Diabetologia (2010) 53:1541–1544
DOI 10.1007/s00125-010-1815-8

COMMENTARY

Cancer and diabetes: are we ready for prime time?

U. Smith · E. A. M. Gale

Received: 17 May 2010 / Accepted: 17 May 2010 / Published online: 13 June 2010

Abbreviations
ACS American Cancer Society
IGFBP IGF binding protein

From time to time workers in apparently unrelated fields look sideways to discover that others are working on the same problem from a different angle. This happened recently when investigators in diabetes and cancer found that they were exploring much the same territory, a discovery triggered in part by publications in this journal last year [1–5]. Controversial though some of the reports have proved, the effect has been an explosion of interest in this previously underexplored area. The result has been an increased appreciation of the intimate connection between metabolism, cell growth and turnover, together with new observations that may come to influence clinical management of diabetes.

An association between diabetes and cancer was first reported as an incidental finding in 1932, in a paper stating that 'it would appear that either diabetics tend to develop cancer or that cancer patients tend to develop symptoms recognised as diabetic'. Cancers of the uterus, pancreas and intestine already featured on the list of associated tumours [6]. Later reports, in contrast, suggested a lower mortality rate from cancer relative to the non-diabetic population because patients with diabetes died earlier from vascular disease [7]. Nonetheless, clinical observation continued to suggest an excess risk of endometrial and pancreatic cancer, but the nature and extent of the association between type 2 diabetes and a range of cancer types only became clear when large-scale cancer registries began to report their findings.

The ADA and the American Cancer Society (ACS) responded to the concerns raised in this journal by holding a meeting (in conjunction with the EASD and the European Cancer Organization) in Atlanta in December 2009. The aims were to analyse the current state of knowledge concerning cancer and diabetes, and to identify the most important gaps in understanding [8, 9]. The meeting focused on four key questions, as follows:

Is there a meaningful association between diabetes and cancer incidence or prognosis?

The key conclusions were that diabetes (primarily type 2) is associated with an increased risk for some cancers (liver, pancreas, endometrium, colon and rectum, breast, bladder), but a reduced risk of prostate cancer. For other cancer sites the evidence is either inconclusive or negative.

The reasons for an increased risk of cancer in diabetes remain unclear, but there are three leading possibilities. The first is that increased cancer risk is directly related to hyperglycaemia, the second is that hyperinsulinaemia and insulin resistance are common factors in the development of diabetes and cancer, and the third is that the association is indirect and mediated by risk factors common to both conditions, such as obesity. Furthermore, cancer risk might

U. Smith
The Lundberg Laboratory for Diabetes Research,
Department of Molecular and Clinical Medicine,
Sahlgrenska University Hospital,
Gothenburg, Sweden

E. A. M. Gale (✉)
Diabetes and Metabolism, Second Floor, Learning and Research,
Southmead Hospital, Westbury-on-Trym,
Bristol BS10 5NB, UK
e-mail: Edwin.Gale@bristol.ac.uk

also be modulated by the direct actions or indirect consequences of therapies used to treat diabetes.

Prospective, population-based studies will be needed to address questions such as these. These should compare the incidence of cancer sub-types in individuals with and without diabetes in relation to insulin production and sensitivity, while allowing for common confounders such as weight, diabetes duration and glucose exposure. Such studies should focus upon cancers known to be associated with diabetes; analyses that fail to discriminate between cancer types should be discouraged.

What risk factors are common to diabetes and cancer?

Cancer, like type 2 diabetes, is an age-related condition. It is slightly more common in men. There are important differences between geographical regions, between socio-economic groups and between different ethnic groups sharing a common environment, for example in the USA. The extent to which these differences are caused by genes, environmental exposures, lifestyle, risk factor distribution or access to medical screening and therapy remains a matter for conjecture.

It is, however, clear from human and animal studies that potentially modifiable environmental factors such as energy balance and weight gain contribute to the burden of cancer, whereas weight loss (when not attributable to undiagnosed cancer) reduces cancer risk in women following successful diet-induced weight loss or bariatric surgery. Conversely, weight gain increases the risk of a number of cancers, notably of the breast.

