Review

Diabetes and Cancer

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Summary

Diabetes and cancer are common conditions, and their co-diagnosis in the same individual is not infrequent. A link between the two conditions has been postulated for almost 80 years, but only in the past decade has significant epidemiological evidence been amassed to suggest that diabetes and cancer are associated, and the link appears causal. Hyperinsulinaemia, adipocytokines, growth factors and epigenetic changes may be implicated in the pathogenesis of cancer amongst patients with diabetes, and recently, diabetes therapies have also been implicated. There is reasonable circumstantial evidence that metformin may decrease the risk of cancer amongst diabetic patients. Much more research is required to elucidate the link between diabetes and cancer, particularly the potential link with diabetes treatments.

Introduction

Burgeoning levels of type 2 diabetes pose a worldwide public health crisis, affecting developed and developing countries. Whilst changes in obesity levels, diet and physical activity on the background of genetic predisposition appear to be fuelling this epidemic, other environmental factors may also be influential in the development of type 2 diabetes.

Whilst it is widely recognized that diabetes is associated with a high risk of cardiovascular and microvascular complications, it is less well recognized that the condition is also associated with an increased risk of cancer, independent of its association with obesity. This association was first alluded to as far back as 1932. This article aims to review the epidemiological evidence suggesting a link between diabetes and cancer, potential pathogenic mechanisms, and the possible links between hyperglycaemic agents and cancer. I also touch on the management of diabetes in patients with cancer.

Is diabetes associated with cancer?

Whilst cancer and diabetes are both common conditions, they are more commonly co-diagnosed in the same individual than would be expected. Many epidemiological studies suggest frequent co-occurrence of diabetes and cancer, a selection of which are tabulated in Table 1. Meta-analyses suggest that a number of cancers, including liver, pancreas, endometrium, colorectal, breast and bladder are associated with diabetes (see below) and diabetes appears to protect against prostate cancer. Lung cancer appears not to be associated with...
<table>
<thead>
<tr>
<th>Study area [reference]</th>
<th>Number of patients</th>
<th>Risk of cancer in diabetic patients—HR (95% CI)</th>
<th>Types of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>97,771 (6,462 cases of cancer)</td>
<td>Men—1.27 (1.14–1.42); women—1.21 (0.99–1.47)</td>
<td>Men—liver, pancreas, kidney; women—stomach, liver</td>
</tr>
<tr>
<td>Korean</td>
<td>1.25 million (26,000 cases of cancer)</td>
<td>Men—1.29 (1.22–1.37); women—1.23 (1.09–1.39)</td>
<td>Men—pancreatic, oesophageal, liver, colorectal; women—liver, cervix</td>
</tr>
<tr>
<td>Sweden</td>
<td>65,000 (2,478 cases of cancer)</td>
<td>Women—1.26 (1.09–1.47); men—no increased risk</td>
<td>Pancreas, endometrium, urinary tract, malignant melanoma</td>
</tr>
<tr>
<td>Canada</td>
<td>3,107 male cancer cases</td>
<td>Pancreatic OR 2.1 (1.0–4.3); liver OR 3.1 (1.1–8.8)</td>
<td>Pancreas, liver</td>
</tr>
<tr>
<td>Sweden</td>
<td>125,126 diabetic admissions</td>
<td>SIR for pancreatic 6.08 and liver 4.25</td>
<td>Aerodigestive tract, oesophageal, colon, rectal, pancreatic, lung, cervical, endometrial, ovarian, kidney cancers</td>
</tr>
<tr>
<td>Denmark</td>
<td>109,581 diabetic admissions</td>
<td>SIR for primary liver cancer in men 4.0 (3.5–4.6), in women 2.1 (1.6–2.7)</td>
<td>Renal, pancreatic, biliary, endometrial</td>
</tr>
<tr>
<td>USA</td>
<td>594,815 diabetic admissions</td>
<td>Overall 0.93 (93–0.94)</td>
<td>Liver, pancreas biliary, colon, rectum Reduced risk of prostate, brain, buccal, lung, oesophagus, larynx</td>
</tr>
<tr>
<td>USA</td>
<td>467,922 men, 588,321 women</td>
<td>Men: colons 1.20 (1.06–1.37), pancreas 1.48 (1.27–1.73), liver 2.19 (1.76–2.72); bladder 1.43 (1.14–1.80); women: colon 1.24 (1.07–1.43), pancreas 1.44 (1.21–1.72), breast 1.27 (1.11–1.45)</td>
<td>Colon, bladder, liver, pancreas, breast</td>
</tr>
<tr>
<td>European</td>
<td>26,460 men, 18,195 women</td>
<td>Cancer mortality in men with previously undiagnosed diabetes—1.13 (1.00–1.28), pre-diabetes—1.27 (1.02–1.57), known diabetes 1.71 (1.35–2.17); cancer mortality in women—undiagnosed diabetes—1.11 (0.94–1.30), pre-diabetes 1.31 (1.00–1.70), known diabetes 1.43 (1.01–2.02)</td>
<td>Men—stomach, colon-rectum, liver; women—liver, pancreas</td>
</tr>
<tr>
<td>New Zealand</td>
<td>46,575 (634 cancer cases)</td>
<td>HbA1c 6–6.9%—1.40 (1.11–1.76)</td>
<td></td>
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diabetes, and data is inconclusive for renal cell cancer and lymphoma.

