Diabetes and cancer: two diseases with obesity as a common risk factor

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There is a growing body of evidence to support a connection between diabetes (predominantly type 2), obesity and cancer. Multiple meta-analyses of epidemiological data show that people with diabetes are at increased risk of developing many different types of cancers, along with an increased risk of cancer mortality. Several pathophysiological mechanisms for this relationship have been postulated, including insulin resistance and hyperinsulinaemia, enhanced inflammatory processes, dysregulation of sex hormone production and hyperglycaemia. In addition to these potential mechanisms, a number of common risk factors, including obesity, may be behind the association between diabetes and cancer. Indeed, obesity is associated with an increased risk of cancer and diabetes. Abdominal adiposity has been shown to play a role in creating a systemic pro-inflammatory environment, which could result in the development of both diabetes and cancer. Here, we examine the relationship between diabetes, obesity and cancer, and investigate the potential underlying causes of increased cancer risk in individuals with diabetes. Current treatment recommendations for reducing the overall disease burden are also explored and possible areas for future research are considered.

Keywords: antidiabetic drug, diabetes complications, diabetes mellitus, type 2 diabetes

Introduction

Worldwide, cancer is the 2nd and diabetes the 12th leading cause of death [1]. There is a growing evidence base to support a connection between diabetes, predominantly type 2 diabetes mellitus (T2DM), and certain types of cancer [2]. In fact, meta-analyses have revealed T2DM to be an independent risk factor for the development of several different types of cancer [2]. As yet, few studies have explored a relationship between type 1 diabetes mellitus and cancer [3].

The connection between diabetes and cancer was first postulated more than 75 years ago. Although these two conditions share many common risk factors, there continues to be a lack of understanding of the biological relationship between them, [2,3] which poses a challenge for patient care. Current thinking suggests that the relationship may not be entirely attributable to the direct effects of diabetes, such as hyperglycaemia [3,4]. Instead, it may be that diabetes is a marker of altered cancer risk due to changes in underlying metabolic conditions, such as insulin resistance or hyperinsulinaemia [3].

Alternatively, the relationship may be due, wholly or in part, to the sharing of common predisposing conditions, such as obesity [3]. In fact, both obesity and T2DM have been shown to be independently associated with an increased risk of cancer and mortality [5].

Unravelling the pathology behind the link between these diseases may be further complicated by the multidrug therapy required for the treatment of diabetes, obesity and cancer [3]. There is even some evidence to suggest that established glucose-lowering therapies play a role in cancer development. Several observational studies in people with diabetes have shown a higher risk of cancer or cancer death with certain antidiabetic agents [6–9]. However, some of the evidence is conflicting, and the non-randomized nature of these studies means that potential for selection bias to confound results is high. Furthermore, the relative contributions of increased risk due to one diabetes medication versus another cannot be determined from these studies [3]. Recently presented prospective trials and database analyses have reported no increase in cancer with insulin glargine treatment [10–14].

Individually, the health consequences and economic costs of diabetes, obesity and cancer are high, and their impact is exacerbated when all three conditions co-present. In order to address some of the mounting concerns regarding the management of diabetes and cancer, the American Diabetes Association and American Cancer Society have published a consensus report providing recommendations for clinical care [3].
The aims of this review article are to further examine the association between diabetes, obesity and cancer, discuss the potential underlying causes and explore the current treatment recommendations for reducing the overall burden associated with these conditions.

### Evidence for a Link between Diabetes and Certain Types of Cancer

Numerous clinical studies have suggested a link between diabetes and a variety of different types of cancer, including breast [15], colorectal [16,17], endometrial [18,19] and pancreatic [20–22] cancers. Multiple meta-analyses of case–control and prospective cohort studies have confirmed that T2DM is an independent risk factor for the development of several different types of cancer including non-Hodgkin lymphoma (NHL) and cancers of the bladder, breast, colorectum, endometrium, liver and pancreas (Table 1) [23–35,38]. Larsson et al. conducted three separate meta-analyses of case–control and cohort studies investigating the risk of breast, bladder and colorectal cancers in association with T2DM (Table 1). The authors reported modest associations between T2DM and both breast and bladder cancers, while a strong association was reported for colorectal cancer and associated mortality (relative risk 1.26, 95% confidence interval [CI] 1.05, 1.50) [23,24,26]. A positive association between T2DM and NHL has also been observed (Table 1) [30,31]. As altered immune function and chronic inflammation are implicated in the pathogenesis of NHL, the underlying low-grade, systemic, pro-inflammatory state associated with T2DM may, therefore, contribute to the pathogenesis of NHL [31].

Owing to the co-morbidities frequently associated with diabetes, as well as the complex nature of T2DM itself, each site-specific cancer needs to be evaluated individually in order to differentiate between risk factors associated with cancers in general and those that influence specific cancers [36].

### Diabetes and Prostate Cancer

A negative association has been shown between diabetes and the risk of prostate cancer (Table 1), with this negative association increasing with increased duration of diabetes [34,35,37–39]. This reduced risk was not seen in all studies, with a significant increased risk for prostate cancer seen in Asian populations [38,39]. It has been suggested that the increased risk in these populations could be the result of different distributions of AR, SRD5A2 and VDR genotypes which are associated with prostate cancer risk [38,40]. Two large cohort studies found that men with diabetes are at higher risk for advanced prostate cancer at diagnosis [41,42]. This higher risk could be related to the lower levels of testosterone and prostate-specific antigen (PSA) observed in men with diabetes, which results in a lower likelihood of PSA screening identifying early prostate cancer [41,43]. Levels of PSA have been shown to be lowest in people who have had diabetes for a long duration; however, studies have not found a clear link between decreased PSA and decreased prostate cancer risk [44]. The mechanism by which diabetes causes reduced PSA levels is also currently unknown [39].

