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EDITORIAL

Diabetes and cancer: Doubts of a causal link

A link between diabetes and cancer was noted as early as 1914,[1] but received little attention until the 2000s. Excess body fatness, a key risk factor for type 2 diabetes, is associated with at least 13 obesity-related cancers, namely esophageal adenocarcinoma, gastric cardia, colorectal, liver, gallbladder, pancreatic, post-menopausal breast, endometrial, ovarian, kidney renal-cell, meningioma, thyroid and multiple myeloma.[2] With several plausible biological mechanisms, including hyperinsulinemia, it is widely held that excess adiposity is now a common causal factor for cancer. In 2009, against a backdrop of the then new controversy linking long-acting insulin analogues and cancer, a consensus meeting was held under the auspices of the American Diabetes Association, the American Cancer Society, the European Association for the Study of Diabetes and the European Organisation for Oncology.[3] This consensus concluded that "type 2 diabetes is associated with increased risk of several cancer types, including post-menopausal breast, colorectal, endometrial, liver and pancreatic cancers, and non-Hodgkin lymphoma; that these associations seem to be independent of body mass index (BMI); and that in several examples these associations differed from conventional associations between BMI and cancer."[3] By the start of the 2010s, the prevailing opinion favored a causal link between diabetes and cancer.

In the intervening decade, doubts started to emerge. Examples included two reviews[4,5] that used novel methods to account for confounding and biases. Specifically, Tsilidis et al[5] (an umbrella review of 18 meta-analyses) used an assessment of between-study heterogeneity, an assessment of small study effects, and an evaluation of excess significance. On the other hand, Ling et al[4] (a review based on 151 cohorts incorporating over 32 million people and 1.1 million cancer cases) employed a bias analysis for unmeasured confounding, quantifying the proportion of studies with a scientifically meaningful effect size. Both reviews concluded that, when these methodological issues are taken into account, associations between diabetes and cancer are either lost or substantially diminished.

In this edition, Lohi et al[6] add to these doubts. If diabetes is causally associated with increased cancer risk, it is reasonable to speculate that accumulative exposure (here approximated as duration of diabetes) might be associated with increasing cancer risk. A matched design of 185,258 individuals with new-onset diabetes versus 187,921 individuals without diabetes was used. With a median follow-up of 10.6 years, there were 25,899 cancer cases in the diabetes group, 23,900 cancers in the non-diabetic group. They found no clear relationship between the duration of diabetes mellitus and most cancer types examined and concluded that the "… findings indicate that diabetes does not independently increase the risk of cancer. Instead, the development of diabetes may be attributed to shared risk factors with cancer such as obesity and/or … hyperinsulinemia."

These findings build upon two previous studies[7,8] that evaluated the relationships between duration of diabetes with cancer risk, both of which similarly found that duration of diabetes was not associated with increased cancer risk, but that most of the increased cancer risk seen was due to detection time bias. The present study had greater numbers of cancer events and thus is a useful contribution to the literature.

Another strand of doubt comes from Mendelian Randomization (MR) studies. Vincent and Yaghootar[9] recently reviewed the literature to use genetics to decipher the link between type 2 diabetes and cancer. They broadly considered two pathways—namely (a) horizontal pleiotropy, where the increased risk of cancer in individuals with diabetes could be due to shared genetic etiology between the two diseases; and (b) vertical pleiotropy, where the increased risk of cancer in individuals with diabetes may be due to the tumorigenic effects driven through either diabetes itself or driven through an associated trait such as hyperinsulinemia or other metabolic consequences of obesity. They concluded that "it seems unlikely that the observational association between type 2 diabetes and cancer risk is driven by shared genetic etiology" and speculated that "(it is) more likely to be driven by a particular metabolic feature of type 2 diabetes itself, such as increased fasting insulin levels, or by an associated trait, such as higher adiposity."

Are anti-diabetes medications relevant for cancer risk? In many clinical guidelines, metformin is initial medication, followed by stepwise addition of sulfonylureas, gliptides, SGLT-2 inhibitors, pioglitazone and/or a GLP-1 analogue to control hyperglycemia, finally adding insulin or an insulin analogue. Initial reports suggested that metformin might be cancer-protective; while long-acting insulin analogues might increase cancer risk. We now appreciate that many of these observations were based on sub-optimal analytical designs, mainly failing to account for immortal time bias, and were spurious.[1] In general, the impact of anti-diabetes medications is likely to be minimal but this question will require continual monitoring as newer drugs mature. For example, a recent 1:1 randomized controlled trial tested if Semaglutide, a GPL-1 analogue, reduced the risk of adverse cardiovascular events in obese individuals without diabetes.[10] With a median follow-up 39 months, as a secondary outcome analysis, there were 80 cancers or 0.9% in the Semaglutide group compared to a slightly higher rate of 107 or 1.2% in the placebo group ($P = .07$). This potential protective effect of Semaglutide now needs longer follow-up.

A link between diabetes and cancer remains a clinically very relevant question as both conditions are very common. If there were a causal link, it might be relevant to test whether optimizing long-term glycemic control, the biochemical hallmark of diabetes, might reduce cancer risk. Alternatively, if diabetes is not on the causal pathway, but rather the key drivers are obesity-related metabolic aberrations, then testing whether long-term weight management might reduce cancer risk would be worthwhile.

How should the question of causal association then be pursued? More studies using conventional epidemiological methods are plagued by confounding and biases. More advanced methods such as mediation analyses or matched-population studies may offer greater ability to infer causality. MR studies equally might have merit as there is less susceptible to confounding and reverse causation. Advanced techniques such as MR with Mediation analysis might add specific strengths. We champion the concept of triangulation, the combination of evidence that yields causal estimates with different potential sources of bias, but where these biases are independent. In the coming years, triangulation may require the networking of researchers to revise the consensus of this 110 year conundrum.

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