Diabetes and Cancer

11

Riccardo Vigneri and Laura Sciacca

Contents

Abstract

Cancer incidence and mortality are higher in diabetic patients. Although epidemiological data on the diabetes-cancer association mainly concern type 2 diabetes, recent data confirm that cancer incidence is also increased in type 1.

R. Vigneri (✉) · L. Sciacca
Endocrinology, Department of Clinical and Experimental Medicine, University of Catania, Garibaldi-Nesima Hospital, Catania, Italy
e-mail: vigneri@unict.it; lsciacca@unict.it

E. Bonora, R. A. DeFronzo (eds.), *Diabetes Complications, Comorbidities and Related Disorders*, Endocrinology, https://doi.org/10.1007/978-3-030-36694-0_12

The increased incidence of cancer in diabetic patients is documented for many organs (i.e., liver, pancreas, stomach, kidney, endometrium, breast) but not for all (prostate, lung).

Diabetes promotes cancer by multiple mechanisms that are both general (i.e., hyperinsulinemia and hyperglycemia) and site specific (i.e., increased hepatosteatosis and hepatitis in diabetes favor liver cancer).

Also the increased cancer mortality in diabetic patients is due to several mechanisms that, on one side, can make the cancer more aggressive and, on the other side, make the patient a fragile subject because of the frequent chronic complications of diabetes. Moreover, because of these complications, many diabetic patients receive less than optimal cancer therapy.

A matter of concern for cancer promotion is all conditions causing hyperinsulinemia, both endogenous (insulin-resistant diseases with compensatory hyperinsulinemia, like obesity and prediabetes) and exogenous. Treatments with high doses of insulin (with special attention to long-acting analogs) and with secretagogues like sulfonylureas may promote the growth of silent, subclinical tumors. In contrast, metformin, the most used first-line hypoglycemic agent, can decrease cancer risk because of its indirect effect (insulin sensitizer, reducing insulin resistance and hyperinsulinemia) and also with a direct effect, reducing cancer cell proliferation with multiple actions.

One additional problem in patients with diabetes and cancer is the hyperglycemic effect of many cancer drugs. Glucocorticoids, antiandrogens, and recent biological drugs targeting the insulin and insulin-like growth factor 1 (IGF-1) signaling pathways may cause hyperglycemia, sometimes severe. This complication can concern patients unaware of diabetes or prediabetes and may adversely affect both patient well-being and cancer progression.

In conclusion, cancer and diabetes are two very prevalent diseases and each one can negatively influence the other one. Cancer-related death accounts for approximately one-third of deaths in diabetic patients. It is important, therefore, to promote all preventive measures (often similar for the two diseases) and personalize the treatment according to the features of the diseases and the characteristics of the patient.

Keywords

Diabetes and cancer · Hyperglycemia and cancer · Insulin and cancer · Hypoglycemic agent and cancer · Cancer drugs and hyperglycemia · Insulin receptor and cancer

Introduction

Diabetes and cancer are both prevalent diseases in the industrialized world and their incidence is increasing worldwide. Epidemiological studies and meta-analyses indicate that both cancer incidence and cancer-related mortality are increased in diabetic patients, especially in type 2 diabetics (Belfiore et al. 2009).

Both diabetes and cancer are chronic diseases, each with heterogeneous etiopathogenesis and variable clinical expression which, in addition, significantly changes in a time-dependent manner.

The two diseases share many common risk factors including age, diet, smoking, alcohol, sedentary life, and obesity, and this explains a certain degree of association between the two diseases. Diabetic patients, however, have additional metabolic, hormonal, and clinical characteristics that may favor cancer incidence and cancer-related mortality.

In this chapter we will try to analyze the diabetes-cancer association in terms of epidemiology, pathogenesis, and risk factors. These elements should be considered for a rational approach to the prevention and treatment of cancer in the diabetic patient.

Diabetes-Cancer Association: Epidemiology

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia. The two most frequent subtypes of diabetes mellitus differ for both metabolic and hormonal characteristics: in type 1 diabetic patients (5–10% of all diabetics), hyperglycemia is associated with an absolute deficiency of endogenous insulin secretion and the absolute requirement for exogenous insulin administration. In type 2 diabetes mellitus (T2DM), hyperglycemia and hyperinsulinemia coexist for a long time because of the insulin resistance of peripheral tissues. Only when the β-cell function fails the patient will require substitute insulin treatment.

In spite of these considerable pathogenetic and clinical differences, many studies on the association between diabetes and cancer were carried out without an appropriate distinction between the two major forms of diabetes. However, since both cancer and type 2 diabetes are more prevalent in advanced age and T2DM is the most frequent type of DM (90% of all diabetic patients) for obvious epidemiological reasons, most studies on the association between cancer and diabetes have been carried out in patients with T2DM (Kido et al. 2001).

Many epidemiological studies indicate that in type 2 diabetic patients, the risk for several solid and hematologic malignancies (including liver, pancreas, colorectal, kidney, bladder, endometrial, and breast cancers and non-Hodgkin's lymphoma) is more elevated. Data on lung cancer associated with diabetes are controversial, and for prostate cancer a reduced incidence has been reported in diabetic patients (Table 1). If we accept that cancer is more frequent in diabetes, the positive association between diabetes and cancer risk might actually be somewhat underestimated since type 2 diabetes is an underdiagnosed disease (3–5% of the adult population has undiagnosed diabetes) (Harris et al. 1998). Thus, the control population very likely includes individuals with diabetes, which will apparently increase the cancer risk in the nondiabetic population.

