# What are the drivers of cancer risk in people with diabetes?

*Krishnan Bhaskaran*

**It is well established that overweight, obesity and diabetes are associated with an increase in the risk of certain cancers, but is it possible to untangle the risk factors and determine the specific drivers that increase the risk of cancer for people with diabesity? Do some factors affect the risk of particular types of cancers, and what effect do anti-diabetes treatments have on cancer incidence. This article will summarise some of the key thinking and evidence on the potential drivers of cancer risk, as well as asking whether a better understanding of these issues could change what healthcare advice is recommended to people with diabetes.**

The risk of most cancers seems to be higher in people with type 2 diabetes than the general population (Tsilidis et al, 2015). For example, the increased risk of cancer among people with diabetes has been reported as ranging from 20% higher (breast cancer) to more than double (liver, pancreas and endometrial cancer [Vigneri et al, 2009]). But what are the causes for this increased risk? Overweight and obesity are possibly the most important risk factors for type 2 diabetes and are also established risk factors for many cancers (Bhaskaran et al, 2014). There are common risk factors for cancer associated with type 2 diabetes and overweight and obesity, but could an increased cancer risk in diabesity be explained purely by shared risk factors? What about direct and indirect effects of diabetes itself – does impaired blood glucose control increase risk? Might some of the treatments for diabetes have the unintended side effect of causing cancer in some individuals? The answers to these questions may be complex and may differ by cancer site (*Figure 1*). This article will summarise some of the key thinking and evidence on these questions, as well as asking whether a better understanding of these issues would actually change the healthcare advice for people with diabetes.

## Overweight, obesity and other shared risk factors

The simplest explanation for an increased risk of cancer among people with diabetes might be that patient characteristics and lifestyles that confer a high risk of diabetes also confer a high risk of cancer. This is almost certainly at least part of the picture. Older age, poor diet, physical inactivity, smoking and alcohol use are all likely to increase the risks of both diabetes and cancer (Giovannucci et al, 2010). But the clearest example of a shared risk factor is excess weight; overweight and obesity are major risk factors for type 2 diabetes and cancer (Bhaskaran et al, 2014). Changes in hormone metabolism are thought to be among the mechanisms mediating increased cancer risks associated with excess adiposity, including pathways involving insulin and insulin-like growth factors (IGFs). This is consistent with the observations that obesity is linked to increased cancer risk (Roberts et al, 2010).

In our recent study using the electronic health records of over 5 million people in the UK, we found clear links between higher BMI and higher risks of a number of cancer types, including cancer of the uterus, liver, pancreas, colon and (among postmenopausal women) breast (Bhaskaran et al, 2014). These findings

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### Article points

1. Cancer risk is higher in people with type 2 diabetes and obesity than the general population.
2. It is difficult to untangle the shared factors related to obesity and type 2 diabetes that increase the risk of cancer.
3. More research is needed into the role of anti-diabetes treatments, but it is likely that cancer risk will be minimised by encouraging weight loss and maintaining optimal diabetes control.

### Key words

- Cancer
- Obesity
- Type 2 diabetes

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**Page points**

1. The role of insulin and insulin-like growth factors in increased cancer risk raises the question of whether diabetes has a direct effect on cancer risk, in addition to the shared risk factors with obesity.
2. $HbA_{1c}$ has been observed to positively correlate with cancer risk, in particular for colorectal, gastric, pancreatic, breast and liver cancers; this is a relationship that is evident in the pre-diabetes $HbA_{1c}$ range as well.
3. It is not yet clear whether the observed association between $HbA_{1c}$ and cancer risk represents a direct causal effect of hyperglycaemia or confounding by coincident hyperinsulinaemia and insulin receptor activation.

