# Cancer now the leading cause of death with diabetes

**As total mortality rate with diabetes declines, deaths from cancer now exceed those from vascular disease, and dementia-related deaths are rising exponentially.**

A recently published epidemiological analysis,[1] examining trends in the causes of death with diabetes in England between 2001 and 2018, while observing an overall decline in total mortality rates, has identified that cancer has now replaced vascular disease as the leading contributor to diabetes-related death. From primary care records database, over 300,000 individuals with diagnosed diabetes and a similar number of matched individuals without diabetes, were studied in terms of total mortality and in respect of 12 specified 'cluster' causes of death, including vascular diseases and cancers. Despite observing an almost one-third decline in mortality rate with diabetes over this period of time, a significant excess mortality gap still persists between those with and those without diabetes. For both groups all but two of the 12 causes of death were reduced. However, with diabetes the death rate for each cause remained greater and the declines consistently less, other than with vascular diseases where the decline actually exceeded that observed for those without diabetes.

The substantial reduction in deaths from vascular diseases in diabetes has been the most striking change, primarily due to improved screening and targeted therapies, resulting in a consequent diversification of other causes of death. Certain diabetes-associated cancers (colorectal, pancreatic, gall bladder, breast, endometrial) are already recognised, but total cancer deaths also appear greater with diabetes than without. By 2018, cancers accounted for a larger proportion of deaths for both populations, with an almost 50% higher mortality burden in those with diabetes.

Although primarily focused on cancer mortality, it is of interest that the two specified causes not to have declined for both groups were those of dementia and liver disease, again both being that much greater with diabetes. 2018 Office for National Statistics figures indicate that dementia is becoming a leading cause of death in England, up to 2.5 times greater with diabetes. It is suggested the increase in liver disease death rates is likely to relate to risk factors such as obesity and sustained high alcohol consumption.

This study was unable to record sufficient data in respect of documented risk factors to enable more detailed analysis of the observed changes in mortality patterns. Nor was it possible to stratify between type 1 and type 2 diabetes, where potentially significant differences in outcome might occur. Evidence of increased cancer risk primarily relates to type 2 diabetes,[2] although risk does appear to be increased with type 1 diabetes, albeit with a different spectrum of cancers including those of stomach or cervical origin.

In a recent issue of *Practical Diabetes*,[3] Anne Kilvert and Charles Fox discussed possible pathogenic mechanisms predisposing type 2 diabetes to increased risk of cancer, commenting on evidence that hyperinsulinism, secondary to obesity-linked insulin resistance, might be a significant contributory factor. Although not considered to be a direct carcinogen, insulin may potentiate mitogenicity, via insulin receptor signalling pathways and stimulation of IGF-1 receptors, thereby promoting tumour growth in pre-existing, pre-malignant lesions where mitotic transformation has already occurred. Reports that metformin, an insulin sensitiser, may reduce cancer risk appear to support this suggestion.

The increased cancer risk with type 1 diabetes is less clear. Suboptimal glycaemic control consistently correlates with a magnification of diverse risk, but if hyperinsulinism is a predisposing factor with type 2 diabetes, what are the consequences of insulin administered by injection? All new insulins in development are subject to rigorous assessment in respect of potential adverse mitogenic risk. However, to date, there has been no convincing evidence to link injected insulin with cancer risk, a very reassuring observation in this forthcoming centenary year commemorating the first person with diabetes to receive insulin.

The overall decline in mortality rate and the reduction in deaths from vascular disease with diabetes is clearly good news. Nonetheless, the rising rate of deaths from cancer may not immediately seem a particularly welcome alternative; nor does the prospect of increasing risk of dementia along with the added frailty of old age. With this in mind, clinical care guidelines for diabetes should now include specific consideration of cancer risk and a continued strive to lessen the 'gap', aspiring as ever to decent longevity while preserving as good a quality of life as possible.

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## References

1. Pearson-Stuttard J, *et al*. Trends in predominant causes of death in individuals with and without diabetes in England from 2001 to 2018: an epidemiological analysis of linked primary care records. *Lancet Diabetes Endocrinol* 2021;9(3):165–73. https://doi.org/10.1016/S2213-8587(20)30431-9.
2. Giovannucci E, *et al*. Diabetes and cancer: a consensus report. *Diabetes Care* 2010;33(7):1674–85.
3. Kilvert A, Fox C. Hyperinsulinaemia and cancer risk: cause and effect? *Pract Diabetes* 2020;37(6):223–7a.