Table 1 Relative risk (RR) of cancer in different organs of diabetic patients

Cancer		RR (95% CI)
Endometrium (Friberg et al. 2007; Liao et al. 2014)	13 case-control studies 23 cohort studies	2.22 (1.80–2.74) 1.61 (1.51–1.71)
Liver (Wang et al. 2012)	13 cohort studies	2.01 (1.61–2.51)
Pancreas (Ben et al. 2011)	35 cohort studies	1.94 (1.66–2.27)
Kidney (Bao et al. 2013)	7 case-control studies 11 cohort studies	1.39 (1.13–1.72) 1.39 (1.09–1.78)
Colon-rectum (Guraya 2015)	8 cohort studies	1.21 (1.02–1.42)
Bladder (Xu et al. 2013b; Zhu et al. 2013)	6 cohort studies 19 cohort studies	1.32 (1.18–1.49) 1.35 (1.12–1.62)
Non-Hodgkin's lymphoma (Castillo et al. 2012)	10 case-control studies 11 cohort studies	1.24 (1.03–1.49) 1.21 (1.02–1.45)
Breast (Larsson et al. 2007; De Bruijn et al. 2013)	5 case-control studies 20 cohort studies	1.18 (1.05–1.32) 1.23 (1.12–1.34)
Prostate (Bansal et al. 2013)	16 case-control studies 29 cohort studies	0.85 (0.74–0.96) 0.87 (0.80–0.94)

Diabetes and Cancer Incidence in Different Tissues

Liver cancer. Several meta-analyses indicate that the strongest association between diabetes and increased cancer risk concerns pancreatic and liver cancer (Table 1), i.e., two key organs involved in the metabolic derangements typical of diabetes.

Most epidemiologic studies indicate a two- to threefold increase in *hepatocellular carcinomas (HCC)* in both male and female diabetic patients (Hassan et al. 2010; Wang et al. 2012). Whether diabetes per se is a direct risk factor for liver cancer or whether diabetes-related liver diseases are mainly responsible is debated. Indeed hepatosteatosis and cirrhosis, both well-known risk factors for HCC, are more frequent in diabetic patients. Likewise, the nonalcoholic fatty liver disease (NAFLD) is very common in both diabetes and obesity and even more frequent in T2DM patients with obesity, a condition occurring in over 80% of T2DM patients. Additional factors that may favor HCC in DM include HBV and HCV infections, also more frequent in diabetic subjects as compared to the nondiabetic population, and risk factors for cirrhosis and HCC (Chen et al. 2006; Davila et al. 2005).

In conclusion, increased liver cancer incidence in diabetes is well documented although the exact mechanisms underlying this association are still unclear.

Meta-analyses indicate that diabetes is associated with an increased risk of *pancreatic cancer*, with a twofold increase relative to the control population (RRs, 1.94; 95% C.I.) (Ben et al. 2011). Most earlier studies investigating this association can be partially misleading because they did not distinguish between pre-existing diabetes (a condition possibly favoring exocrine pancreatic cancer) and new-onset diabetes in a pancreatic cancer patient, when diabetes is a possible consequence of the functional damage of the pancreas affected by a still undiagnosed cancer (Noy and Bilezikian 1994). The latter situation is frequent enough to suggest pancreatic cancer screening when hyperglycemia and diabetes appear after the age of 45–50 years in a lean subject

with no family history of diabetes (Noy and Bilezikian 1994; Chari et al. 2008; Pannala et al. 2009). Similarly, elderly subjects with new-onset diabetes have a 3-year risk of pancreatic cancer nearly eight times higher than a nondiabetic person of similar age and sex (Chari et al. 2005). Laboratory and clinical evidences suggest that diabetes caused by pancreatic cancer is due to cytokines produced by the tumor (Basso et al. 2002) rather than to functional failure of the endocrine pancreatic tissue because of cancer invasion and damage (Pannala et al. 2009). This conclusion is supported also by the observation that hyperglycemia occurs at an early stage of pancreatic cancer and is independent of tumor size and stage (Chari et al. 2008; Pannala et al. 2008).

The RR for pancreatic cancer in subjects affected by DM at least 1 year prior to the diagnosis is 2.1 (95% C.I., 1.6–2.8). The RR is similar (RR, 2.0) in patients having a 5-year history of pre-diagnosed diabetes (Everhart and Wright 1995). These data exclude the reverse causality of diabetes induced by pancreatic cancer and support the possibility that indeed diabetes is a relevant risk factor for pancreatic cancer.

Also the "prediabetes" condition is a risk factor for pancreatic cancer. A large study analyzing the association between post-load glucose levels and pancreatic tumors in 35,658 individuals reported a higher RR of this cancer with increasing glucose tolerance impairment. After adjusting for age, race, cigarette smoking, and BMI, the risk of pancreatic cancer mortality progressively increased from normal subjects to subjects with slightly altered post-load glycemia (RR, 1.65) and then to diabetic patients (RR, 2.15) (Gapstur et al. 2000).