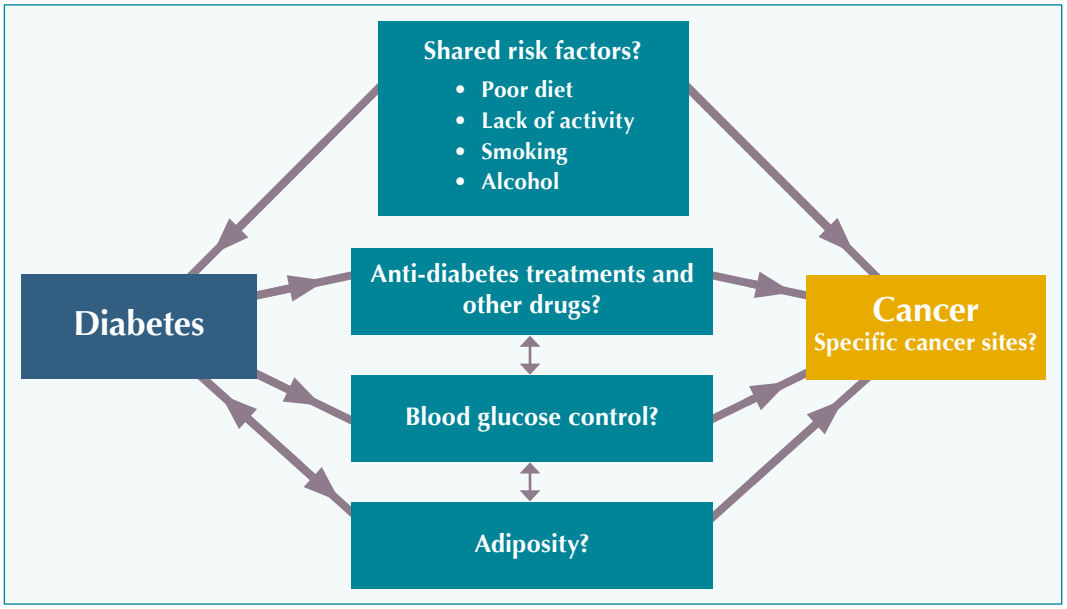


*Figure 1. Possible drivers of cancer risk among people with type 2 diabetes.*

were in agreement with previous research (Renehan et al, 2008), and there is overlap between the list of cancer sites affected by higher BMI, and those that have been noted to occur more frequently in people with diabetes (Tsilidis et al, 2015).

## Does diabetes directly increase cancer risk?

The role of insulin and IGFs in increased cancer risk raises the question of whether diabetes has a direct effect on cancer risk. Onset of diabetes is characterised by increasing insulin resistance and compensatory hyperinsulinaemia, and the consequences of this process may affect the likelihood of malignant tumours developing. Circulating insulin has mitogenic properties and can bind to the IGF-1 receptor, which may be overexpressed in tumour cells (Buysschaert and Sadikot, 2013). High levels of circulating insulin also lead to reductions in the level of IGF-1 binding proteins, and, therefore, increase free IGF-1 and cause overstimulation of IGF-1 receptors (Simon and Balkau, 2010).

As well as hyperinsulinaemia, diabetes is also characterised by impaired blood glucose control and hyperglycaemia. $HbA_{1c}$ has been observed to positively correlate with cancer risk, in particular for colorectal, gastric, pancreatic, breast and liver cancers; this is a relationship that is evident in the pre-diabetes $HbA_{1c}$ range as well (de Beer and Liebenberg, 2014; Liao et al, 2015). It makes intuitive sense that chronic hyperglycaemia would help to promote cancer growth since cancers need a lot of energy, delivered via glucose, to develop and grow; this is the very principle on which FDG-PET scanning works (Giovannucci et al, 2010). However, it is not yet clear whether the observed association between $HbA_{1c}$ and cancer risk represents a direct causal effect of hyperglycaemia or confounding by coincident hyperinsulinaemia and insulin receptor activation, as described above.

Detailed studies of how cancers respond to glucose in the laboratory may eventually help to clarify the role of impaired glucose control in cancer development. It is also possible that the explanation for the correlation comes back to obesity, which worsens blood glucose control and, as already noted, is an established risk factor for cancer.

## What role do anti-diabetes treatments play in cancer risk?

Perhaps the biggest controversies in the epidemiological literature on diabetes and cancer have concerned the effects of anti-diabetes

treatments. Notably, a suite of studies published in a single issue of the journal *Diabetologia* in 2009 raised widely reported concerns that the insulin analogue insulin glargine may cause an increased risk of cancer, though the conclusions of the four observational studies published in the issue were not unanimous (Colhoun, 2009; Currie et al, 2009; Hemkens et al, 2009; Jonasson et al, 2009). Substantial design flaws were later identified (Pocock and Smeeth, 2009), and subsequent work has suggested that such observed treatment effects could be explained by bias and confounding (van Staa et al, 2012).

Sulphonylureas, another major class of anti-diabetes treatment, have also been linked with changes in cancer risk, although there are studies reporting associations in both protective and harmful directions (Buysschaert and Sadikot, 2013).

Meanwhile, a number of studies reporting reduced cancer risks among individuals taking metformin compared with other anti-diabetes treatments led to increasing interest in metformin for cancer prevention or treatment (Suissa, 2012). However, it has been suggested that methodological pitfalls could also explain these observational findings (Suissa and Azoulay, 2012; van Staa et al, 2012).

As newer drug classes start to be used more widely and gain in popularity, questions are inevitably raised about possible links to cancer. Glucagon-like peptide (GLP)-1 receptor agonists have been linked to pancreatic and thyroid cancer in pre-clinical and epidemiological studies, but the current evidence remains limited and conflicting, suggesting that further careful monitoring will be needed (Butler et al, 2013; Suarez et al, 2014; Tseng et al, 2015).

## Why is there still uncertainty about the effects of anti-diabetes treatments on cancer risk?

Given the level of interest in anti-diabetes treatments and cancer risk over recent years, why is there still so much uncertainty about the effects of these drugs? Most clinical trials have been powered for different outcomes and had insufficient patient numbers and follow-up length to detect differences in cancer incidence between the treatment arms, though it is interesting to note that 5-year follow-up data from a randomised study did contribute reassuring data at the height of the insulin glargine controversy (Rosenstock et al, 2009).