Another possible biological mechanism linking diabetes with a protective effect on prostate cancer risk is the link between hyperinsulinaemia and prostate cell growth. Insulin is positively associated with the growth of both normal and cancerous prostate cells, and, therefore, decreased insulin production, as observed in people with diabetes, may inhibit cell growth [34]. Hypoinsulinaemia may also suppress prostate cancer indirectly. Hypoinsulinaemia triggers a cascade of events which leads to an increase in the level of plasma insulin-like growth factor (IGF)-1 [44]. Elevated IGF-1 levels are seen as a risk factor for prostate cancer [45,46]. However, in a study looking at the association between prostate cancer and diet, it was found that long-term exposure to a diet high in refined carbohydrates (i.e. one which elicits a high insulin response and reduced IGF-1 levels) did not decrease prostate cancer incidence as one would have expected, suggesting that other biological mechanisms may potentially be at work [47]. Owing to their critical role in both prostate growth and prostate cancer development, and the fact that their levels differ according to diabetes status, androgens have been suggested to play a role in driving this inverse relationship between diabetes and prostate cancer [39]. A pooled analysis that included 18 studies (3886 men with prostate cancer and

### Table 1. Diabetes as a risk factor for cancer (summary of meta-analyses) [2].

| Authors            | Tumour type | Case–control studies | Prospective cohort studies |
|--------------------|-------------|-----------------------|----------------------------|
|                    | n | RR (95% CI)   | n | RR (95% CI)   |
| Larsson et al. [23] | Bladder 7 | 1.4 (1.0–1.8) | 3 | 1.4 (1.2–1.7) |
| Larsson et al. [24] | Breast 5 | 1.2 (1.1–1.3) | 15 | 1.2 (1.1–1.3) |
| Wolf et al. [25]   | Breast 4 | 1.1 (1.0–1.3) | 6 | 1.3 (1.2–1.3) |
| Larsson et al. [26] | Colorectal 6 | 1.4 (1.2–1.5) | 9 | 1.3 (1.2–1.4) |
| Friberg et al. [28] | Endometrium 13 | 2.2 (1.8–2.7) | 3 | 1.6 (1.2–2.2) |
| El-Serag et al. [29] | HCC 13 | 2.5 (1.9–3.2) | 12 | 2.5 (1.9–3.2) |
| Chao et al. [31]   | NHL 10 | 1.2 (1.0–1.4) | 3 | 1.8 (1.3–2.5) |
| Mirri et al. [30]  | NHL 11 | 1.1 (0.9–1.3) | 5 | 1.4 (1.1–1.9) |
| Everhart et al. [32] | Pancreatic 11 | 1.8 (1.1–2.7) | 9 | 2.6 (1.6–4.1) |
| Huxley et al. [33] | Pancreatic 17 | 1.9 (1.5–2.5) | 19 | 1.7 (1.6–1.9) |
| Bonovas et al. [34] | Prostate 5 | 0.9 (0.7–1.2) | 9 | 0.9 (0.9–1.0) |
| Kasper et al. [35] | Prostate 7 | 0.9 (0.7–1.1) | 12 | 0.8 (0.7–0.9) |
| Bansal et al. [38] | Prostate 16 | 0.85 (0.74–0.96) | 29 | 0.87 (0.80–0.94) |

CI, confidence interval; HCC, hepatocellular carcinoma; NHL, non-Hodgkin lymphoma; RR, pooled relative risk. Adapted with permission from Ref. [2].
6438 controls) found no association between risk of prostate cancer and serum concentrations of eight sex hormones (including testosterone, dihydrotestosterone and estradiol), whilst there was a modest inverse association with sex hormone-binding globulin (p = 0.01) [48]. Kasper et al. found that both testosterone and sex hormone-binding globulin levels increased significantly with increasing diabetes duration (p = 0.02 and 0.002, respectively) [49]. At the same time, they observed that the ratio of testosterone to sex hormone-binding globulin decreased, which suggested that levels of bioavailable testosterone were reduced [49]. Low levels of testosterone and sex hormone-binding globulin have also been shown to be predictive factors for the development of both metabolic syndrome and diabetes in middle-aged men [39,50]. This suggests that the interaction between diabetes, sex-hormone levels and prostate cancer is complex, with increased levels of sex hormone-binding globulin being a possible factor in the reduced incidence of prostate cancer.

Diabetes and Pancreatic Cancer

There is an added level of complexity in the association between diabetes and pancreatic cancer, as both diseases involve the same organ, with studies suggesting that diabetes could be both an early manifestation of pancreatic cancer and an aetiological factor [51–53]. This is because pancreatic cancer can cause abnormal glucose metabolism, and risk factors for pancreatic cancer include obesity, chronic pancreatitis and diabetes [54]. A meta-analysis of cohort studies by Ben et al. found that diabetes is associated with a mean 1.94 greater risk of pancreatic cancer [52]. The highest risk of pancreatic cancer (relative risk: 5.38; 95% CI: 3.49–8.30, p < 0.001) was observed in those diagnosed with diabetes for less than a year, supporting the hypothesis that diabetes, at least in some cases, may be induced by pancreatic cancer and thus may be an early indicator of this cancer. The relative risk of developing pancreatic cancer decreased in those people who had been diagnosed with diabetes for at least 10 years (relative risk: 1.47; 95% CI: 0.94–2.31) [52]. Likewise, results from two case–control studies including 688 pancreatic cancer cases and 2204 controls reported that the odds ratios (ORs) for pancreatic cancer were more pronounced among those diagnosed with diabetes in the previous 2 years (OR: 5.17; 95% CI: 2.71–9.87) than among those with diabetes diagnosed more than 2 years ago (OR: 2.35; 95% CI: 1.70–3.26). The ORs remained significantly elevated 2–4 years and 5–9 years since diagnosis of diabetes, after which a non-significant 20% increased risk for pancreatic cancer was observed [55].