The biological mechanisms underlying the association between diabetes and pancreatic cancer are unclear. Endogenous hyperinsulinemia has been indicated as a possible factor because exocrine pancreatic cells, which give rise to most pancreatic cancers, are exposed to very high insulin concentrations because of the common blood supply with the adjacent insulin-secreting islets (Williams and Goldfine 1985). High insulin levels could act as a tumor growth-promoting factor in many different ways (see later). This mechanism, however, does not justify the excess of pancreatic cancer in insulin-treated diabetic patients (Green and Jensen 1985) or in type 1 diabetes mellitus (T1DM) (Stevens et al. 2007) when pancreatic cells are not exposed to insulin levels higher than those of other tissues. In these studies, however, the analysis is hampered by the insufficient number of cases because of the lower prevalence of type 1 diabetes (less than 10% of all DM cases) and because of the younger patient age (pancreatic cancer is rare before age 40).

Other Cancers in Diabetes

An increased frequency of malignancies in many organs other than the liver and pancreas has been reported in diabetic patients. The RR for these cancers is smaller than that of the liver and pancreas and has been ascribed to a variety of general and local mechanisms. Even if the risk increase is low, however, it is clinically relevant for many organs (i.e., breast, endometrium, and colon-rectum) that have a high prevalence of cancer in the general population.

The risk of *colorectal adenomas and carcinomas* is reported to be increased in T2DM patients in most, but not all, studies (Elwing et al. 2006; Limburg et al. 2006). The risk is increased in both women and men for both colon and rectal cancers (Larsson et al. 2005; Luo et al. 2012; Guraya 2015). In addition to hyperinsulinemia, hypothesized mechanisms include slower bowel transit time and the elevated fecal bile acid concentrations often observed in DM patients (Stadler et al. 1988; Will et al. 1998).

The risk of cancer in *female reproductive organs* is also increased in DM patients. Both breast and endometrial cancers are more frequent in diabetic women, and this risk is independent from obesity (a well-established factor promoting breast cancer) as it persists after correcting epidemiological data for this disease.

Several biological mechanisms may be involved, mostly regarding sex hormone abnormalities. Hyperinsulinemia may increase the levels of bioactive estrogens by decreasing the concentration of circulating sex hormone-binding globulin and might also stimulate androgen synthesis in the ovarian stroma (Kaaks 1996). Other possible mechanisms include delayed menarche, especially in type 1 diabetic women, who also have a higher incidence of irregular menses and fertility disorders.

In diabetic patients the increased incidence and increased mortality for *kidney* cancer have been attributed to both general mechanisms (hyperinsulinemia, obesity) and to specific factors, mainly hypertension (Chow et al. 2000; Yuan et al. 1998; Zucchetto et al. 2007) and the frequent kidney diseases occurring in diabetic patients (Lindblad and Adami 2002).

Individuals with DM also display a modest increase in the risk of *bladder* cancer. For this tumor, the increased frequency of urinary tract infections is a likely site-specific factor promoting this cancer in diabetic patients.

Large prospective cohort studies and case-control studies have shown a moderate increase of *non-Hodgkin's lymphoma* in diabetic patients, a possible consequence of the immune dysfunction related to impaired neutrophil activity and abnormalities in cellular and humoral immunity in diabetes (Mitri et al. 2008).

Data on the association between diabetes and *lung cancer* are inconsistent. This inconsistency is probably due to the variable influence of confounding factors (primarily smoking) that may occur differently in diabetic versus nondiabetic individuals. A meta-analysis of observational studies (10 case-control studies and 24 cohort studies) found that diabetes was significantly associated with the increased risk of lung cancer compared with nondiabetic controls when limiting the analysis to studies in which data were adjusted for the patient smoking status (RR 1.11, 95% C.I., 1.02–1.20). By contrast, this association disappeared when only series not adjusted for the smoking status were considered, probably because cigarette smoking is less prevalent in diabetic patients (RR 0.99, 95% C.I., 0.88–1.11). When stratifying by sex, an increased risk of lung cancer was significant in diabetic women (RR 1.14, 95% C.I., 1.09–1.20) but not in diabetic men (Lee et al. 2013).

In contrast to the increased risk for most cancers, a reduced risk of *prostate cancer* is found in many studies in men with diabetes. A meta-analysis (Kasper and Giovannucci 2006) including both the 14 studies carried out in the pre-PSA era

(Bonovas et al. 2004) and also 5 additional studies carried out in the PSA era (and including, therefore, earlier diagnosed and smaller cancers) found a significantly reduced risk of prostate cancer in diabetic patients. A comprehensive review of studies on the association between DM and prostate cancer suggested an inverse relationship between DM and prostate cancers of different stage or grade (Xu et al. 2013a). The moderately (average ~15%) decreased risk of developing prostate cancer in diabetic patients has been attributed to their decreased testosterone levels (Barrett-Connor 1992; Betancourt-Albrecht and Cunningham 2003). However, other metabolic and hormonal factors, the diffuse use of medications like statins and metformin, and the changes in diet and lifestyle in order to control diabetes have also been hypothesized as possible factors contributing to the inverse association between diabetes and prostate cancer (Kasper and Giovannucci 2006).

Type 1 Diabetes and Cancer

T1DM patients, unlike patients with T2DM, do not have a long-lasting history of endogenous hyperinsulinemia and insulin resistance. Moreover, T1DM is less frequently associated with obesity and may have either hypoinsulinemia or hyperinsulinemia of exogenous origin without the liver-periphery gradient. It is questionable, therefore, whether data obtained in T2DM patients can be automatically extended to type 1 diabetic patients. This concern is particularly relevant for the older reports in which the distinction between type 1 and type 2 diabetes was mostly based on surrogate indicators, like patient young age or insulin treatment (assumed as type 1 in all cases) versus insulin-independent diabetes (assumed as type 2). This distinction does not take into account many specific conditions, including type 2 diabetic patients that are treated with insulin because of secondary failure to oral hypoglycemic agents (OHA) and other less frequent conditions.