In the main though, we have had to rely on observational data to provide information on how anti-diabetes treatments affect cancer risk. As outlined above, some such studies have been found to have serious design flaws, but the more fundamental problem is that treatment changes in diabetes are inextricably tied to underlying diabetes control, making the effects of each on cancer risk difficult to distinguish (Giovannucci et al, 2010). Is it simply coincidence that metformin, the drug most often hailed as protective against cancer, is the one that is used as the first-line pharmacological treatment for people with newly diagnosed type 2 diabetes, and that the drug that raised the greatest controversy over increased cancer risks is an insulin analogue that would generally only be used in those with diabetes that can no longer be controlled with other medication? This issue cannot be ignored, especially given that comparisons are often made between anti-diabetes treatments, and, therefore, between people who are typically at different stages of the condition. Given the potential for diabetes, hyperinsulinaemia and hyperglycaemia to have direct effects on cancer risk, it seems clear that such treatment comparisons cannot be made in isolation, yet disentangling the effects of anti-diabetes treatment from other potential drivers of risk remains a challenge that the discipline of observational pharmacoepidemiology has yet to fully overcome.

## Conclusions and implications for practice

It is clear that the relationship between diabetes and cancer matters. An average increase risk of 25% across all cancers (Buysschaert and Sadikot, 2013), if causal, would implicate diabetes in over a quarter of a million of the new cancers diagnosed worldwide each year. There is a complex web of interrelated factors potentially driving the increased cancer risk observed in people with diabetes, and we can be virtually

### Page points

1. Perhaps the biggest controversies in the epidemiological literature on diabetes and cancer have concerned the effects of anti-diabetes treatments.
2. Clinical trials have so far been unable to provide conclusive data on the effect of anti-diabetes treatments on diabetes and cancer. This is due, in part, to design flaws and trials being powered for different outcomes and having insufficient patients and follow-up to detect differences in cancer incidence.
3. Disentangling the effects of anti-diabetes treatment from other potential drivers of risk remains a challenge that the discipline of observational pharmacoepidemiology has yet to fully overcome.

## Page points

1. Disentangling the effects of diabetes itself on cancer risk has proven extremely challenging, and there remain more questions than answers.
2. Of the potential causal pathways, those involving anti-diabetes treatment have perhaps the greatest potential implications for clinical practice and diabetes management.
3. For those with the misfortune to develop cancer, increased awareness supported by targeted evidence-based screening with a goal of earlier detection may be the best way to improve outcomes.

certain that shared risk factors explain at least part of the association. Disentangling the effects of diabetes itself (via pathways involving insulin and IGFs, blood glucose control and treatment) has proven extremely challenging, and there remain more questions than answers. Nevertheless, it is worth considering whether, and how, a more complete understanding of the pathways leading to increased cancer risks in people with diabetes would change recommendations for these individuals.

Firstly, it is now beyond doubt that obesity is a risk factor for many cancers (Campbell, 2014). Higher resolution data on which cancers are most affected by obesity and type 2 diabetes and which individuals are most at risk may ultimately lead to earlier cancer detection and better outcomes through increased awareness among patients and their clinicians. But in terms of prevention, the clear message to individuals about the benefits of maintaining a healthy weight is unlikely to change. Hyperinsulinaemia and hyperglycaemia both may play a part in further increasing cancer risk, but the solution to this is optimal diabetes control, which is, of course, the broader goal of diabetes management, which aims to improve the overall quality of life of people with diabetes and reduce the risks of cardiovascular diseases and other complications. Stronger evidence that these aspects of the condition directly increase cancer risk would be another motivation for optimal control, although may not change recommendations, given the already compelling reasons to optimise treatment. That said, it is possible that disentangling the drivers of cancer risk would change the risk–benefit balance in terms of when to start treatment; for example, if a causally increased risk of cancer was proven at pre-diabetes $HbA_{1c}$ levels. In this case, a more individualised approach to treatment might also be indicated, with those at higher baseline risk of cancer being considered for anti-diabetes therapy at an earlier stage.

Of the potential causal pathways that have been discussed, those involving anti-diabetes treatment have perhaps the greatest potential implications for clinical practice and diabetes management. There are a number of different classes of drug, with a number of different drugs within classes, and perfect information on how drug choice affects cancer risk would likely feed into treatment decisions at each stage. If insulin glargine really does increase cancer risk, alternatives offering equal benefit would be favoured, particularly among those at high risk of cancer. If metformin does offer genuine protection against cancer, its use may be broadened further. As yet, the evidence has not been strong enough to make these recommendations, but encouragingly, researchers are increasingly aware of the challenges. The clear design flaws of early observational studies on the topic are now less frequently seen, and novel study designs and analytical methods are starting to overcome some of the earlier seen methodological difficulties (Tsilidis et al, 2014). In the case of metformin, clinical trial data may eventually help to clarify whether and how this popular drug modifies cancer risk (Hatoum and McGowan, 2015).

## Final thoughts

One fact disputed by few is that regardless of the reasons, the risks of several cancers are considerably higher in people with type 2 diabetes than those without. Implementing interventions that encourage weight loss and minimisation of other modifiable risk factors common to diabetes and obesity may ultimately be the best strategy to reduce cancer risk. For those with the misfortune to develop cancer, increased awareness supported by targeted evidence-based screening with a goal of earlier detection may be the best way to improve outcomes. ■

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