Specific data for patients with type 1 diabetes and cancer risk is conflicting. A survey of 28,900 British patients with insulin-treated diabetes followed for 520,517 person-years, compared cancer incidence and mortality with national expectations. Relative risks of cancer overall were close to unity, but ovarian cancer risk was highly significantly raised in patients with diabetes diagnosed under age 30 years (mostly thought to be type 1) [standardized incidence ratio (SIR) = 2.14; 95% confidence interval (CI) 1.22–3.48]. Risks of cancer at other major sites were not substantially raised for people with type 1 diabetes. Data from a Swedish cohort study examined cancer incidence among 29,187 patients in Sweden who were hospitalized for type 1 diabetes from 1965 to 1999. 355 incident cases of cancer were observed; corresponding to a 20% increase in overall cancer incidence among type 1 diabetes patients compared to the background age matched population (SIR = 1.2, 95% CI = 1.0–1.3). Patients with type 1 diabetes had elevated risks of cancers of the stomach, cervix and endometrium.

**Does diabetes increase mortality in cancer?**

The diagnosis of diabetes appears to increase mortality amongst patients with cancer. In patients with breast cancer, hazard ratio for 5-year mortality amongst patients with diabetes was 1.39 compared to non diabetic women with breast cancer. Similar results are seen in colorectal cancer; with a 32% increased all cause mortality.

Meta-analysis suggests that diabetes is associated with an increased mortality compared with normoglycemic individuals across all cancer types [hazard ratio (HR) 1.41 (95% CI 1.28–1.55)] particularly in patients with cancers of the endometrium, breast and colorectal. There is evidence that poor glycaemic control can lead to poorer outcomes in cancer therapy. In a retrospective review of 652 patients with type 2 diabetes diagnosed with colonic adenomatous polyps (AP), HbA1c levels were evaluated as an index of glycaemic control over the year that preceded the diagnosis of APs. Amongst patients with poorly controlled diabetes (HbA1c > 7.5%), a significantly increased incidence of right-sided polyps ($P = 0.001$), a greater number of polyps ($P < 0.005$), more advanced polyps and ($P < 0.005$), and a younger age of presentation ($P = 0.001$) was noted.

Pre-operative diagnosis of diabetes appears to increase risk of post-operative mortality for some cancers. In a meta-analysis of 15 reported studies, pre-existing diabetes was associated with increased odds of postoperative mortality across all cancer types, when controlled for confounders and publication bias [odds ratio (OR) = 1.51 (1.13–2.02)], compared with their non-diabetic patients undergoing operative treatment for cancer.

**Which cancers are associated with diabetes?**

**Pancreatic cancer**

Meta-analysis of 36 case–control and cohort studies suggests that the age and sex adjusted odds ratio for the development of pancreatic cancer in people with diabetes was 1.8 (95% CI 1.7–1.9). The fact that this association is stronger for new onset diabetes, suggests that pancreatic cancer is likely to be a diabetogenic state, and hence a suggested ‘reverse causality’. This association has led some to suggest that new onset diabetes should be a reason to screen for pancreatic cancer.