Observational studies suggest that diets low in red or processed meat, and high in vegetables, fruits and whole grains protect against some cancers, possibly by modulating insulin sensitivity. Higher levels of physical activity also reduce the risks of certain types of cancer (colon, postmenopausal breast and endometrial) and are considered beneficial in diabetes, whereas smoking is equally harmful in both conditions. All levels of alcohol consumption appear to increase the risk of certain types of cancer, whereas moderate (but not high) alcohol intake is associated with a reduced rate of diabetes. Since many of these behaviours associate together, it is currently next to impossible to examine the benefits of individual components of lifestyle in isolation.

What are possible biological links between diabetes and cancer risk?

Malignant transformation is a complex process, which may be considered as passing through the three stages of initiation, promotion and progression. Factors influencing any one of these stages may modify cancer outcomes. The panel at the Atlanta meeting concluded that possible mechanisms for a direct link between diabetes and cancer include hyperinsulinaemia, hyperglycaemia and inflammation.

Most cancer cells produce or overproduce IGF-1 and insulin receptors, the latter most commonly as the A isoform, which can stimulate insulin-mediated mitogenesis even when IGF-1 receptors are lacking. Since glucose uptake in cancer cells is constitutive and unrelated to insulin binding, activation of the insulin receptor probably benefits the cancer cell by promoting cell survival and division. In all events, multiple downstream signalling events resulting from activation of the IGF–insulin axis contribute to cancer cell growth. The growth-promoting effects of the IGF–insulin axis may extend to normal smooth muscle cells, thus establishing a common pathway for accelerated atherosclerosis and accelerated cancer development in diabetes.

Hyperinsulinaemia may impact upon tumour growth either directly, or indirectly by inhibiting hepatic production of IGF binding protein (IGFBP) 1 and possibly also of IGFBP-2, thus increasing levels of bioactive IGF-1. However, not all studies have shown that high levels of the insulin receptor are clinically harmful, while none of those performed link circulating or interstitial insulin levels with insulin receptor production on tumour cells. Even so, biological plausibility and correlative studies in humans imply that insulin may, via its receptors, influence (for example) breast cancer risk and progression. Nor does the story end there, for high circulating levels of insulin also reduce hepatic synthesis and release of sex hormone binding globulin, thus increasing levels of bioavailable oestrogen in both sexes and of bioavailable testosterone in women but not in men. Insulin promotes androgen synthesis in the ovaries (and possibly the adrenals) in women before the menopause, and raised endogenous sex steroid levels are associated with increased risk of breast and endometrial cancer in post-menopausal women.

Hyperglycaemia might also promote cancer progression. In this context, the panel noted the recent resurgence of interest in the Warburg hypothesis and tumour energetics. This said, it should be noted that tumour cells are adapted to maximise glucose uptake by insulin-independent constitutive mechanisms, and given that these pathways are already functioning at near-maximal efficiency, the added effect of hyperglycaemia is likely to be limited. At our present level of understanding hyperglycaemia might, possibly, have an additive effect on growth and progression of some tumours, but the panel concluded that the insulin–IGF-1 axis is probably of greater importance.

Inflammation is the third alternative pathway linking diabetes with cancer. Fat cells release a range of cytokines,

including IL-6, monocyte chemoattractant protein, plasminogen activator inhibitor-1, adiponectin, leptin and TNF-α, all of which have the potential to influence cancer cell growth and survival. Recent experimental results have shown that IL-6 may induce epigenetic changes and transformation of breast cells to a more invasive phenotype [10].

Do treatments for diabetes influence risk of cancer or cancer prognosis?

This question has become a major focus of interest and concern for those treating diabetes. There is now abundant evidence that metformin has properties that render it of great interest as a possible anti-cancer agent, and this has already translated into clinical benefit in a number of cancer treatment scenarios. Several observational studies indicate that diabetic patients treated with metformin have a lower risk of cancer, but these should be interpreted with caution because of potential confounders, most notably confounding by indication. Thiazolidinediones have also attracted interest as a possible adjunct to cancer therapy, although studies in cancer patients have largely been negative. It was, however, noted that the glitazones are also potential carcinogens in some contexts; for example, they can promote tumour growth in rats. Thus, in theory at least, glitazones might increase, decrease or have no effect upon cancer risk and progression in humans. The clinical evidence for an effect in diabetic patients involved in observational studies or clinical trials remains equivocal, although a meta-analysis of recent trials with rosiglitazone was reassuring, despite the relatively small number of cancer endpoints. Sulfonylureas have been associated with an increased risk of cancer in observational studies, although this finding might also have been produced by a protective effect of metformin in the comparator group.

