The global implications of diabetes and cancer

Diabetes and cancer are common diseases that are increasing rapidly in prevalence worldwide. The International Diabetes Federation (IDF) has projected that the number of people with diabetes in the world will increase from 382 million in 2013 to 592 million by 2035, with 80% of cases occurring in low-income and middle-income countries. In China alone, about 114 million adults have diabetes and most cases are undiagnosed.

Meanwhile, WHO-projected global cancer incidence will increase from 14 million in 2012 to 22 million in 2032, with more than 60% of incident cancers and 70% of cancer deaths occurring in central and south America, Africa, and Asia. Incidence of cancer is rising rapidly in developing economies such as China, India, and Russia; alarmingly, cancer mortality rates in these countries are twice as high as those in the UK or USA.

Diabetes and cancer have been closely linked to each other epidemiologically and biologically. Convincing evidence indicates that diabetes (mainly type 2) is associated with increased risk for several cancers (colorectal, breast, endometrium, liver, pancreas, and bladder). Diabetes is associated with reduced incidence of prostate cancer, but people with diabetes have an increased risk of mortality if they develop prostate cancer. Diabetes is also associated with premature death from cancers of the liver, pancreas, ovary, colorectum, lung, bladder, and breast. The consistent associations between diabetes and cancer incidence and mortality are unlikely to be explained by methodological issues such as early detection bias and reverse causation (ie, diabetes as a consequence of pre-existing or subclinical cancer).

One possible explanation for the link between diabetes and cancer is that these two disorders share many risk factors, including ageing, obesity, smoking, unhealthy diet, and physical inactivity. Obesity, the most important risk factor for diabetes, is now a well-recognised risk factor for several cancers. However, the associations between diabetes and cancer incidence or mortality are not explained by adiposity. In addition, these associations appear to be independent of age, smoking, physical activity, and several dietary factors in epidemiological analyses.

Potential biological explanations for the link concern the role of hyperinsulinaemia (mainly due to insulin resistance), hyperglycaemia, sex hormones, and inflammatory cytokines in the neoplastic process. Insulin is a growth factor that can have direct tumorigenic effects through activation of insulin receptors in tissues. It might also exert indirect influence through increased bioactive insulin-like growth factor I (IGF-I), which has potent mitogenic actions on preneoplastic and neoplastic cells. In addition, increased insulin and bioactive IGF-I concentrations in diabetes downregulate production of sex hormone binding globulin (SHBG), which increases free oestradiol and testosterone (in women, but not in men). Increased concentrations of sex hormones, particularly oestrogen, have been strongly associated with endometrial and postmenopausal breast cancers. Furthermore, diabetes is a proinflammatory state that is characterised by increased production of cytokines such as TNFα, C-reactive protein, and interleukin 6, and reduced production of adiponectin; these adipocytokines have been implicated in pathways connecting obesity with the development of several cancers.

Whether specific antidiabetic medications influence cancer risk is an area of active research. A growing amount of observational evidence suggests that metformin is associated with decreased incidence of and mortality owing to breast cancer, but a more definitive conclusion awaits the results from several ongoing trials, including a phase 3 trial of metformin in survivors of early stage breast cancer. A possible mechanism for the anticancer effects of metformin involves the reduction of circulating insulin and glucose concentrations by suppressing hepatic glucose production and improving insulin sensitivity, as well as the inhibition of tumour cell growth and proliferation through AMP kinase activation. The role of insulin therapy in cancer risk has long been debated, but current clinical trial evidence does not consistently support increased risk of malignancy associated with long-term use of exogenous insulin (eg, the long-acting insulin analogue glargine). Moreover, the postulated links between incretin-based therapies, such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors, and pancreatic cancer have not been substantiated.

A consensus report by the American Diabetes Association and American Cancer Society concluded that cancer
risk should not be a major factor in the choice between available diabetes therapies for most patients.\textsuperscript{5}

Overall, the link between diabetes and increased cancer incidence and progression is firmly established, although the underlying biological mechanisms are not well understood. The rapidly increasing global diabetes epidemic has several important implications for cancer occurrence and prevention. First, the rate of increase in cancer incidence and mortality worldwide will accelerate, in part because of the escalating obesity and diabetes epidemics and population ageing. Second, health professionals should recognise patients with diabetes as a high-risk group for cancer and strongly encourage following of appropriate cancer screening and prevention guidelines. Preventive strategies such as weight control and lifestyle modifications will be key in improvement of both diabetes and cancer outcomes. Finally, to reduce the global burden of diabetes and cancer and improve population health, international organisations and national governments should develop public policies to improve nutritional and built environments that enable individuals to adopt a healthy diet and lifestyle.

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\textcopyright{} Sex disparity in the risk of diabetes-associated stroke

In the general population, stroke is more prevalent in men than in women. Men also have a higher age-specific stroke incidence than women, except for women aged 35–44 years and those older than 85 years. Factors such as pregnancy and the use of oral contraceptives are believed to contribute to the increased risk of stroke in women in their mid-30s to mid-40s, and their relative longevity contributes to the higher risk of stroke in older women.\textsuperscript{1}

Diabetes is a well-established independent risk factor for stroke, conferring a two to three times increase in relative risk.\textsuperscript{2,3} Diabetes is also associated with an increased risk of stroke recurrence and mortality.\textsuperscript{4,6} Investigators of the UK Prospective Diabetes Study (UKPDS)\textsuperscript{5} reported that women with diabetes had more than twice the risk of men with diabetes for stroke case fatality; this increased risk for women was larger than that associated with a 1% increase in glycated haemoglobin or a 10 mm Hg increase