**Colorectal cancer**

A number of cohort studies have shown an increased risk of colorectal cancer in people with diabetes. Meta-analysis of 15 case–control and cohort studies in the USA and in Europe studies of 2,593,935 participants, found that diabetes was associated with an increased risk of colorectal cancer, compared with no diabetes [risk ratio (RR) 1.30, 95% CI 1.20–1.40]. The association did not differ significantly by sex, or by cancer sub-site. Diabetes was positively associated with colorectal cancer mortality.

**Breast cancer**

Meta-analysis of 20 case–control and cohort has shown a statistically significant 20% increased risk of breast cancer (RR 1.20; 95% CI 1.12–1.28).

**Prostate cancer**

The association between diabetes and prostate cancer is controversial, with a number of studies suggesting positive and negative associations. Meta-analysis of 14 studies, between 1971 and 2002 (five case–control studies, nine cohort studies) showed a significant inverse association between diabetes and prostate cancer (RR 0.91, 95% CI 0.86–0.96), which has been confirmed in a subsequent meta-analysis incorporating more studies. This reduction is risk of prostate cancer has been
suggested as due to lower levels of testosterone in men with diabetes.

Liver cancer

Whilst no meta-analysis has yet been published, many studies suggest a link between liver cancer and diabetes, which may be mediated through higher risk of non-alcoholic steatohepatitis, leading to cirrhosis and liver cancer.

Endometrial cancer

Meta-analysis of 16 studies (3 cohort and 13 case–control studies), including 96,003 participants and 7,596 cases of endometrial cancer showed a significantly increased risk of endometrial cancer amongst subjects with diabetes [RR 2.10, 95% CI 1.75–2.53]. A stronger association of type 1 diabetes and endometrial cancer noted (RR 3.15, 95% CI 1.07–9.29).

Bladder cancer

Meta-analysis of 16 studies showed that diabetes was associated with an increased risk of bladder cancer, compared with no diabetes (RR = 1.24, 95% CI 1.08–1.42), suggesting that individuals with diabetes may have a modestly increased risk of bladder cancer.

Renal cancer

A number of epidemiological studies suggest a higher risk of renal cell cancer in people with diabetes, although numbers in these studies are small, and no meta-analysis has as yet been performed.

How might diabetes cause cancer?

Obesity is a common risk factor for diabetes and cancer. Cancers consistently associated with obesity include breast, endometrium, pancreas, oesophageal, renal cell, colorectal and liver. Weight loss may reduce the risk of cancer in obese subjects, although the effect is not marked. Whilst bariatric surgery can reduce or even reverse development of diabetes, the significant weight loss seen with bariatric surgery does not appear to reduce cancer risk so dramatically. The link between diabetes, obesity and cancer may be mediated by insulin and the insulin-like growth factor (IGF) axis.

Insulin and IGF

Insulin is a growth factor, and elevated levels of insulin have been shown to be a risk factor for a number of cancers. Meta-analysis shows excess risks of colorectal, pancreatic and breast cancers associated with higher levels of circulating C-peptide/insulin and with markers of glycaemia. Elevated plasma insulin is also associated with poorer outcomes of cancer and disease recurrence. Insulin itself exerts a mitogenic effect on various tissues including breast cancer cell lines, which are oestrogen receptor positive. In breast cancer, insulin induces aromatase activity and reduces sex hormone binding globulin (SHBG), leading to increased free oestrogen levels, which in turn increases mitogenicity. Interestingly, breast cancer cells appear to have high levels of insulin receptors, compared to normal breast tissue.

Insulin may exert a mitogenic effect through insulin-like growth factor-1 (IGF-1) receptors. Prospective studies have shown that people with circulating IGF-1 have an increased risk of common epithelial cancers such as breast, colon and prostate. A recent large population based survey showed that women with high blood concentrations of IGF-1 are more likely than those with low concentrations to develop breast cancer; women with the highest concentration of IGF-1 were found to have a 28% higher risk of developing breast cancer than women with the lowest concentration [OR 1.28 (95% CI 1.14–1.44)].

Hyperinsulinaemia also results in reduced levels of IGF binding protein-1 (IGFBP-1), thus increasing levels of bioactive IGF-1 (Figure 1).