Thus, if cancer association with type 1 diabetes has specific characteristics, most likely these have been obscured by the large majority of cancers diagnosed in type 2 diabetic patients. Even the few studies specifically addressing cancer incidence in type 1 diabetic patients suffer from the poor assessment of the diabetes type. A Swedish study evaluating cancer incidence in nearly 30,000 T1DM patients found an increased risk for stomach, endometrial, and cervical cancer (Zendehdel et al. 2003). These positive associations have been attributed to the high prevalence of *Helicobacter pylori* infection or of pernicious anemia (for gastric carcinomas) (De Block et al. 1999; Oldenburg et al. 1996) and to the higher incidence of irregular menses and fertility disorders in type 1 diabetic women (for uterine malignancies). At variance with type 2 diabetic patients, no increased risk of breast, pancreatic, colorectal, or kidney cancer was found in that cohort. In contrast with this report, a meta-analysis including three cohort studies and six case-control studies found that the risk for pancreatic cancer was doubled in type 1 and in young-onset diabetic patients in comparison with nondiabetic subjects (Stevens et al. 2007). A recent study resolving five nationwide diabetes registers and 9,149 cancers in T1DM patients found that the overall HR for cancer was 1.01 among T1DM male and

Table 2 Hazard ratios (HR) of different cancers in type 1 diabetic patients. (From Carstensen et al. 2016)

Cancer	Men HR (95% C.I.)	Women HR (95% C.I.)
All	1.01 (0.58–1.04)	1.07 (1.04–1.10)
Liver	2.0 (1.67–2.40)	1.55 (1.14–2.10)
Pancreas	1.53 (1.30–1.79)	1.25 (1.02–1.53)
Stomach	1.23 (1.04–1.46)	1.78 (1.49–2.13)
Kidney	1.30 (1.12–1.49)	1.47 (1.23–1.77)
Endometrium	=	1.42 (1.27–1.58)
Breast	=	0.90 (0.85–0.94)
Prostate	0.56 (0.51–0.61)	=

1.07 among T1DM female patients. The risk of several cancers, however, was significantly increased in T1DM patients (Table 2), resembling data found in T2DM patients except for breast cancer whose HR was reduced in T1DM. Therefore, both type 1 and type 2 diabetes are associated with an excess risk for a number of site-specific cancers as pancreas, liver, kidney, and endometrium cancer (Carstensen et al. 2016; Harding et al. 2015).

Cancer-Related Mortality and Diabetes

Data on cancer mortality in diabetic patients are less abundant and less homogeneous than data on cancer incidence.

The hazard ratio for death in cancer patients with diabetes was estimated at 1.41 (95% C.I. 1.28–1.55) in respect to cancer patients without diabetes (Barone et al. 2008). Mortality was significantly increased for cancers of the breast, endometrium, colon, and rectum, while it was not significantly increased for lung, gastric, liver, pancreatic, and prostate cancers. However, the heterogeneity of the studies analyzed and the length of the observation period (1969–2008, 40 years during which treatment for both cancer and diabetes changed markedly) hamper, at least in part, the significance of these results. The analysis of the cause of death in 820,900 people in 97 studies, after adjusting for age, sex, smoking, and body mass index, found that in diabetic patients, the hazard ratio for death from cancer was 1.25 (95%, C.I. 1.19–1.31) relative to the nondiabetic subjects. In the same studied cohorts, the hazard ratio of death for vascular diseases in diabetic patients was 2.32 (2.11–2.56) (Bansal et al. 2013).

Mortality data regarding different cancers in diabetic patients are variable but always indicate an increased risk of mortality.

A positive association between *breast cancer mortality* and diabetes was found in three out of five studies, with a RR from the pooled data of the five studies of 1.24 (95% C.I., 0.95–1.62) (Larsson et al. 2007). In the largest study (cohort size 588,321 with 4,346 deaths for breast cancer), after adjusting for age, race, BMI, physical activity, smoking, and alcohol, cancer-related death in diabetic women was 1.27

(1.11–1.45) in comparison with the nondiabetic female population. In a recent systematic review and meta-analysis, the increase of breast cancer-related mortality was 1.38 in patients with DM (De Bruijn et al. 2013). A similar value (hazard ratio in diabetic women 1.39) was found in a study evaluating mortality for breast cancer after a 5-year mean follow-up, suggesting that also early survival is reduced in women with diabetes and breast cancer (Lipscombe et al. 2008). This reduced survival might be the consequence of more aggressive breast cancer but also of diabetes-related comorbidities.

