Diabetes increases the risk of cancer, with a higher risk in women

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Diabetes is a risk factor for all-site cancer for both men and women, but the increased risk is higher in women than in men, according to a new article in *Diabetologia* (the journal of the European Association for the

Study of Diabetes).

Cancer is the second leading cause of death in the world. It is estimated that 1 in 4 women, and 1 in 3 men, develop cancer during their lifetime. In 2015 there were 17.5 million incident cancer cases and 8.7 million cancer deaths globally, and these figures are expected to increase in the next decades. Diabetes prevalence has also grown rapidly: 415 million adults were reported to have the condition in 2015, with 5 million deaths attributed. In the same year 12% of global health expenditure was spent on diabetes and its complications.

Previous studies have indicated that diabetes is associated with a risk of all-site and some site-specific cancers. For other conditions, such as stroke, coronary heart disease and dementia, there is published evidence (from these same authors) that excess risk of these conditions associated with diabetes is greater in women than in men. This study, conducted by Dr. Toshiaki Ohkuma, Dr. Sanne Peters and Professor Mark Woodward of the George Institute for Global Health at the University of New South Wales, Sydney, Australia and the University of Oxford, Oxford, UK, assessed whether there are sex differences in the association between diabetes and cancer.

In December 2016, the authors undertook a systematic search in PubMed MEDLINE to identify reports on the links between diabetes and cancer. Additional reports were identified from the reference lists of the relevant studies. Only those cohort studies providing relative risks (RRs) for the association between diabetes and cancer for both women and men were included—studies with data only for one sex were excluded, as were studies that had not adjusted for at least age as a confounder. In total, 107 relevant articles were identified, along with 36 cohorts of individual participant data.

Statistical analysis considered diabetes (types 1 and 2 combined) with all-

site cancer events. Additionally, for those cancers that can occur in both sexes, site-specific cancer events were analysed. Relative risks (RRs) for cancer were obtained for those individuals with diabetes versus those without diabetes, for both men and women. The women-to-men ratios of these relative risk ratios (RRRs) were then calculated, to work out the excess risk in women if present.

Data on all-site cancer was available from 47 studies, involving 121 cohorts and 19,239,302 individuals. Women with diabetes had a 27% higher risk of all-site cancer compared to women without diabetes; for men with diabetes the risk was 19% higher than for men without. Calculation of the women-to-men ratio revealed that women with diabetes had a 6% greater excess risk of all-site cancer compared to men with diabetes.

Data on site-specific cancer were available for 50 sites. The women-to-men ratios showed statistically significant higher risks for women with diabetes for kidney (11% higher); oral (13% higher); stomach (14% higher); and leukaemia (15% higher) cancers, compared to men with diabetes. For liver cancer the risk for women with diabetes was 12% lower than for men with diabetes.

The authors suggest that there are several possible explanations for the excess risk of all-site cancer conferred by diabetes in women. Hyperglycaemia (i.e. heightened blood glucose) may have carcinogenic effects by causing DNA damage—an effect that would be potentially more pronounced in women because historically women were likely to be undertreated, receive less intensive care, or show lower adherence to antidiabetic medication compared to men.

Alternatively, because the average duration of impaired glucose tolerance or impaired fasting glucose has been found to be over 2 years longer in women, they may have more exposure to untreated

hyperinsulinaemia (high levels of insulin) in the prediabetic state—hyperinsulinaemia has been found to promote cancer cell proliferation. Another factor that may impact on the lower risk ratio for all-site cancer in men may be the apparent protective effect of diabetes in prostate cancer, a type that affects men only.

The authors also found that diabetes conferred a higher site-specific risk for women than men for oral, stomach and kidney cancers and leukaemia, but a lower risk for liver cancer. The authors note that the literature around mechanisms underpinning the sex differences in site-specific cancers is scant. However, unmeasured confounding factors specific to each site, for example Helicobacter pylori infection for stomach cancer, and hepatitis virus infection for liver cancer may be involved."

Diabetes has been associated with the risk of all-site, and some site-specific, cancers in several systematic reviews and meta-analyses. Previously, however, there has been no systematic overview of the evidence available that sex differences may impact on this risk. This study confirms that diabetes is indeed a risk factor for all-site cancer in both sexes, but shows also that the effect is stronger in women than in men, and that this increase in risk for women varies with cancer site.

The authors stress "the importance of a sex-specific approach to quantification of the role of diabetes in cancer research, prevention and treatment," and conclude that "further studies are needed to clarify the mechanisms underlying the sex differences in the diabetes-cancer association."

More information: Toshiaki Ohkuma et al. Sex differences in the association between diabetes and cancer: a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million events, *Diabetologia* (2018). DOI: 10.1007/s00125-018-4664-5

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