![Figure 1. The possible link between insulin resistance and breast cancer. SHBG: sex hormone binding globulin; IGF-BP: insulin-like growth factor binding protein; IGF-1: insulin-like growth factor-1.](image-url)
Leptin

Leptin, an adipocytokine, is increased in obesity and in type 2 diabetes independently of body mass index (BMI). Leptin is positively correlated with insulin and C-peptide levels and strongly linked with metabolic syndrome and elevated C-reactive protein (CRP) levels—a sensitive marker of inflammation. Fasting serum leptin, insulin and triglycerides are all elevated in patients with breast cancer compared to controls, even after adjustment for BMI and age. There is some evidence that leptin may be involved in local invasion and metastasis of established solid tumours.

Adiponectin

Adiponectin is also an adipocytokine, whose plasma concentration is inversely associated with BMI. Prospective study has shown that higher levels of baseline adiponectin are associated with 40% reduction in risk of development of type 2 diabetes. Low levels of adiponectin have been shown to be associated with many components of the metabolic syndrome, including hypertension, low high-density lipoprotein (HDL) cholesterol, elevated CRP. A number of epidemiological studies have shown strong inverse relationships between cancer and adiponectin levels. Adiponectin appears to exert an anti-proliferative effect in breast cancer cell lines.

Epigenetic modulation

Low birth weight appears to predispose insulin resistance and diabetes. The thrifty phenotype hypothesis suggests that insulin resistance is an adaptive response to calorie restriction in utero, whilst the thrifty genotype hypothesis suggests that genetic predisposition to insulin resistance provides a survival benefit in calorie poor environments. It is becoming increasingly apparent that epigenetics may be a common path for the interaction between genes and environment. Epigenetic processes are ones that influence gene expression enabling increased or decreased gene expression according to environmental influences. Such processes include DNA methylation, histone modification, chromatin remodelling, non-coding RNAs and microRNAs. There is increasing evidence that cancer development and progression is related to epigenetic dysregulation.

Diet is a key regulator of epigenetic processes, and there is considerable evidence that diet can affect the level of DNA methylation and histone post-translational modulation, by influencing the availability of methyl donors such as folate, choline and methionine. Common signalling pathways may influence both metabolic syndrome and cancer, suggesting a possible common pathogenetic pathway.

Does hyperglycaemic therapy influence cancer risk?

There has been some concern that therapies used for treatment of diabetes may increase the risk of cancer. This may be modulated by their effect of insulin levels. Drugs which increase endogenous insulin levels (sulphonylureas, subcutaneous insulin) have been suggested as increasing cancer risk, whilst drugs that reduce insulin levels and improve insulin sensitivity (biguanides and thiazolidinediones) may reduce cancer risk. There may be a relationship between timing of cancer diagnosis and duration of therapy. If cancer risk is exposure related, one would expect to see a time-related increase in cancer development, and current analyses are focusing upon this issue.

Sulphonylureas

Some studies suggest an increased risk of malignancies in type 2 diabetic patients treated with different sulphonylureas. One case-control study examined 195 diabetic patients aged with incident malignancy and 195 diabetic patients, unaffected by cancer, matched with the corresponding case for age, sex, duration of diabetes, BMI, HbA1c, comorbidity, smoking and alcohol abuse. Exposure to hypoglycaemic drugs during the 10 years preceding cancer was assessed. After adjustment for concomitant therapies, exposure to metformin and gliclazide for more than 36 months was associated with a significant reduction in the risk of cancer [OR 0.28, 95% CI 0.13–0.57, P < 0.001 and 0.40 (0.21–0.57), P= 0.004, respectively]. Conversely, use of glibenclamide for at least 36 months was associated with increased incidence of malignancies [OR 2.62 (1.26–5.42); P= 0.009]. Treatment with insulin, thiazolidinediones, or acarbose, was not associated with significant differences in the incidence of cancer. The same researchers examined this association again, using a retrospective observational cohort study of 568 outpatients with type 2 diabetes treated with either glibenclamide (n = 378) or gliclazide (n = 190). Information on all-cause mortality and on causes of death were obtained, and over a mean follow-up of 5 years, 33 and 11 deaths were observed in the glibenclamide and gliclazide groups, with a yearly mortality rate of 4.3 and 2.2%, respectively (P < 0.05). After adjustment for
potential confounders, including comorbidity, glibenclamide treatment was associated with a significant increase in all-cause mortality (OR 2.1 (1.2–2.7), \( P < 0.05 \)).