Diabetes was also positively associated with *colorectal cancer mortality*. A study aimed at evaluating the influence of diabetes on the long-term outcome of patients resected for colon cancer (3,759 patients, 287 with DM) found that diabetes negatively affected survival in colon cancer patients (Meyerhardt et al. 2003). Data were adjusted for predictors of colon cancer outcome (age, gender, race, clinical status, TNM class, Dukes stage, location of primary tumor, and grade of differentiation) and indicated that both disease-free survival (DFS) and overall survival (OS) at 5 years were significantly reduced in diabetic patients. A statistically significant association between diabetes and colorectal cancer-related death was found in three out of six studies (Larsson et al. 2005), and a not significant positive association was reported in a fourth one. Pooled data from the six studies indicated a positive association between diabetes and colorectal cancer mortality (RR, 1.26; 95% C.I., 1.05–1.50), but heterogeneity issues may partially invalidate the significance of these results. In a more recent systematic review and meta-analysis, the overall HR for colorectal cancer-specific mortality was 1.30 in patients with DM compared with subjects without diabetes (De Bruijn et al. 2013).

For other cancers available data are not sufficient to establish an association between cancer-related death and diabetes. For instance, a positive association was found between diabetes and *endometrial cancer mortality* in two studies, but it was significant only in one of them (RR, 2.38; 95% C.I., 1.05–5.37) (Coughlin et al. 2004; Folsom et al. 2004), and in a recent meta-analysis, diabetes was not positively associated with endometrial cancer mortality (Zhang et al. 2013). It is interesting to note that, although diabetic patients have a reduced risk for *prostate cancer*, once an insulin-resistant and overweight man has been diagnosed with prostate cancer, his likelihood of dying to the disease is increased in respect to nondiabetic individuals (Ma et al. 2008).

Several possible mechanisms can explain the increased risk of cancer-related death in DM. It is still unclear whether diabetes, through a number of mechanisms (see later), can make the cancer more aggressive or whether the host organism (the diabetic individual) is less resistant to cancer progression. It is also possible that diabetic patients receive reduced/insufficient cancer treatment. Oncologists may employ lower chemotherapy doses in diabetic patients, concerned about their general health condition and the possible damage of heart, liver, and kidney function caused by diabetes. The less than optimal dosage of chemotherapy might contribute to the increased cancer-related mortality observed in diabetic patients.

Mechanisms of the Cancer-Promoting Effect of Diabetes

The reasons why cancer incidence and mortality are increased in diabetic patients are complex and not yet fully understood.

One preliminary, unresolved question is whether diabetes favors cancer initiation or cancer progression or both.

Diabetes could activate carcinogenic mechanisms that will facilitate the malignant transformation of cells resulting in an increased number of new cancers. The increased incidence of cancer in diabetic patients, however, may be apparent, due to the effect of diabetes on the progression of clinically silent cancers that will grow faster and become more aggressive and clinically relevant because of the abnormal metabolic environment and the general fragility of the diabetic patient.

An apparent increase of cancer incidence is also possible because of the increased detection of subclinical cancers in patients that usually undergo more frequent medical controls. This possibility, however, is unlikely to significantly contribute to the increased incidence of cancer because also cancer-related mortality is increased in diabetic patients.

Because of the high heterogeneity of both diabetes and cancer in terms of molecular abnormalities, etiopathogenetic sequences, involved organs, and also patient characteristics (including individual lifestyle, accompanying morbidities, and treatments), the association between diabetes and increased cancer incidence may be favored by a series of heterogeneous mechanisms in different individuals. In such a complex and multifactorial system, it is difficult to quantify the role of a single factor or mechanism that may favor cancer in diabetic patients. The involved mechanisms are not only multiple but most likely different in different patients and for different cancers.

For the sake of clarity, we can identify two major categories of mechanisms (Table 3):

Table 3 Pathogenetic mechanisms influencing cancer incidence in diabetic patients

General mechanisms
• Hyperglycemia
• Hyperinsulinemia
• Inflammation
• Reduced immunological response
• Antidiabetic drugs
• Obesity
Site-specific mechanisms
• Liver: hepatosteatosis-viral hepatitis
• Kidney and urinary tract: infections
• Breast and endometrium: less pregnancies, delayed menarche, hormone abnormalities (obesity)
• Colon-rectum: slow bowel transit
• Prostate (reduced): reduced androgens
• Lung (not increased): reduced smoking

(a) General mechanisms that promote cancer because typical of the diabetic condition (i.e., hyperglycemia and hyperinsulinemia and also inflammation cytokines)
(b) Site-specific mechanisms regarding single organs and tissues whose structure and function may be altered in the diabetic patient, producing a condition that will promote cancer in specific organs

General Mechanisms

Hyperglycemia and hyperinsulinemia, two conditions present in most diabetic patients, are believed to be the major general mechanisms that increase the risk of malignant transformation or that will promote the growth of malignantly transformed cells in diabetic individuals. Most diabetic patients, in fact, have type 2 diabetes characterized by hyperglycemia, hyperinsulinemia, and obesity, abnormalities that often are already present many years before diabetes is diagnosed. Because of the simultaneous presence of the increased levels of both glucose and insulin, it is difficult to dissect the specific role of each one in increasing cancer risk. Probably both contribute in different but synergic ways.

Hyperglycemia favors cancer because malignant cells have an altered metabolism due to mitochondrion and enzymatic abnormalities: in contrast to normal cells, to generate the energy needed for cellular processes and growth, cancer cells mainly rely on aerobic glycolysis, a phenomenon termed "the Warburg effect" (Warburg 1956). The aerobic glycolytic pathway will generate less energy in terms of adenosine 5′-triphosphate production, and therefore, from a given amount of glucose, cancer cells will obtain less energy than normal cells. To satisfy the energy requirement (higher than normal not only for the altered metabolism but also because of the increased proliferation rate), glucose is processed much faster in malignant cells and its requirement is increased. The increased glucose transport in these cells is associated with an increased and deregulated expression of the cell membrane glucose transporter proteins, mainly with overexpression of Glut-1 (Macheda et al. 2005).