In addition, it has been found that individuals who develop exocrine pancreatic cancer tend to have moderate increases in glycated haemoglobin (HbA1c) levels, relatively independent of obesity and insulin resistance [56]. Indeed, a study by Pan nala et al. reported that 85% of people with pancreatic cancer have either impaired glucose tolerance or diabetes mellitus [51]. Furthermore, diabetes was predominantly of new onset (<2-year duration) in 74% of those with diabetes and pancreatic cancer. Following pancreaticoduodenectomy, diabetes resolved in 57% of patients with new-onset diabetes, whilst its prevalence was unchanged in those with long-standing diabetes [51,57]. A retrospective analysis of clinical data from 331 pancreatic patients by Huang et al. confirmed these findings. Results from this analysis reported that most patients were diagnosed with diabetes mellitus either concomitantly with pancreatic cancer (39.0%) or within 6 months before cancer diagnosis (6.9%); only 7.9% of patients were diagnosed with diabetes 24 months before pancreatic cancer diagnosis [53]. Because subjects with new-onset diabetes over the age of 50 years have an eightfold increased risk of pancreatic cancer, new-onset diabetes with weight loss may be a potential indicator of pancreatic cancer in this population [57]. It has been suggested that diabetes secondary to benign or malignant disease of the exocrine pancreas is type 3c (secondary) diabetes to distinguish its aetiology [54].

Diabetes and Cancer Mortality

Mortality rates in diabetes, obesity and cancer populations are high, with both T2DM and obesity being independently associated with an increased risk of cancer-related mortality [5,58–64]. Evidence from a large, prospective, US cohort has shown diabetes to be an independent predictor of mortality associated with cancer of the colon and the pancreas in both men and women, with breast cancer in women, and with cancer of the liver and bladder in men [58]. Furthermore, a meta-analysis of 23 studies has shown that preexisting diabetes may be a mortality risk factor [hazard ratio (HR): 1.41; 95% CI: 1.28–1.55] in people with newly diagnosed cancer compared with normoglycaemic individuals across all types of cancer [61]. In particular, a significant increase in mortality risk was observed for endometrial, breast and colorectal cancers [2,61]. A recent analysis of 17 cohorts involved in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study has further corroborated an increased cancer risk in people with diabetes, with differences in cancer risk observed between men and women [60] (Table 2).

The Health, Eating, Activity, and Lifestyle (HEAL) study of women diagnosed with stage I-IIIA breast cancer found that increasing insulin resistance and beta-cell dysfunction were associated with reduced breast cancer survival (HR: 1.12; 95% CI: 1.05–1.20) and reduced all-cause survival (HR: 1.09; 95% CI: 1.02–1.15) [65]. In a study of people with early-stage breast cancer, the risk of all-cause mortality was found to be twice as high in women with HbA1c ≥ 7% (≥53 mmol/mol) compared with women with HbA1c < 6.5% (<47.5 mmol/mol; HR: 2.35; 95% CI: 1.56–3.54) [66]. Interestingly, another study has linked current tamoxifen therapy with an increased incidence of diabetes in older breast cancer survivors, suggesting that tamoxifen treatment exacerbates an underlying risk of diabetes in susceptible women [67].

There are a number of possible reasons for this elevated mortality. These include presentation of more advanced disease at diagnosis in people with diabetes [68], which may be compounded by increased tumour cell proliferation and metastases in a physiological environment of hyperinsulinaemia and hyperglycaemia [69]. Owing to screening issues with diabetes, cancer is often not diagnosed as early in people with diabetes as in those without diabetes; for example, women with diabetes were less likely to undergo...
Table 2. Cancer mortality in men and women with diabetes [60].

| Type of cancer       | Men          | Women         |
|----------------------|--------------|---------------|
| All cancer           | 8.52         | 5.04          |
| HR (95% CI)          | 1.44 (1.21–1.70) | 1.35 (1.08–1.68) |
| Stomach              | 1.74         | 0.24          |
| Mortality            | 1.84 (1.25–2.71) | 0.48 (0.19–1.21) |
| Liver                |              |               |
| Mortality            | 0.73         | 0.43          |
| HR (95% CI)          | 5.16 (2.56–10.41) | 6.37 (2.18–18.62) |
| Pancreas             | 0.77         | 0.62          |
| Mortality            | 1.67 (0.94–2.97) | 2.13 (1.09–4.16) |
| Bronchus/lung        | 1.21         | 0.52          |
| Mortality            | 0.88 (0.58–1.35) | 0.93 (0.48–1.81) |
| Prostate             | 1.31         | —             |
| Mortality            | 1.30 (0.84–2.01) | —             |
| Breast               | —            | 0.81          |
| Mortality            | —            | 1.65 (0.93–2.93) |
| Kidney/bladder       | 0.53         | 0.33          |
| Mortality            | 1.20 (0.61–2.37) | 1.97 (0.75–5.15) |

Data for all-cause diabetes expressed as per 1000 person-years; HR adjusted for study cohort, age, body mass index, systolic blood pressure, cholesterol and smoking status. CI, confidence interval; HR, hazard ratio.