A population-based cohort study using administrative databases from Canada compared cancer-related mortality among inception cohorts of metformin users and sulphonylurea monotherapy users.\(^5^3\) A total of 10,309 new users of metformin or sulphonylureas were followed for an average 5 years, and cancer mortality over follow-up was 4.9% (162 of 3340) for sulphonylurea monotherapy users, compared to 3.5% (245 of 6969) of metformin users, and 5.8% (84 of 1443) for subjects who used insulin. Sulphonylurea treated patients had a greater cancer-related mortality compared with the metformin cohort [adjusted HR 1.3 (95% CI 1.1–1.6); \( P = 0.012 \)]. Insulin use was associated with an adjusted HR of cancer-related mortality of 1.9 (95% CI 1.5–2.4; \( P < 0.0001 \)).

In a study of 420 patients with hepatocellular cancer (HCC), compared to 1104 healthy controls, the prevalence of diabetes mellitus was 33.3% in patients with HCC and 10.4% in the control group.\(^5^4\) Examination of therapy in the patients with HCC showed adjusted ORs for HCC of 0.3 (95% CI 0.2–0.6) for metformin therapy, 0.3 (95% CI 0.1–0.7) for thiazolidinedione therapy, 7.1 (95% CI 2.9–16.9) for sulphonylurea use and 1.9 (95% CI 0.8–4.6) for insulin use.

Whilst an association between sulphonylurea use and cancer is plausible, it is unclear whether these studies reflect an increased risk of cancer, or a decreased risk with the use of other agents (e.g. metformin).

**Metformin**

*In vitro* studies of cancer cell lines, shows that metformin can inhibit cancer cell growth and proliferation in a dose dependent manner.\(^5^5\) Metformin has been also shown to inhibit cellular transformation and selectively kill cancer stem cells in four genetically different types of breast cancer.\(^5^6\) The mechanism by which metformin may inhibit carcinogenesis is far from clear, but in epithelial cells, metformin-induced AMP kinase activation has been shown to activate growth inhibitory and protein synthesis pathways. Upstream of AMPK, LKB1 is a tumour suppressor gene, and reduction in its activity is seen in Peutz-Jeghers syndrome, which is characterized by significantly increased risk of cancer. AMPK activation strongly suppresses cell proliferation in both malignant and non-malignant cells, possibly mediated by cell-cycle regulation and protein synthesis inhibition.\(^5^7\)

A number of population based studies suggest that metformin has a protective role in the development of cancers in patients with diabetes. In a large retrospective cohort study of people treated in UK general practices, a total of 62,809 patients were divided into four groups according to whether they received monotherapy with metformin or sulphonylurea, combined therapy, or insulin.\(^5^8\) Insulin users were grouped according to treatment with insulin glargine, long-acting human insulin, biphasic analogue and human biphasic insulin. Results showed that metformin monotherapy carried the lowest risk of cancer; in comparison, the adjusted HR was 1.08 (95% CI 0.96–1.21) for metformin plus sulphonylurea, 1.36 (95% CI 1.19–1.54) for sulphonylurea monotherapy, and 1.42 (95% CI 1.27–1.60) for insulin-based regimens. Adding metformin to insulin reduced progression to cancer (HR 0.54, 95% CI 0.43–0.66). The risk for those on basal human insulin alone vs. insulin glargine alone was 1.24 (95% CI 0.90–1.70). Compared with metformin, insulin therapy increased the risk of colorectal (HR 1.69, 95% CI 1.23–2.33) or pancreatic cancer (HR 4.63, 95% CI 2.64–8.10), but did not influence the risk of breast or prostate cancer.

A nested case control study of 22,000 female users of oral anti-diabetic drugs using the UK-based General Practice Research Database (GPRD), showed 305 cases of incident breast cancer.\(^5^9\) Long-term use of metformin, based on 17 exposed cases and 120 exposed controls, was associated with an adjusted OR of 0.44 (95% CI 0.24–0.82) for developing breast cancer, as compared with no use of metformin.