The correlation between glycemic control and cancer risk is supported by the observation that both the fasting glucose and the HbA1c increase are associated with an increased risk of cancer (Yang et al. 2010; Muti et al. 2002; Shin et al. 2014) and its unfavorable outcome (Yang et al. 2016).

Many epidemiological studies, in vitro experiments, and clinical evidences (including the increased uptake of 2-deoxy-2-[^{18}F] fluoro-D-glucose by tumors evidenced by positron-emission tomography – PET) document the importance of glucose availability for cancer cell biology. Hyperglycemia assures the availability of this nutrient to cancer cells. The statement "sugar fuels cancer" emphasizes this primary metabolic requirement in a deregulated system with accelerated growth.

The other major factor that may promote cancer in diabetic patients is the increased circulating insulin. Compensatory hyperinsulinemia is typical of type 2 diabetes, but also T1DM patients are often hyperinsulinemic because of the abnormal distribution of subcutaneously injected insulin in comparison with pancreas-secreted endogenous insulin. While endogenous insulin through the portal system

first goes to the liver where it is in part degraded, subcutaneously injected insulin loses the liver-periphery gradient: to have sufficient insulin at liver level, peripheral tissues will be exposed to hyperinsulinemia.

Insulin does not play a major role for glucose utilization in malignant cells because these cells overexpress Glut-1 and are mostly insulin-independent for their uptake of glucose. Insulin, however, in addition to being a metabolic hormone, is also a growth factor with mitogenic effects via activation of the mitogen-activated protein (MAP) kinase intracellular pathway and the mTOR signaling (Kido et al. 2001; Dibble and Cantley 2015), and hyperinsulinemia can favor cancer by promoting its growth. This effect of insulin can be exerted via its own receptor but also by activating the cognate insulin-like growth factor-1 receptor (IGF-1R) receptor that has a potent mitogen and transforming potential and that will cross-react with insulin when the increased concentration of the ligand will overcome the reduced IGF-1R-insulin affinity. These effects may occur in diabetic patients because of their hyperinsulinemia, both endogenous (secondary to insulin resistance) and also exogenous (due to high-dose insulin treatment). This has raised some concerns regarding the possible cancer risk associated with insulin administration, especially with long-acting analogs (vide infra).

The growth-promoting effect of hyperinsulinemia is increased in cancer cells because of two independent mechanisms related to the insulin receptor biology in cancer cells (Table 4). First, most cancer cells overexpress the insulin receptor and, therefore, are more responsive than normal cells to the mitogenic effect of insulin (Papa et al. 1990; Vella et al. 2001).

Second, dedifferentiation makes cancer cells similar to fetal cells in terms of insulin receptor isoform prevalence. As in fetal cells, also in cancer cells the alternative splicing of the IR transcript will favor the exon 11-isoform A of the insulin receptor protein (IR-A) (Frasca et al. 1999, 2008; Sciacca et al. 2013). The IR-A isoform, compared with the B isoform, has a more pronounced mitogenic rather than metabolic effect and will make cancer cell proliferation especially responsive to hyperinsulinemia (Belfiore et al. 2009; Frasca et al. 1999). Moreover, IR-A is a high-affinity receptor for IGF-2 (Fig. 1) and locally (autocrine/paracrine) produced IGF-2 will further stimulate cancer growth via the overexpressed IR-A (Frasca et al. 1999; Sciacca et al. 1999; Vella et al. 2002; Kalli et al. 2002).

In addition to the pro-cancer effect of increased glucose and insulin, diabetes may activate additional general mechanisms promoting cancer. Among them a major role is probably played by the chronic pro-inflammatory state, with overproduction of pro-tumoral cytokines like TNF-α (Kern et al. 2001; Szlosarek et al. 2006). Moreover, the increased concentrations of free radicals due to inflammation and the decrease of intracellular antioxidant capacity can damage cell DNA or interfere

Table 4 The insulin-receptor role in favoring cancer progression

The insulin receptors (IRs) are overexpressed in many cancers
The IR isoform A (IR-A with predominant mitogenic activity) is the prevalent IR isoform in many cancers
IR-A is a high-affinity receptor for IGF-2 produced by the tumor at autocrine/paracrine level