Adapted with permission from Ref [60], Table 3.

mammography or colorectal screening, and diabetes increased the likelihood of a breast cancer diagnosis at a late stage of malignancy by 19% [70,71]. Also, obese women are reported to have lower breast and cervical cancer screening rates [63,72]. Alternatively, the presence of cancer may result in suboptimal treatment of diabetes and diabetes-related co-morbidities [61], while a diabetes diagnosis and/or diabetes-related co-morbidities could influence the selection of cancer treatment. Analysis of registry data from 58 498 people with cancer in The Netherlands showed a general trend towards less aggressive cancer treatment in people with diabetes (n = 5555) than in those without diabetes (n = 52 943; p < 0.05) [62]. There is also some evidence to suggest that people with diabetes may be less responsive to chemotherapy than people without diabetes [73]. Lastly, individuals with diabetes are more likely to have a cancer recurrence [74] and to have an increased risk of complications (e.g. infections) resulting in poorer outcome [75]. Mortality risk has also been observed to increase in postoperative cancer patients who also have diabetes [76].

Biological Link between Diabetes and Cancer

Several diabetes-related pathophysiological mechanisms, including hyperinsulinaemia, hyperglycaemia and inflammation, have been implicated in increasing cancer risk via their influence on neoplastic processes (figure 1) [4].

Insulin resistance, hyperinsulinaemia (either endogenous due to insulin resistance or exogenous due to administered insulin or insulin secretagogues) and elevated levels of IGF-1 reduce apoptosis and increase cell proliferation in target cells, leading to tumour development [36,77–79]. Insulin itself is also known to have mitogenic properties [80], and, in particular, both the liver and the pancreas are exposed to a high level of endogenously produced insulin.

The effects of insulin and hyperinsulinaemia on tumorigenesis are thought to be mediated by the insulin receptor, which is expressed in both normal tissues and tumours [81,82]. Activation of insulin receptor signalling pathways leads to proliferative and antiapoptotic events [82]. Dysregulation of these signalling pathways during insulin resistance and hyperinsulinaemia can result in enhanced cell proliferation [83], and in cancer cells, this could enhance disease progression. IGF-1 and its receptor have also been implicated in the development of cancer by activating pathways of cell survival and proliferation [84]. Insulin inhibits the production of IGF binding protein (IGFBP)-1 (and possibly IGFBP-2), leading to an increase in the levels of ‘free’ IGF-1, that is, the active form of the growth factor [85]. This ‘free’ form of IGF-1 is then available to bind with IGF-1 receptors, which, like insulin receptors, are expressed in high numbers by cancer tissues [86]. This binding initiates a signalling pathway within the cancer cells which favours tumour growth, activating mitogenesis and inhibiting apoptosis [87].

Production of the sex hormone oestrogen can also be modulated by insulin and hyperinsulinaemia, and this is thought to play a role in tumorigenesis [2]. Indeed, it has been postulated that several mechanisms may underlie the association between breast cancer and diabetes, including activation of the insulin pathway, activation of the IGF pathway and altered regulation of sex hormones [88].

The production of pro-inflammatory cytokines, such as interleukin (IL)-6 and tumour necrosis factor (TNF)-α, is
also thought to mediate an increase in the dysregulation of metabolic pathways leading to insulin resistance, which in turn leads to an increase in insulin levels, thus further increasing the inflammatory response [89]. This is important because adipose tissue is regarded as a paracrine organ that secretes pro-inflammatory mediators [90]. Diabetes is usually associated with a low-grade pro-inflammatory state, and this could be a key factor in encouraging tumorigenesis [91].

Elevated fasting serum glucose levels have been shown to be an independent risk factor for certain cancers, and the risk increases with rising glucose levels, as does cancer-related mortality [92]. Hyperglycaemia has been shown to confer resistance to chemotherapy on breast cancer cells, as well as reduced overall survival [93,94], but appears to confer no growth advantage; given the molecular heterogeneity of cancer cells, a possible growth advantage of hyperglycaemia should not be ruled out [4]. A study by Turturro et al. in the MDA-MB-231 cell line showed that the expression of the oxidative stress gene TXNIP is regulated by glucose level which in turn regulates reactive oxygen species levels, which can stimulate mitogenesis of cancer cells [95]. Overall, however, the data suggest that insulin receptor activation is more integral to the development of cancer than hyperglycaemia [3].

### Links between Cancer Chemotherapy and Hyperglycaemia/Diabetes

Hyperglycaemia may impact on the outcome of chemotherapy for cancer [95–98]. Experiments have shown that glucose increases the cytotoxicity of 5-fluorouracil [99], with a case series in seven people with diabetes suggesting that the degree of toxicity was directly related to the severity of hyperglycaemia [97]. In vitro studies involving breast cancer cell lines have shown that hyperglycaemia directly impacts these cells [95,96]. Results from a study that investigated the effect of hyperglycaemia on the cytotoxic effects of carboplatin and 5-fluorouracil in MCF-7 cells reported that a hyperglycaemic state increased the toxicity of the drugs by approximately 30% and reduced their IC₅₀ by 1.5- and 1.3-fold, respectively [96]. This increased cytotoxicity was seen to be potentiated by reduced P-glycoprotein expression, and possibly by increased reactive oxygen species levels. An explanation for this is that the reduced P-glycoprotein level increases accumulation and retention of the chemotherapeutic agent [96]. Cancer chemotherapy may also result in hyperglycaemia, with drug-induced diabetes having been reported following treatment with a number of agents including 5-fluorouracil [100], glucocorticoids [101], androgen-deprivation therapy [41] and carboplatin/paclitaxel [102]. These drugs may also worsen preexisting diabetes [103].