Liraglutide has been shown to increase the risk of thyroid medullary cell cancer in rodents, and there is one preliminary report of pancreatic ductal hyperplasia (a potentially pre-malignant condition) in a transgenic rodent model of type 2 diabetes treated with exenatide. To date, no effect of incretin-based therapies upon cancer risk in humans has been reported, but the period of exposure to these agents is short.

Insulin therapy is typically given to people who have already been exposed to high levels of endogenous insulin. Thus the estimated duration of such exposure should be taken into consideration when estimating risk, as should the use of multiple treatments for diabetes. With regard to the insulin analogues, the Atlanta panel acknowledged that in vitro studies of binding affinity and mitogenic potency show that some insulin analogues, and insulin glargine in particular, have a higher affinity for the IGF-1 receptor. However, they also noted that it would be simplistic to assume that these effects are directly transposable to a clinical context. Observational studies linking increased cancer risk to insulin glargine have not fully accounted for all potential confounders, whereas published trial-based data relating to cancer risk in patients treated with insulin glargine or NPH insulins, although negative, have limited power to exclude such an association. More studies are clearly needed.

Where next?

As this brief summary indicates, the ADA/ACS report holds few surprises for those who have been following the literature in this area. It does, however, represent a consensus view from leading experts in cancer and diabetes. As such, it provides a useful overview of the territory and has established a common basis for future research. The territory gained to date may seem modest to some readers, and it should be appreciated that we are confronted with daunting complexity, underpinned by a dense array of epidemiological and mechanistic considerations and equally wide-ranging speculation. Indeed, we stand on the frontiers of terra incognita, but this report represents a useful starting point for the journey.

The quest for factors common to diabetes, obesity and other insulin-resistant states must be central to any such endeavour, but the most immediate concern for the practising clinician, as for the person with diabetes, is that the therapies we use might modify the risk of cancer. We may anticipate a number of new developments in this area over the coming months. The intensive focus on metformin as an adjunct to tumour therapy will bring new knowledge as to its potential use in the non-diabetic population. To date, the auguries look good. It remains to be established whether metformin really does reduce cancer risk in patients with type 2 diabetes, but the observational studies, for all their limitations, consistently point in the same direction. Reanalysis of the major trials that have examined cardiovascular risk in type 2 diabetes should allow the risk of cancer to be examined in patients randomly allocated to metformin or other treatments, and could, if adequately powered, overcome the problem of confounding by indication.

The hope that metformin might offer some protection against the development of cancer is balanced by concern that insulin-based therapies might actually promote it. No certain conclusions can be drawn at this point, given that the risks of insulin therapy are typically measured in relation to those of metformin, which may turn out to be protective. Several of the diabetes-related cancers are

associated with higher levels of endogenous insulin secretion, and the clearest indication that exogenous insulin (or an increased requirement for insulin) is related to cancer risk would come from the demonstration of a dose-dependent relationship between the two; there are preliminary indications that this might be the case [11]. Additional evidence may soon appear to answer this important question. With respect to the vexed question of the long-acting analogues, further data from large-scale observational studies should soon allow us to refute or confirm the preliminary data that came to light last year. The Atlanta panel agreed that, in the light of current evidence, cancer risk should not be a major factor in choosing between available diabetes therapies for the average patient, although such issues may require more careful consideration for selected patients at high risk of cancer occurrence or recurrence.

It was also noted that people with type 2 diabetes, a group at increased risk for some cancers, may be less likely to undergo appropriate screening [12]. The panel therefore emphasised that cancer screening, as recommended for all people in their age and sex groups, should be strongly recommended. A further concern is that people with diabetes who develop cancer appear to be more likely to die from it [13], although this observation might be explained on other grounds, such as diabetes-related contraindications to some types of chemotherapy or the higher mortality rate associated with diabetes itself. This issue surely requires further investigation.

The panel of experts clearly recognised that much additional work needs to be done to come up with firm answers to these questions, as in many other areas of cancer research. The consensus document summarises the best available evidence in this complicated area and provides directions for future research. Having recognised this need, the EASD recently initiated via the EFSD a large European research programme in cancer and diabetes, which will fund the most competitive applications in the field over the period 2011 to 2013. This programme also aims to promote scientific interaction and collaboration between cancer and diabetes researchers, since these complex questions require the broadest possible scientific collaboration and expertise. There are challenging new areas of investigation ahead, and some of the answers may prove uncomfortable.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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