Study of almost 900,000 people shows prediabetes increases the risk of cancer by 15 percent

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A meta-analysis comprising 16 studies and 891,426 participants from various regions of the world shows that prediabetes increases the risk of cancer by 15%, with differing risks depending on the type of cancer. The study, published in *Diabetologia* (the journal of the European Association for the Study of Diabetes) is by Professor Yuli Huang, The First People's Hospital of Shunde, Daliang Town, Shunde District, China, and colleagues.

Prediabetes is a general term that refers to an intermediate stage between normoglycaemia and overt diabetes mellitus. It includes individuals with impaired glucose tolerance (IGT), impaired fasting glucose (IFG) or a combination of the two. Results to date from prospective cohort studies investigating the link between prediabetes and risk of cancer are controversial. Thus in this new study, the authors did a meta-analysis to evaluate the risk of cancer in association with the impaired fasting glucose and impaired glucose tolerance population. Of the 16 studies included, four were from Asia, 11 were from the USA and Europe, and one was from Africa.

The researchers found that prediabetes was associated with a 15% increased risk of cancer overall. The results were consistent across cancer endpoint, age, duration of follow-up and ethnicity. There was no significant difference for the risk of cancer with different definitions of prediabetes (IGT or IFG). The authors note that it has been reported that

obesity, an important risk factor for diabetes, is also linked to the development of cancer. For this reason, they performed a sensitivity analysis that only included studies that adjusted for BMI in the meta-analysis. They say: "We found that, after controlling for BMI, the presence of prediabetes remained associated with an increased risk of cancer of 22%."

The risk of all cancer was also increased when a lower definition of IFG (5.6-6.9 mmol/l) was used, according to the current American Diabetes Association definition of IFG, although this definition has not been accepted by either WHO's special working group on diabetes or other international guidelines. The difference of risk of cancer was not significant between IFG defined as 5.6-6.9 mmol/l or 6.1-6.9mmol/l.

In a site-specific cancer analysis, prediabetes was significantly associated with increased risks of cancer of the stomach/colorectum (relative risk, RR 1.55), liver (RR 2.01), pancreas (RR 1.19), breast (RR 1.19) and endometrium (RR 1.60) (all statistically significant), but not associated with cancer of the bronchus/lung, prostate, ovary, kidney or bladder.

The authors say several possible mechanisms could explain the results. First, chronic hyperglycaemia and its related conditions, such as chronic oxidative stress and the accumulation of advanced glycated endproducts (that are made in conditions of excessively high blood sugar) may act as carcinogenic factors. Second, increased insulin resistance leads to increased insulin secretion, which can in turn allow cancer cells to grow and divide. Third, there could be genetic mutations which predispose individuals to an increased risk of cancer, with one recent study showing that a malfunction in a tumour suppressor gene exposed individuals to increased risk of both cancer and prediabetes.

The authors say: "These findings have important clinical and public health implications. For example, in the US population aged ≥18 years,

the age-adjusted prevalence of prediabetes increased from 29% in 1999–2002 to 36% in 2007–2010. Many other countries, both developed and developing, are also seeing steep rises in the number of people with both full-blown type 2 diabetes and prediabetes. Considering the high prevalence of prediabetes, as well as the robust and significant association between prediabetes and cancer demonstrated in our study, successful intervention in this large population could have a major public health impact."

They add: "It should be noted that metformin—one of several first line therapies available to treat type 2 diabetes—is now considered as having some 'protective' anticancer properties. Notably, metformin mediates an approximately 30% reduction in the lifetime risk of cancer in diabetic patients. However, whether this is true in prediabetic individuals is not yet known. Long-term, large-scale studies of high-risk individuals, especially those with IGT or a combination of IGT and IFG, are urgently needed to explore the effects of metformin interventions on the risk of cancer in people with prediabetes."

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