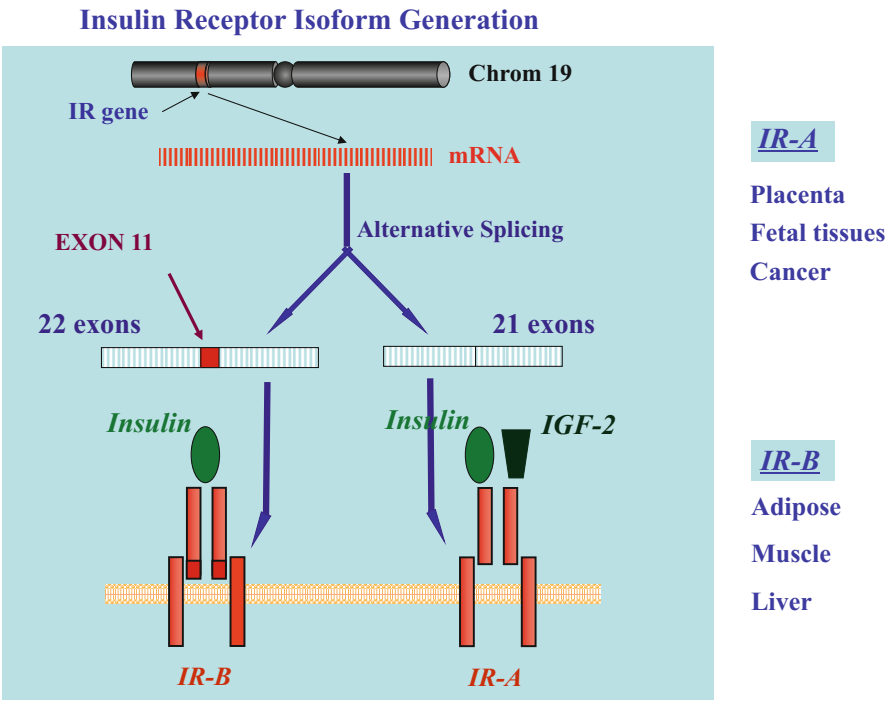

Fig. 1 Insulin receptor isoforms. The insulin receptor gene on chromosome 19 gives origin to a 22-exon mRNA transcript that during maturation may either include or not include exon 11. This alternative splicing produces two isoforms of the insulin receptor, IR-A and IR-B, differing for 12 amino acids at the COOH terminal of the α-subunit. This difference causes different binding characteristics and post-receptor signaling: the shorter isoform (IR-A) binds with high affinity not only insulin but also IGF-2 and has more mitogenic effects. IR-A is predominantly expressed in fetal tissues and in cancer cells. In contrast, IR-B has more metabolic effects and is the predominant isoform of insulin receptor in insulin target tissues (liver, muscle, and adipose tissue)

with the mechanisms of DNA repair, two processes that can contribute to the multistage sequence of carcinogenesis.

Another general mechanism causing an increased cancer risk in diabetic patients is overweight/obesity which affects over 80% of type 2 diabetic patients and is a well-recognized risk factor for cancer incidence and mortality (Aiello et al. 2006; Calle et al. 2003). In obese individuals the pro-inflammatory condition and the increased levels of leptin, an adipocyte-derived cytokine, can also promote cancer cell proliferation (Garofalo and Surmacz 2006; Barone et al. 2012).

Site-Specific Mechanisms

In addition to the general, not organ-specific mechanisms, different organ-related mechanisms may contribute to the increased cancer incidence and mortality in

diabetic patients. Most of these mechanisms have already been described when discussing cancer incidence in diabetic patients (vide supra).

Diabetes can damage the structure and function of specific organs favoring site-specific risk factors for cancer. A typical example is cancer of the liver, the most prevalent cancer in diabetic patients (two- to threefold increase) (El-Serag et al. 2006). As already mentioned, the diabetes-related diseases of the liver, like steatohepatitis and cirrhosis and also hepatitis B and C viral infections, are all well-known risk factors for hepatocellular cancer and are more frequent in diabetic patients.

Another organ-specific mechanism is the abnormal steroid metabolism due to obesity that often accompanies type 2 diabetes. The obese women with diabetes have increased estrogen levels because of the augmented aromatase activity of the adipose tissue. Higher levels of estrogens, in turn, will favor estrogen-dependent cancers.

Mechanisms of Increased Cancer-Related Mortality in Diabetes

The reasons and mechanisms for the increased cancer-related mortality in diabetic patients are less studied but more intuitive than those responsible for the increased cancer incidence.

First, an increased number of cancers and/or more aggressive cancers due to the already mentioned reasons will per se explain an increased mortality. Second, the general conditions typical of diabetes (hyperglycemia, hyperinsulinemia, inflammation) and of most cancer cells (overexpressing insulin receptors and mainly the A isoform) will favor cancer progression. Third, the diabetic patient is a fragile patient, often with multiple organ pathologies and under multiple drug treatment. The patient fragility will not only increase per se the death risk but will also induce oncologists to treat with a reduced anticancer dosage, especially when heart, liver, or kidney functions are defective. These reasons, often combined, can easily explain the increased cancer-related death rate in the diabetic patients (Bansal et al. 2013).

In conclusion, the mechanisms for the increased cancer incidence and mortality in diabetes, although still not fully clear, are certainly multiple, often associated or interrelated. Their relevance may differ in different diabetic patients because they will predominantly depend on the single-patient characteristics, including the genetic and environmental factors (i.e., associated diseases and treatments) involved in diabetes and in the different types of cancer.

For this reason the approach to the diabetic patient at risk of cancer or with an already diagnosed cancer will have to consider this heterogeneity and provide a personalized intervention with individually appropriate diagnostic and therapeutic procedures.

Antidiabetes Drugs and Cancer Risk

Many studies have investigated the possible effects of antidiabetic drugs on cancer incidence and mortality, but data evaluating whether a specific antidiabetes drug use is causally related to cancer are often inconclusive or difficult to interpret.

The reason for this uncertainty is the complexity of the pharmacological treatment in diabetic patients, with the possibility of drug-drug interactions. Moreover, the changes in the treatment that often occur in a chronic disease lasting many years (decades) will also be a confounding factor.