#### Biological Link between Obesity and Cancer

Clinical Studies

Obesity is a major confounding factor in studies of diabetes and cancer as the risk of developing T2DM increases with growing body mass [104]. Clinical evidence has shown that increased measures of obesity, such as body mass index (BMI) and waist circumference, are associated with increased prevalence of certain cancers, such as pancreatic and prostate cancers (Table 3) [105–109]. The European Prospective Investigation into Cancer and Nutrition (EPIC; ∼520000 participants) has shown a link between increasing grades (magnitudes) of obesity

### Table 3. Risk ratio for cancer per 5 kg/m² higher body mass index [109].

| Cancer type                  | Men (RR [95% CI]) | Women (RR [95% CI]) | Suggested causal mechanism                     |
|------------------------------|-------------------|---------------------|------------------------------------------------|
| Oesophageal adenocarcinoma   | 1.52 (1.33–1.74)* | 1.51 (1.31–1.74)*   | Reflux oesophagitis and chronic irritation      |
| Thyroid                      | 1.33 (1.04–1.70)† | 1.14 (1.06–1.23)‡   | Unknown                                        |
| Colon                        | 1.24 (1.20–1.28)* | 1.09 (1.05–1.13)*   | Insulin                                        |
| Renal                        | 1.24 (1.15–1.34)* | 1.34 (1.25–1.43)*   | Hypertension is one factor                     |
| Liver                        | 1.24 (0.95–1.62)  | 1.07 (0.55–2.08)    | Fatty liver cirrhosis                         |
| Malignant melanoma           | 1.17 (1.05–1.30)‡ | 0.69 (0.92–1.01)    | Unknown                                        |
| Multiple myeloma             | 1.11 (1.05–1.18)* | 1.11 (1.07–1.15)*   | Inflammatory pathways—IL-6                    |
| Rectum                       | 1.09 (1.06–1.12)* | 1.02 (1.00–1.05)    | Unknown                                        |
| Gallbladder                  | 1.09 (0.99–1.21)  | 1.59 (1.02–2.47)†   | Chronic secretion—gallstones and irritation    |
| Leukemia                     | 1.08 (1.02–1.14)‡ | 1.17 (1.04–1.32)‡   | Unknown                                        |
| Pancreas                     | 1.07 (0.93–1.23)  | 1.12 (1.02–1.22)‡   | Possibly insulin pathways                     |
| Non-Hodgkin’s lymphoma       | 1.06 (1.03–1.09)* | 1.07 (1.00–1.14)    | Inflammatory pathways—IL-6                    |
| Prostate*                    | 1.03 (1.00–1.07)  | —                   | Unknown                                        |
| Lung                         | 0.76 (0.70–0.83)* | 0.80 (0.66–0.97)‡   | People who smoke are more likely to be lean leading to bias and this cancer is caused by smoking |
| Oesophageal squamous         | 0.71 (0.60–0.85)* | 0.57 (0.47–0.69)*   | People who smoke are more likely to be lean leading to bias and this cancer is caused by smoking |
| Endometrium                  | —                 | 1.59 (1.50–1.68)*   | Endogenous oestrogen                           |
| Breast (postmenopausal)      | —                 | 1.12 (1.08–1.16)†   | Endogenous oestrogen                           |
| Breast (premenopausal)       | —                 | 0.92 (0.88–0.97)†   | Irregular menstrual cycles, hormones           |

RR, risk ratio; CI, confidence interval.

* Biased to null because this includes predominantly low-grade lesions.

Adapted with permission from Ref. [109] Tables 1 and 2.
and certain cancers [110–113]. Studies also suggest that obesity can lead to inferior treatment outcomes and a poorer response to treatment, both chemo- and radiotherapy [114–116].

Body fat distribution can also be a marker of future risk, with abdominal adiposity being a potential mechanism of cancer development owing to increased levels of free fatty acids and cytokines, leading to insulin resistance and increased IGF availability [117]. It has been reported that, after adjustment for BMI, there is an almost linear association between waist circumference and risk of death from colon cancer [64]. Mortality risk has also been observed to increase in obese individuals with T2DM [118]. Hormones are involved in the pathogenesis of obesity as well as in that of T2DM and cancer, as outlined previously. Elevated levels of endogenous oestrogen are thought to be linked to insulin resistance and hyperinsulinaemia as a direct result of inhibition of insulin receptor function [119].

Observations of increased risk of premenopausal breast cancer in obese individuals have been linked to altered regulation of inflammatory mediators and adipokine levels [120].