In a Dutch study, 1353 patients with type 2 diabetes were followed for 10 years, and in patients taking metformin compared with patients not taking metformin at baseline, the adjusted HR for cancer mortality was 0.43 (95% CI 0.23–0.80), and the HR with every increase of 1 g of metformin was 0.58 (95% CI 0.36–0.93).\(^6^0\)

Perhaps the main limitation in all of these population-based studies is the fact that metformin is frequently used early in the condition, and that other drugs are introduced later, perhaps when control has been poorer for some time. It is therefore difficult to conclusively suggest that metformin inhibits cancer in people with diabetes, but results appear highly suggestive. Nevertheless, many researchers suggest that use of metformin as an adjunct to chemotherapy in patients with cancer needs exploration.
Thiazolidinediones

These drugs act as insulin sensitisers by virtue of their effect on peroxisome proliferator activated receptor-γ (PPARγ). In vitro studies suggest some anti-cancer properties of these agents, such as inhibiting cell growth, inducing apoptosis and cell differentiation, although some animal data suggests PPAR agonists may potentiate tumourigenesis. Meta-analysis of studies of rosiglitazone shows no effect of the drug on incidence of cancer, although exposure to these drugs was for a relatively short time. One epidemiological study of 1003 patients on thiazolidinediones suggests an increased risk of cancer with these agents (OR 1.59).

Incretin therapies

Glucagon-like peptide-1 (GLP-1) is secreted from the small intestine in response to nutrient, and has the effect of improving insulin secretion and delaying gastric emptying. Dipeptidyl-peptidase-4 (DPP-4) inactivates GLP-1. GLP-1 analogues (exenatide and lixisenatide) and DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin) enhance GLP-1 effects, improving glycaemia and reducing weight. In animal studies, lixisenatide has been found to increase risk of medullary thyroid cancer, and sitagliptin has been shown to induce pancreatic ductal hyperplasia. Recently GLP-1 therapies have also been shown to induce pancreatic ductal hyperplasia, hence possibly increasing risk of chronic pancreatitis and therefore pancreatic cancer.

Insulin

Around a quarter of all patients with diabetes use some form of insulin therapy, and the use of insulin is thus growing. Subcutaneous insulin results in high levels of systemic insulin, increasing the risk of adverse effects, and perhaps increasing the risk of cancer associated with hyperinsulinaemia. Several observational studies suggest a possible association of insulin therapy with increased risk of developing cancer. In particular, insulin analogues such as insulin glargine have been implicated, possibly due to its higher binding affinity for the IGF-1 receptor. Evidence for insulin-induced mitogenicity is, however, highly controversial.

A number of recent studies have been recently published around the issue of insulin glargine and risk of cancer. Examination of a German cohort of 127,031 patients followed for 1.63 years showed a positive association between cancer incidence and insulin dose for all insulin types. After adjusting for dose, a dose-dependent increase in cancer risk was found for treatment with glargine compared with human insulin [HR 1.09 (95% CI 1.00–1.19), for a daily dose of 10 IU and 1.19 (95% CI 1.10–1.30) for a daily dose of 30 IU, and 1.31 (95% CI 1.20–1.42) for a daily dose of 50 IU]. No increased risk was found for insulins aspart or lispro.

Evidence for insulin-induced mitogenicity is, however, highly controversial. In contrast to the observational studies above, randomized controlled trials of long duration (>5 years) therapy with insulin glargine has not shown an excess in cancer risk or mortality. In addition, a UK general practice database cohort study did not show a link between insulin glargine and cancer. A further nested case–control study of 1340 insulin-treated diabetic patients followed up for a median of 75.9 months, 112 cases of incident cancer were compared with 370 matched controls. A significantly higher mean daily dose of glargine was observed in cases than in controls, and incident cancer was associated higher doses. No association between incident cancer and insulin doses was found for human insulin or other analogues.

The observational studies above linking excess cancer risk to insulin glargine have not fully controlled for potential confounders such as duration of diabetes, BMI, insulin dose and duration, degree of glucose control and use of other therapies. Whilst the data is inconclusive, current evidence suggests that the benefits of insulin in terms of reducing micro- and macrovascular complications of diabetes outweigh the risks at this time, but there is a clear need for further research in the area, and larger studies are under way.
Do cancer therapies cause or exacerbate diabetes?

