BMJ 2014;350:g7707 doi: 10.1136/bmj.g7707 (Published 2 January 2015)

EDITORIALS

Type 2 diabetes and risk of cancer

Strong evidence points to an association between diabetes and several major cancers

Ambika Satija *doctoral student*[1], Donna Spiegelman *professor*[2], Edward Giovannucci *professor*[2], Frank B Hu *professor*[2]

[1]Departments of Nutrition and Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; [2]Departments of Biostatistics, Epidemiology, and Nutrition, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA

Over the past 50 years, numerous studies have linked diabetes, in particular type 2 diabetes, to an increased risk of cancer. In 2010, a consensus report by the American Diabetes Association and American Cancer Society concluded that type 2 diabetes is convincingly associated with an increased risk for several cancers (colorectal, breast, endometrial, liver, pancreatic, and bladder), while the evidence is less conclusive for others (such as kidney cancer, leukemia, and esophageal cancer).[1]

In a linked article, Tsilidis and colleagues (doi:10.1136/bmj.g7607) present an umbrella review of 27 meta-analyses summarizing the associations between type 2 diabetes and cancer.[2] This review represents one of the most comprehensive efforts to summarize an important, albeit complex, question in epidemiology. In their review, Tsilidis and colleagues confirmed robust associations between type 2 diabetes and the risk of breast, colorectal, intrahepatic cholangiocarcinoma, and endometrial cancer. For most other cancer sites, however, they concluded that the associations with type 2 diabetes were not convincing, despite clinically and statistically significant summary estimates from the meta-analyses. A main reason for this largely negative conclusion is the use of a number of stringent and debatable criteria to define a valid and "robust" association. For instance, one of the criteria they used was $P \leq 0.001$ for both fixed and random effects summary estimates. While this would help to reduce false positive findings, it is likely to yield high rates of false negative results.[3]

Another criterion the authors used to judge the validity of a positive association from a meta-analysis is that its 95% prediction interval had to exclude the null value. Prediction intervals are designed to provide a range within which we are 95% sure that the true effect in a new study will fall.[4] This is not, however, what is of interest if we are trying to make causal inferences; what is of interest is an accurate estimate of the average effect size, which is reflected by the summary estimate and its 95% confidence interval. Unlike 95% confidence intervals, 95% prediction intervals do not provide information about the average effect size or its statistical significance.[5] A 95% prediction interval that includes the null value of 1 should not be interpreted as a null association overall but merely as an indication that the estimate obtained in the next study might not always be significantly different from the null. In general, substantial heterogeneity could lead to a wide prediction interval, in which case it would be important to identify the sources of heterogeneity. Inappropriate use of 95% prediction intervals in this review resulted in the refutation of some important and well established associations. For example, a meta-analysis of type 2 diabetes and pancreatic cancer found that the summary relative risk was 2.22 (95% confidence interval 2.15 to 2.29; $P<0.001$) from a fixed effects model and 1.95 (1.66 to 2.28; $P<0.001$) from a random effects model, providing strong evidence for a positive association.[6] Because the 95% prediction interval (0.87 to 4.34) included 1, however, the authors excluded pancreatic cancer from their list of convincing associations. The same occurred for hepatocellular cancer incidence as well as total cancer incidence and mortality.

The authors judged that associations between type 2 diabetes and cancers at several sites were biased because of significant heterogeneity in the summary estimates. While such heterogeneity can be caused by methodological differences across studies, it can also be driven by true underlying effect modification or biological heterogeneity. Indeed, biological heterogeneity is expected in the relation between type 2 diabetes and cancer. The biological mechanisms underlying this could include insulin resistance, hyperinsulinemia, hyperglycemia, chronic inflammation, and dysregulations of sex hormones.[1 7] As a growth factor, and through its interaction with insulin-like growth factor I, insulin could encourage growth of tumors both directly and indirectly. A diagnosis of type 2 diabetes is generally a positive marker for a combination of all these physiologic processes, but, being an inherently heterogeneous condition, type 2 diabetes is an imperfect and variable marker. For instance, insulin concentrations are usually higher in the early stages of type 2 diabetes because of insulin resistance and fall over time because of loss of islet cells and impaired insulin secretion. Thus, duration of diabetes can modify any association between type 2 diabetes and incidence of cancer. Indeed, a pooled analysis found a stronger association between type 2

Correspondence to: Frank B Hu frank.hu@channing.harvard.edu

diabetes and pancreatic cancer among individuals with a shorter duration of type 2 diabetes (two to eight years) than among individuals with a longer duration (nine years and more).[8]

Lastly, the authors mixed meta-analyses on cancer incidence and cancer mortality and treated them equally. The number of deaths from cancer in these meta-analyses, however, was substantially smaller (for example, only 103 deaths from endometrial cancer and 299 deaths from hepatocellular cancer) than the number of incident cases. Cancer mortality involves both incidence and survival, which could have different etiologies and associations with type 2 diabetes. For example, diabetes is associated with a reduced incidence of prostate cancer but people with diabetes have increased mortality from it.[9 10]

So, where does the totality of evidence currently stand on the link between type 2 diabetes and cancer? Strong epidemiologic evidence from this and previous reviews points to a consistent positive association between type 2 diabetes and risk of several major cancers. Although more research is needed to quantify these relations, the rising incidences of both diseases worldwide require prompt action from clinical and public health communities, including following appropriate cancer screening guidelines among people with diabetes and a greater emphasis on lifestyle modifications, which are crucial for improving both diabetes and cancer outcomes.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. *Diabetes Care* 2010;33:1674-85.
2 Tsilidis K, Kasimis J, Lopez D, Ntzani EE, Ioannadis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. *BMJ* 2015;350:g7707.
3 Ioannidis JP, Tarone R, McLaughlin JK. The false-positive to false-negative ratio in epidemiologic studies. *Epidemiology* 2011;22:450-6.
4 Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549.
5 Guddat C, Grouven U, Bender R, Skipka G. A note on the graphical presentation of prediction intervals in random-effects meta-analyses. *Syst Rev* 2012;1:34.
6 Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. *Eur J Cancer* 2011;47:1928-37.
7 Shi Y, Hu FB. The global implications of diabetes and cancer. *Lancet* 2014;383:1947-8.
8 Elena JW, Steplowski E, Yu K, Hartage P, Tobias GS, Brotzman MJ, et al. Diabetes and risk of pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. *Cancer Causes Control* 2013;24:13-25.
9 Bansal D, Bhansali A, Kapil G, Undela K, Tiwari P. Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. *Prostate Cancer Prostatic Dis* 2013;16:151-8,S1.
10 Bensimon L, Yin H, Suissa S, Pollack NM, Azoulay L. Type 2 diabetes and the risk of mortality among patients with prostate cancer. *Cancer Causes Control* 2014;25:329-38.

Cite this as: *BMJ* 2015;350:g7707