Mechanism of Action
Several mechanisms have been proposed for obesity-induced cancers, including abnormalities in adipokine secretion, including hyperleptinaemia, by central adipose tissue, which plays a role in various stages of obesity-induced carcinogenesis [121–124]. Diet is one of the main determinants of a person’s body composition and plays an important role in obesity [122]. The chronic state of over-nutrition associated with obesity may also be a factor, leading to the production of reactive oxygen species, which stimulate cancer cell mitogenesis [125]. There is also the possibility that carcinogenic compounds within foods consumed could have more of an effect owing to the increased diet [122]. Additionally, the inflammatory effects on the body that obesity causes may promote cancer progression and survival [126]. Systemic inflammatory responses, such as increased production of TNF-α, IL-6, IL-1, C-reactive protein, plasminogen activator inhibitor-1 and fibrinogen, and tissue-specific hormone activity mediated through the activation of nuclear factor kappa-light-chain-enhancer of activated B cells and peroxisome proliferator-activated receptor gamma pathways appear to be mechanistically linked with obesity [127]. Weight loss has been shown to lead to a decrease in the production of these inflammatory markers [128]. Other health issues related to obesity can also result in higher risk of cancer, for example, the increased incidence of gastro-oesophageal reflux and Barrett’s oesophagus in obese people increases the risk for oesophageal adenocarcinoma [109,122].

Obese people have also been shown to have poorer outcomes from treatment. For example, obese people undergoing surgical resection for colorectal cancer have been reported to have significantly longer operating times for laparoscopic surgery, as well as a greater likelihood of conversion from laparoscopic to open surgery [129–133]. In some instances, the effectiveness of radiotherapy is reduced as there can be difficulties positioning obese patients and adjusting the volume of radiation needed for treatment [114,116]. Many chemotherapeutic agents have a narrow therapeutic index, which can result in very obese people being underdosed owing to concerns that the large doses that are calculated based upon body weight will cause excess toxicity [109]. However, studies have not shown an increase in chemotherapy-related toxicity in obese people treated at full intensity, suggesting that obese individuals are underdosed, thereby reducing the efficacy of the chemotherapy [109,115,134]. Therefore, optimal dosing strategies for chemotherapeutic agents in obese people with cancer need to be defined [109].

Current Diabetes Treatments May Play a Role in Cancer Development
Current diabetes treatments have been implicated in the development of cancer. Consequently, cancer risk may now play a part in the risk–benefit analysis that a physician undertakes when prescribing diabetes medication. The potential increased risk of cancer associated with diabetes medications may be a result of direct or indirect effects on insulin resistance and levels of circulating insulin or other mechanisms [135–138].

Metformin
Metformin, the most commonly used therapy in people with T2DM [139], may have a protective effect against cancer, possibly because of a reduction in glucose and insulin levels or other mechanisms including the effects on adenosine monophosphate-activated protein kinase (AMPK) signalling pathways [8,140–143]. In preclinical studies, metformin has been shown to inhibit cell proliferation, reduce colony formation and cause partial arrest in cancer cell lines [2]. Other in vitro research has also shown that metformin may selectively kill cancer stem cells and enhance the effectiveness of breast cancer treatment regimens [3]. Many new studies are investigating the possible mechanisms of the antineoplastic effects of metformin, and these have recently been eloquently summarized by Kourielis et al. (figure 2) [144]. After a review of in vitro and in vivo studies, Kourielis et al. postulated that there are at least seven mechanisms that could account for the anticancer effects of metformin. These include: (i) activation of the liver kinase B1/AMPK pathway, in which metformin activates the AMPK pathways that inhibit the mammalian target of rapamycin pathway via phosphorylation, stabilizing TSC2, a tumour suppressor gene [145]; (ii) induction of cell cycle arrest and/or apoptosis; (iii) inhibition of protein synthesis; (iv) reduction in circulating insulin levels; (v) inhibition of the unfolded protein response; (vi) activation of the immune system; and (vii) eradication of cancer stem cells (figure 2) [144].

A recent meta-analysis of 12 randomized controlled trials which compared metformin with other glucose-lowering therapies or placebo/usual care found no significant difference between the groups in terms of cancer risk [146]. However, cancer data were absent from five of the trials investigated and the comparators were not homogeneous. In a recent large-scale study of the association between metformin use and the incidence of breast cancer in a T2DM population, there was about a 20% reduction in the rate of incident invasive breast cancer among women with...
T2DM using metformin compared with both non-metformin users and other antidiabetic medication users [147]. Another study found that metformin had a statistically significant negative association with the development of pancreatic cancer [148].

The protective effect of metformin on cancer seen in epidemiological studies is so strong that metformin is now being investigated as an adjuvant therapy for cancer in three ongoing prospective trials. The Effect of Metformin on Breast Cancer Metabolism Study (NCT01266486) is investigating biomarkers that indicate a change in biological response in S6 kinase, 4E binding protein 1 and AMPK over a 2-week period. This study in metformin-naïve women with breast cancer aims to assess any metformin-induced phosphorylation of S6 kinase, 4E binding protein 1 and AMPK via immunohistochemical analysis, as well as investigating whether metformin could be used as a cancer therapy [144]. The Metformin Hydrochloride as First-Line Therapy in Treating Patients With Locally Advanced or Metastatic Prostate Cancer Study (NCT01243385) is investigating whether metformin can be used to treat early prostate cancer in metformin-naïve men. The trial is also using immunohistochemistry to analyze the phosphoinositide 3 kinase-dependent pathway. The Metformin Combined with Chemotherapy for Pancreatic Cancer Study (NCT01210911) is investigating whether metformin added to erlotinib and gemcitabine enhances the progression-free survival rate in people with locally advanced and metastatic pancreatic cancer [143]. The anticancer effect has been proposed because it has been suggested that metformin activates AMPK, which inhibits mammalian target of rapamycin and phosphoinositide 3 kinase that are involved in tumour cell proliferation [45].

**Figure 2.** Possible mechanism by which metformin may be able to inhibit cancer cell growth. AMPK, adenosine monophosphate-activated protein kinase; ER, endoplasmic reticulum; IGF, insulin-like growth factor; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; TSP, thrombospondin; UPR, unfolded protein response. Adapted with permission from Ref. [144].