Many cancer chemotherapeutic regimes include steroid therapy, which may induce diabetes or exacerbate pre-existing diabetes. Steroids may also be used in cancer patients to treat allergy or inflammation induced by chemotherapy, or alleviate fatigue and anorexia. It is also clear, however, that some non-steroid cancer therapies may cause hyperglycaemia.

Androgen-deprivation therapy (ADT) with luteinizing hormone releasing hormone agonists for prostate cancer has been linked with increased risk for the development of type 2 diabetes, possibly due to loss of insulin sensitivity, and other hormonal effects such as loss of bone mass, changes in body composition and a deterioration of arterial stiffness. In a retrospective review, 11.3% of 396 patients with prostate cancer treated with ADT developed new onset diabetes, over 5 years follow-up. Longitudinal study of over 70,000 patients on ADT has shown a 44% increased risk for developing diabetes. Use of ADT in 29 patients with pre-existing type 2 diabetes and prostate cancer led substantial worsening of glycaemic control over 2 years, along with increased insulin requirements.

Chemoradiation may also induce hyperglycaemia. A study of 91 non-diabetic patients with locally advanced head and neck cancer who underwent chemoradiation showed a significant increase in fasting glucose during chemoradiation. Platinum based chemotherapy (e.g. cisplatin), mTOR kinase inhibitors (e.g. everolimus) and ABL kinase inhibitors (e.g. nilotinib) have all been associated with hyperglycaemia.

Managing diabetes in patients with cancer

Managing pre-existing or newly diagnosed diabetes in patients with cancer can be challenging. Many patients undergoing treatment are unwell with multiple co-morbidities, and are battling with significant side effects of their cancer therapy. Nevertheless, it appears to be important to manage hyperglycaemia in patients with cancer, as poorer glycaemic control appears to increase morbidity and mortality in patients with cancer. In vitro studies also show that hyperglycaemia reduces efficacy of chemotherapy on breast cancer cells.

The cyclical nature of chemotherapy often needs a flexible approach to hyperglycaemia management. There is little published data in this area, but in the authors’ experience, use of intermittent oral or injectable hyperglycaemic therapy is not infrequently required. Careful self monitoring of glucose levels, close liaison with the diabetes clinical team and education of the patient to anticipate commencement or escalation of therapy during chemotherapy is helpful in managing such patients. Equally, withdrawal of frequent monitoring or hyperglycaemic therapy in patients with advanced or incurable cancer undergoing palliative care can be challenging, although can come as a relief to patients and their families in later stages of life.

Conclusions and further research

There is growing epidemiological evidence from observational studies that diabetes is associated with an increased risk of a number of cancer types, and a reduced risk of prostate cancer. There is also growing evidence that degree of hyperglycaemia, and treatment modalities for hyperglycaemia influence the risk of cancer. Whilst the epidemiological evidence for the above is strong, it is far from conclusive. A definitive answer would be given from long-term prospective population based studies looking at cancer subtypes and treatment modalities for diabetes. Furthermore, long-term follow-up of randomized controlled trials of hyperglycaemic therapies is required to ensure that such therapies are not associated with increased risk of cancer.

Recently the American and European Diabetes and Oncology associations published a consensus report on diabetes and cancer. They agreed that most observational evidence suggests a strong link between diabetes and breast, colorectal, endometrial, liver and pancreatic cancers, and that the likely pathogenesis of the link is due to hyperinsulinaemia, hyperglycaemia, inflammation and possibly diabetes therapies. They concluded that metformin is likely to decrease and insulin likely to increase the risk of cancer in diabetic patients, although they suggested that cancer risk could not be a major factor currently in choosing between available therapies for diabetes. Finally, they suggested that significant research funding should be directed into this important area, as basic science research into the link may prove fruitful for treatment and prevention of both diabetes and related cancers.

Conflict of interest: None declared.

References


34. Pisani P. Hyper-insulinaemia and cancer, meta-analyses of epidemiological studies. *Arch Physiol Biochem* 2008; **114**:63–70.


