above, cancer cells are characterized by their high metabolic activity and avid glucose requirement (4). It would therefore be logical to speculate that tumor growth might be regulated by glucose availability (4,5). Support for this proposal comes from the well-established observation that cancer risk increases in proportion to A1C in diabetes (6,7). Furthermore—and given that patients with poor glucose control are more likely to be offered insulin treatment—it is reasonable to hypothesize that the reported associations between insulin treatment and cancer risk in diabetes might be driven by high glucose levels rather than any direct effect of insulin. On this hypothesis, well-controlled diabetes might be expected to delay tumor growth in those with preclinical cancers, relative to those with poorly controlled diabetes. This issue of *Diabetes* contains an article by Yang et al. (5) that sets out to evaluate the relative risks of hyperglycemia and insulin therapy in patients with type 2 diabetes.

Before reviewing their findings, we should pause to consider the potential limitations of the tools available. How do we evaluate the potential of diabetes therapies—for harm or for good—in relation to the increased risk of certain types of cancer? The difficulties are legion. The risks of cancer vary widely with age, sex, and geographical region, greatly complicating comparisons between one study population and another. The biological features of cancer vary in relation to their tissue of origin, and global measures of cancer risk may therefore mask the potential impact of a specific therapeutic agent upon a specific type of cancer. The latter type of analysis requires very large sample sizes, limiting the relevance of controlled clinical trials, which are the gold standard for this type of comparison. Patients typically receive multiple therapies for diabetes, either sequentially or concurrently, making it difficult to dissect out the influence of any given medication, especially when escalating doses may also need to be taken into consideration. Even assuming all this can be done, correction still needs to be made for other confounders, which might in themselves account for the observed effects.

Which brings us to one further layer of complexity: the emerging possibility that some therapies used for diabetes could modulate cancer risk independent of their effects upon circulating insulin and glucose. This is linked to a growing awareness that pathways involved in cell metabolism and cell growth are inextricably enmeshed, and that our attempts to lower blood glucose may have unpredictable effects upon cell proliferation and growth. Hence, metformin and the thiazolidinediones are currently in trial as anti-tumor agents (8). Conversely, the possibility has been raised that the GLP-1–based therapies may promote the growth of pancreatic duct cells, causing duct hyperplasia, overt or subclinical pancreatitis, and potentially carcinoma of the pancreas (9).

When confronted with all these complexities, it is easy to sympathize with those who consider observational studies part of the problem rather than part of the solution. Such cynicism is clearly justified when observational studies are poorly conducted or overinterpreted. On the other hand, properly conducted and sensibly interpreted

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DOI: 10.2337/db10-0334

See accompanying original article, p. 1254.

observational studies must form an essential part of any future solution, bearing in mind that the information we require may never be available from controlled clinical trials. The obvious limitation of descriptive studies, however, is that they describe but do not necessarily explain. How then do we judge the article by Yang et al. (5)? The authors have employed a "new users" cohort design and data from the well-characterized Hong Kong Diabetes Registry, concluding that better glucose control and insulin use are each associated with a reduced risk of cancer in Chinese patients with type 2 diabetes. The authors make use of several methodologies intended to improve the inference of causality between these exposures (blood glucose level and use of exogenous insulin) and cancer incidence. The new users design is stated to be a strength given that it avoids potential biases associated with comparisons of prevalent insulin users within the cohort. Even so, the article demonstrates some of the difficulties involved in disentangling these exposures and understanding the role of individual therapies in modulating the relationship between diabetes and cancer.

The findings from this study confirm the previously recognized association between hyperglycemia and increased risk of cancer outcomes (incidence and mortality) (6,7). This relationship resembles the one between hyperglycemia and macrovascular outcomes (incidence and mortality) in type 2 diabetes in that the association is strong and consistent, but it is not reversed when glucose control is actually improved. Thus, the recent large-scale randomized controlled trials of intensified glycemic control for type 2 diabetes observed no difference between intensified and conventional treatment arms in terms of secondary outcomes of cancer incidence or mortality (10–16). This in turn might suggest that the relationship between glucose level and cancer outcomes is not causal but confounded by other factors such as insulin resistance and/or hyperinsulinemia (among others) (2,3).

Yang et al. go on to conclude that exposure to exogenous insulin is associated with a reduced risk of cancer (hazard ratio 0.17 [95% CI 0.09–0.32]), with risk estimates that are consistent regardless of how the cohorts were analyzed. A pearl of wisdom often taught in introductory epidemiology courses is that one should be wary of implausibly low (or high) risk estimates. It seems somewhat improbable that simply exposing people with type 2 diabetes to insulin would reduce the risk of cancer by 83%, especially since insulin treatment is typically offered to patients with higher glucose levels, which the authors found to be associated with increased cancer risk within the same study design. This prompts further exploration of the study design and data for alternative explanations including the selection of the comparison groups, matching and residual confounding.

The cohorts of new insulin users and matched nonusers were selected from a larger cohort of over 7,000 patients in the Hong Kong Diabetes Registry after exclusion of those with type 1 diabetes or preexisting cancer. Further, in pursuit of a "new users" design, 1,480 subjects with previous insulin use were also appropriately excluded. A propensity score for insulin exposure was built on a set of physiologic and clinical variables including age, smoking status, duration of diabetes, and A1C. Given that age and smoking status were matching variables, it is not clear why they were also included in the propensity score, whereas duration of diabetes or A1C were not. If A1C were used as a matching variable, its relationship with cancer incidence could not have been evaluated but, as pointed out, this relationship is already well established.

The classification of users and nonusers may also have contributed to the extremely protective risk estimate since to become a member of the insulin user cohort, subjects would have had to survive, cancer free, long enough to receive insulin. Moreover, using drug exposure variables that are fixed with time may introduce further bias into the analyses. There is further scope for residual confounding in the use of additional glucose-lowering treatments by insulin users and nonusers and, given the available evidence, it would have been helpful to control more stringently for the exposures to these other agents. A stronger approach would employ time-varying exposure definitions and even a dose-response gradient, especially in the treatment of type 2 diabetes, which tends to escalate over time.

Apart from these methodological considerations, a more fundamental concern is that the authors postulate that the observed protective effect of insulin is secondary to its glucose-lowering action, but they do not document the extent to which insulin actually lowered blood glucose. This leaves the authors on the horns of a dilemma. If the postulated protective effect of insulin as compared with noninsulin therapies is due to glucose lowering, it follows that patients on insulin would need to achieve lower glucose levels than the comparator. From the evidence presented, this was not the case. The alternative explanation, i.e., that insulin directly suppressed tumor growth, seems even more implausible.

In summary, Yang et al. have contributed to the rapidly growing literature on the relationship between diabetes, glucose-lowering therapy, and cancer, but these new data, while useful in hypothesis generation, potentially give rise to more problems than solutions. The results, unexpected as they are in light of previous reports (17–19), are however a useful reminder of the need to keep an open mind in this complex and evolving area. The worst outcome, in our view, would be for the reader to conclude that observational studies are so intrinsically unreliable as to be of no value at all. The best outcome would be for us all to reach broader consensus as to how further studies should be undertaken in this area, both in terms of improved methodology and sharper focus on prespecified outcomes for which we have a clear mechanistic hypothesis. For all their limitations, observational studies provide the best available evidence of potential harms in situations such as this (20,21). It is of paramount importance, therefore, that such observational studies be appropriately designed, rigorously conducted, and cautiously interpreted. We may be at the start of a long road when we try to disentangle diabetes, diabetes therapy, and cancer, but the road must be taken, wherever it might lead.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

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