**Insulin Analogues**

There have been suggestions of a link between insulin analogues and cancer owing to their altered affinity for the insulin receptor [6–8,140,141,149,150]. Four observational studies published in *Diabetologia* examined a possible link between insulin glargine monotherapy and all cancers or breast cancer, with conflicting results [6,8,9,151]. Further evaluation of these studies confirmed that these data were inconsistent and that the studies in question were subject to a number of important limitations [152,153]. Other observational studies have found no connection between insulin glargine use and all cancers [10–13]. Owing to the four observational studies in *Diabetologia*, the most recent, large clinical studies have focused on insulin glargine and these are discussed below.

The 6-year, international Outcome Reduction with Initial Glargine Intervention (ORIGIN) Study, designed primarily to determine whether insulin glargine and/or omega-3 fatty acids, could reduce cardiovascular events in 12 537 people with elevated blood glucose levels, had cancer incidence as one of its secondary outcomes. The study compared treatment with insulin glargine with standard care and found, over a median of 6.2 years, no significant difference between study arms in the incidence of all cancers combined (HR: 1.00; 95% CI: 0.88–1.13; p = 0.097); site-specific cancers, including lung cancer (HR: 1.21; 95% CI: 0.87–1.67), colon cancer (HR: 1.09; 95% CI: 0.79–1.51), breast cancer (HR: 1.01, 95% CI: 0.70–1.26), melanoma (HR: 0.88; 95% CI: 0.44–1.75) and other cancers (HR: 0.95; 95% CI: 0.80, 1.14); or cancer mortality (HR: 0.94; 95% CI: 0.77–1.15, p = 0.52) between the insulin glargine and
standard of care arms [14]. The investigators concluded that insulin glargine had a neutral effect on cancer incidence [14]. Other studies have also reported no elevated risk of cancer with insulin glargine compared with other insulins/comparators, such as neutral protamine Hagedorn insulin [154,155], and even a reduced cancer risk with general insulin use [156].

To further investigate the potential link between insulin analogues and cancer, an updated meta-analysis of the Northern European Database Study was performed. This included data from epidemiological studies involving 907,008 subjects. A total of 2,597,602 person-years of observation found no increased risk of developing cancer with insulin glargine versus all other insulins (all cancers combined: summary relative risk: 0.90; 95% CI: 0.82–0.99) [13]. There was also no significant increase in the risk of any organ-specific cancer, and the authors concluded that there is no evidence that insulin glargine is associated with an increased risk of cancer compared with all other insulins [13]. Another meta-analysis of data from a small population (n = 8,893) of people receiving insulin detemir reported no evidence of an increased risk of cancer with insulin detemir compared with neutral protamine Hagedorn insulin (0.36 versus 0.92 events per 100 patient-years’ exposure; p < 0.05) and insulin glargine (0.87 versus 1.27; not statistically significant) [157].

Data from two other large database studies (the Kaiser Permanente Collaboration and a US database analysis) were presented at the 2012 American Diabetes Association Scientific Sessions. It was reported that there was no connection between insulin glargine and cancer, and publications on these studies are eagerly awaited [11,12]. The International Study of Insulin and Cancer is still ongoing and will provide further information on any insulin-related cancer risk [158]. However, a recent study raised issues concerning the use of meta-analyses in determining a link between insulin analogues and cancer [103]. It highlighted the fact that current meta-analyses on the subject do not take into account the duration of diabetes or the insulin requirements of the people involved. Both of these variables have implications for the relative distribution of insulin in the liver and periphery, as they affect the amount of insulin being produced in the pancreas and thus the amount required exogenously. Exogenously administered insulin bypasses the first pass through the liver and exposes all tissues to the same dose of insulin, so its clinical role as a potential carcinogenic agent is complex.

Other Antidiabetic Therapies: Oral

Clinical studies have associated sulfonylureas with an increased risk of cancer [7,8,141]. A retrospective cohort study of 62,809 people with diabetes found that sulfonylureas significantly increased the risk of developing any solid tumour (HR: 1.36; 95% CI: 1.19–1.54; p < 0.001) as well as colorectal (HR: 1.80; 95% CI: 1.29–2.53; p = 0.001) or pancreatic cancer (HR: 4.95; 95% CI: 2.74–8.96; p < 0.001) [8]. However, owing to the low number of site-specific cancers reported, the evidence is weak.

In vitro and in vivo studies on thiazolidinediones have produced inconclusive results; it is possible that these drugs may increase, decrease or have a neutral effect on the risk of cancer or cancer progression [3]. Pioglitazone has been shown in a longitudinal study to be weakly associated with an increased risk of bladder cancer after 2 years of use [159]. Rosiglitazone was shown to have a neutral effect on the risk of all cancers combined or any common site-specific cancers in a meta-analysis of clinical trials [160]. However, the results were inconclusive, owing to the low incidence of site-specific cancers during these trials.

