Diabetes, blood glucose lowering drugs and cancer risk

In 2009, a consensus report produced by experts in diabetes, oncology, epidemiology and biology from the USA and Europe stated that type 2 diabetes is associated with a higher risk of certain cancers (Giovannucci et al, 2010). Healthcare professionals are also becoming gradually more aware of the increased incidence of cancer in people with type 1 diabetes, as well as in individuals who have obesity alone. While this increased incidence is becoming more accepted, less is understood about the mechanisms of increased cancer risk, and the part played by diabetes treatments in altering this risk. A number of questions spring to mind when considering this topic, and these are outlined below.

What cancers occur in association with diabetes?

Meta-analyses demonstrate higher rates of hepatic, pancreatic, colon, endometrial, bladder and breast cancer in people with diabetes, with a possible decreased incidence of prostate cancer (Vigneri et al, 2009). There are also gender differences, as type 2 diabetes is associated with an increased risk of colorectal cancer in men, but not in women (Limburg et al, 2006).

What about the risk of cancer with type 1 diabetes?

A cohort study examined the incidence of cancer among 29 187 people in Sweden who were hospitalised for type 1 diabetes from 1965 to 1999 (Zendehdel et al, 2003). This analysis demonstrated a modest excess cancer risk overall and risks of specific cancers that differ from those associated with type 2 diabetes, suggesting perhaps different modes of action and risk. Various reasons for this have been postulated, including fertility and menstrual disorders in women and higher overall rates of pernicious anaemia.

If diabetes is an emerging risk factor for some cancers, does pre-existing diabetes have an effect on all-cause mortality in people newly diagnosed with cancer?

A recent meta-analysis has demonstrated that people diagnosed with cancer who have diabetes are at increased risk for long-term, all-cause mortality compared with those without diabetes (Barone et al, 2008). Several possible explanations for this have been suggested, although it is still unclear whether diabetes, through a number of mechanisms, makes the cancer more aggressive or whether the host is less resistant to the condition (Vigneri et al, 2009). Researchers are still unsure if this excess mortality is a consequence of hyperglycaemia and hyperinsulinaemia with their growth-promoting effect on cancer cells, or the impaired health of individuals due to diabetes comorbidities.

There is increasing evidence that obesity (which is associated with type 2 diabetes) is a risk factor for many cancers. In another epidemiological study conducted in the USA in both men and women, BMI was significantly associated with higher rates of death due to cancer of the oesophagus, colon and rectum, liver, gallbladder, pancreas and kidney (Calle et al, 2003). Increased body weight was associated with increased death rates for all cancers combined and for cancers at multiple specific sites.

What mechanisms may underpin the association between diabetes and cancer?

Obesity and physical inactivity are frequently associated with diabetes, and, along with insulin resistance, these factors appear to play an important role in the risk of cancer and diabetes (Giovannucci, 2003). Diabetes is generally characterised by hyperglycaemia and hyperinsulinaemia, often coupled with insulin resistance in peripheral tissues. Chronic hyperinsulinaemia, however, is a possible risk

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factor for cancer or possible cancer progression in people with diabetes, due to the mitogenic effect of insulin. Insulin is known to have direct growth-promoting properties and is associated with increased levels of insulin-like growth factor (IGF) (Currie et al, 2009). This change in the IGF axis due to hyperinsulinaemia may possibly promote survival and progression of early malignant cells, by increasing tumour growth and decreasing cellular apoptosis.

What effect do glucose-lowering therapies have on cancer risk in type 2 diabetes?

In a retrospective cohort study of people treated in UK general practices, 62 809 people were divided into four groups according to whether they were treated with metformin or sulphonylurea monotherapy, combined therapy (metformin plus sulphonylurea), or insulin. Insulin users were subdivided into four groups: treatment with insulin glargine, long-acting human insulin, biphasic insulin analogue and human biphasic insulin. The outcome measures were progression to any solid tumour, or cancer of the breast, colon, pancreas or prostate (Currie et al, 2009).

The results were interesting: participants treated with insulin or insulin secretagogues were more likely to develop solid cancers than those treated with metformin, and treatment with insulin and metformin in combination cancelled most of this excess risk. Risk of colon or pancreatic cancer was lower in those treated with metformin, but the risk of breast or prostate cancer was not affected. Compared with human insulin, the use of insulin analogues was not associated with increased cancer risk (Currie et al, 2009).

Researchers have focused on trying to elucidate metformin's mechanism of action in diabetes, assuming that similar mechanisms could inhibit cell growth in cancer cells. Although not significant, results showed that metformin had the lowest risk of cancer compared with treatment with metformin and sulphonylurea in combination, sulphonylurea monotherapy and insulin-based regimens (Currie et al, 2009).

The insulin analogue glargine was the focus of five observational studies published in 2009 that suggested an increase in the rates of cancer associated with its use (Colhoun et al, 2009; Currie et al, 2009; Hemkens et al, 2009; Jonasson et al, 2009; Mannucci et al, 2010). Use of insulin analogues overall does not seem to increase cancer risk any more than the use of human insulin. Although an increased risk of cancer was seen with insulin glargine in one trial (Colhoun et al, 2009), multiple flaws prevent the extrapolation of the data to a large population. Furthermore, none of the other studies reported data that insulin glargine is more carcinogenic than the other insulins studied. The European Medicines Agency (2009) reviewed the available data and concluded that there was no cause for concern and that changes to the prescribing advice were therefore not necessary. Until long-term, randomised, prospective studies are available to confirm a correlation with cancer and insulin, the US Food and Drug Administration (2011) suggests continuing treatment with insulin analogues to avert the long-term complications of diabetes.

What actions should we take while awaiting further evidence?

This topic provides substantial data for primary care teams to ponder. Epidemiological evidence is now clear that obesity, type 1 and type 2 diabetes are all associated with an increased incidence of cancer and cancer-associated mortality. We should bear this in mind in taking every opportunity to help obese people to lose weight. We can be vigilant in looking for underlying cancers in people with diabetes, while still finding time to focus on helping them reduce cardiovascular and cerebrovascular risks. A candid disclosure of cancer risks to individuals with diabetes presents ethical and clinical dilemmas, especially in the context where cardiovascular and cerebrovascular mortality is much higher in people with diabetes than cancer mortality (Bergenstal et al, 2010).

It would appear that metformin has a positive effect on cancer outcomes, so we should continue to include it in our glucose-lowering treatment regimens at every opportunity. And finally, while we await more evidence, we should continue to use insulin analogues where appropriate. ■