Dipeptidyl peptidase-4 (DPP-4) inhibitors indirectly increase the level of glucagon-like peptide (GLP)-1 in the body by inhibiting its degradation [161]. The relationships between DPP-4 and cancer biology are complex, and research on these is ongoing [162]. Several studies have found that DPP-4 inhibitors could increase the risk of cancer when used in combination with other agents, including GLP-1 receptor agonists. However, there is currently no evidence that DPP-4 inhibitors increase cancer risk when used alone [163,164].
Intraepithelial neoplasia [174]. An increase in pancreatic mass progression and transformation of premalignant pancreatic of 1269 with pancreatitis, respectively). In addition, a report has people included had received exenatide or sitagliptin (34 and 47 was a post hoc This study must be considered in terms of its limitations, as it pancreatitis [AOR: 2.07 (95% CI: 1.36−1.3)] compared with other antidiabetic medications [OR: 0.95 (95% CI: 0.65−1.38), p = NS] compared with other antidiabetic therapies [169]. Another large, retrospective database study including 24 237 people initiated on exenatide twice daily, examined the risk of acute pancreatitis compared with people initiated on other antidiabetic medications (n = 457 797) [170]. In this analysis inverse weighted propensity scores were used to account for differences in baseline characteristics between the two cohorts, in addition insulin use and the use of any medication known to increase pancreatitis risk were adjusted for. After these adjustments it was found that exposure to exenatide twice daily was not associated with an increased risk for pancreatitis compared with exposure to other antidiabetic medications [OR: 0.95 (95% CI: 0.65−1.38), p = 0.7772]. A secondary analysis that examined whether the risk for pancreatitis was affected by when exenatide exposure had occurred (current, recent or past use), also found that there was no increased risk for any of these exposure times [170]. Other large, database studies comparing use of exenatide or sitagliptin in comparison with other antidiabetic agents have found that there is no increased risk of acute pancreatitis with these drugs [171,172].

However, a recent, population-based, case−control study involving 2538 adults with T2DM reported that treatment with exenatide and sitagliptin was associated with increased odds of hospitalization for acute pancreatitis [173]. After adjusting for available confounders, current use of GLP-1-based therapies within 30 days [adjusted odds ratio (AOR): 2.24 (95% CI: 1.36−3.69), p = 0.01] and recent use past 30 days and less than 2 years [AOR: 2.01 (95% CI: 1.37−3.18), p = 0.01] were associated with significantly increased odds of acute pancreatitis relative to the odds in nonusers [173]. Furthermore, any use was also associated with statistically significant higher odds of acute pancreatitis [AOR: 2.07 (95% CI: 1.36−3.13), p = 0.01] [173]. This study must be considered in terms of its limitations, as it was a post hoc database study and only a small number of the people included had received exenatide or sitagliptin (34 and 47 of 1269 with pancreatitis, respectively). In addition, a report has suggested that based upon results in mice prone to pancreatic cancer, the use of GLP-1-based therapy may be linked to the progression and transformation of premalignant pancreatic intraepithelial neoplasia [174]. An increase in pancreatic mass was observed in people with diabetes mellitus treated with incretin therapy (n = 8) compared with people with diabetes mellitus not treated with incretin therapy (n = 12) [175]. This increase in mass was accompanied by both increased exocrine cell proliferation and dysplasia. However, the extremely small sample size and the lack of clarity on whether the controls were qualified to match the cases (controls were age, sex and BMI matched) means that caution should be used when interpreting these results. In addition, this finding has not yet been replicated and firm conclusions cannot therefore be drawn at this time.

Owing to the conflicting results from different trials, the risk of pancreatitis at present can be neither proposed nor excluded. Prospective long-term studies are needed to properly quantify these risks.

Similar concerns have been raised for the GLP-1 receptor agonist liraglutide and the risk for thyroid cancer [174]. Liraglutide has been shown to be associated with the development of malignant C-cell carcinoma and thyroid C-cell focal hyperplasia in rats and mice, and as a result, it is recommended that it be prescribed only in cases where the potential benefits are considered to outweigh the risks [176]. Liraglutide is currently included in a cancer registry which will monitor its long-term effects over 15 years [177]. To date, there is no evidence suggesting that use of liraglutide in humans might be associated with any thyroid pathology.

Managing the Combined Burden of Diabetes, Obesity and Cancer

Using multidisciplinary treatment strategies that reduce diabetes, obesity and cancer will probably have a greater impact on mortality than tackling each disease individually. Primary prevention should target improvements in lifestyle factors such as smoking cessation and weight management, while patient and physician education on the benefits of these approaches are important. Maintenance of a low waist circumference is a promising way to support cancer prevention and extend life expectancy. Secondary prevention would aim to treat cancer aggressively, manage complications and effectively optimize diabetes management. In general, the American Diabetes Association/American Cancer Society consensus panel recommends that physicians promote a healthy diet, physical activity and weight management for all individuals and routinely screen people with diabetes for cancer. In addition, for the majority of this population, cancer risk should not be a key factor in choosing antidiabetic treatment [3].

Conclusions

Diabetes, diabetes risk factors and some diabetes treatments may be associated with cancer, with certain cancers developing more commonly in people with T2DM. Strong and plausible evidence exists to suggest links between diabetes, obesity and cancer; however, the underlying mechanisms remain unclear and there is little clinical evidence to guide the appropriate management of people presenting with these diseases concurrently. Joint management and reduction of diabetes, cancer and obesity is likely to result in greater improvements in
mortality than treating these diseases separately. Consequently, a multidisciplinary approach is needed to uncover the mechanisms underlying the associations between these diseases and, ultimately, improve clinical outcomes.

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**Conflict of Interest**

S. G. has received honoraria for giving lectures from DexCom, J&J and Sanofi-Aventis; has received grants for clinical research from Novo Nordisk, Eli Lilly and Company, Merck, MannKind, Biodel, Halozyme, DexCom and Sanofi-Aventis; and does not have any stocks in any pharmaceutical or device company. H. M., K. R. and R. S. have no conflicts of interest to disclose.

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