Cigarette smoking, a well-recognized strong carcinogen, will take two or three decades before causing cancer. No antidiabetic drug can be considered a strong carcinogen (like in cigarette smoking) because this eventuality is excluded by the required tests carried out before commercialization. A possible pro-cancer effect of antidiabetes drugs on the multistep carcinogenic process will, therefore, take a long time. Available clinical studies, in contrast, have short (less than a decade) duration and are biased by the changes in dosage, patient conditions, and other drug interferences that may have occurred during the study period.

This comment is valid both for studies investigating a pro-cancer effect of an antidiabetic agent and also for studies excluding this effect.

Insulin Analogs

As already mentioned, insulin is a growth factor acting via its own receptor and, when at higher concentration, also via the cognate IGF-1 receptor. Therefore, when at increased concentration because of endogenous hyperinsulinemia or high-dose exogenous insulin administration, insulin can promote cancer growth.

In the last two decades, diabetic patients are treated more frequently with insulin analogs instead of human native or recombinant insulin because insulin analogs have a pharmacokinetics that can better mimic the endogenous insulin secretion and improve glycemic control without increasing hypoglycemic events.

By recombinant technology and site-directed mutagenesis, the insulin molecule has been modified to either shorten (short-acting analogs, insulin aspart, insulin glulisine, and insulin lispro) or prolong (long-acting analogs insulin glargine, insulin detemir, insulin degludec) its action time. Molecular modifications, however, may change the analog interaction with the insulin receptor (IR), in terms of residence time of the ligand on the IR and post-receptor activation of intracellular pathways. Also the binding affinity to IGF-1R can be modified. Therefore a major question is whether insulin analogs, as a result of an imbalanced metabolic versus mitogenic effect, can favor cancer more than native insulin.

In Vitro Experimental Evidences

Since the molecular structure modifications can change the insulin analog affinity for the IR, the IGF-1R, and their intracellular signaling and biological effects, their clinical use has been approved only after the assessment of their mitogenic effect (growth-promoting activity) in benign and malignant cells in vitro.

Malignant cells can respond to insulin and its analogs differently than normal cells because they predominantly express the IR isoform A that has more pronounced mitogenic activity. Moreover, different cancer cells express the insulin receptor and its isoforms at a different level. The studies aimed at investigating how insulin analogs bind and stimulate each IR isoform are difficult because the

large majority of cells express both IR isoforms and no direct measurement of the isoforms of the IR protein is available. To overcome this problem, some studies have been carried out in either engineered cell models expressing only one IR isoform (either only the IR-A or the IR-B) (Sciacca et al. 2010; Sommerfeld et al. 2010) or in malignant cells that naturally express predominantly one IR isoform. These models are not optimal because transfected receptors are often highly overexpressed and cells have a variable genetic background that may interfere. In these models overall data indicate that short-acting insulin analogs bind to both IR isoforms with an affinity similar to that of native insulin or only slightly different. In contrast, long-acting analogs (glargine and detemir, because degludec insulin has been only recently introduced) have a reduced affinity for both IR isoforms (Sciacca et al. 2010; Sommerfeld et al. 2010; Kurtzhals et al. 2000; Markussen et al. 1996).

Few studies have also measured the insulin analogs' dissociation from the two IR isoforms, an important parameter since the activation of post-receptor pathways also depends on the ligand residency time on the receptor. Although data are scarce and not fully comparable because of the different experimental conditions, in general the short-acting analogs' dissociation from the IR appears similar to that of native insulin, while the long-acting analogs have a slower dissociation rate (about 1.5–3.0 times longer) both when using cell models and solubilized receptors.

When analogs were studied in the same cell model, both short-acting and long-acting insulin analogs activated the phosphorylation of IR isoforms in a similar manner to human insulin (Sciacca et al. 2010; Sommerfeld et al. 2010). However, in spite of similar IR phosphorylation, differences between insulin and insulin analogs were present at downstream post-receptor level. Only subtle differences were observed for short-acting analogs for the stimulation of AKT (a marker of the metabolic signaling pathway) and ERK phosphorylation (a marker of the mitogenic signaling pathway). More relevant differences in comparison with insulin were observed for long-acting analogs. Via the IR-A isoform, both detemir and glargine activated AKT similarly to insulin but ERK significantly more than insulin. Via the IR-B isoform, both long-acting analogs activated AKT less than insulin but ERK similarly to insulin. In both cases the result was an abnormal ERK/AKT activation ratio, clearly shifted in favor of ERK (Sciacca et al. 2010; Vigneri et al. 2010) (Fig. 2).

The data regarding the insulin stimulation of the IGF-1 receptor (IGF-1R) are somewhat controversial. Since the cancer risk associated with the IGF-1R activation is well recognized (Furstenberger and Senn 2002; LeRoith and Roberts 2003; Renehan et al. 2004; LeRoith and Yakar 2007), it is a serious concern the possibility that the modified molecular structure of insulin analogs may cause an increased affinity for the IGF-1R. If this is the case, in fact, the mitogenic potential of the analogs could be increased in respect to insulin.

Different cell models and different experimental protocols were used to measure analogs' affinity for the IGF-1R overcoming the difficulties due to the interference of the IR present in the cell. The most cited study by Kurtzhals et al. (in the Novo Laboratories) indicated that lispro has a slightly higher affinity for the IGF-1R in comparison to insulin (Kurtzhals et al. 2000), while aspart insulin bound IGF-1R less

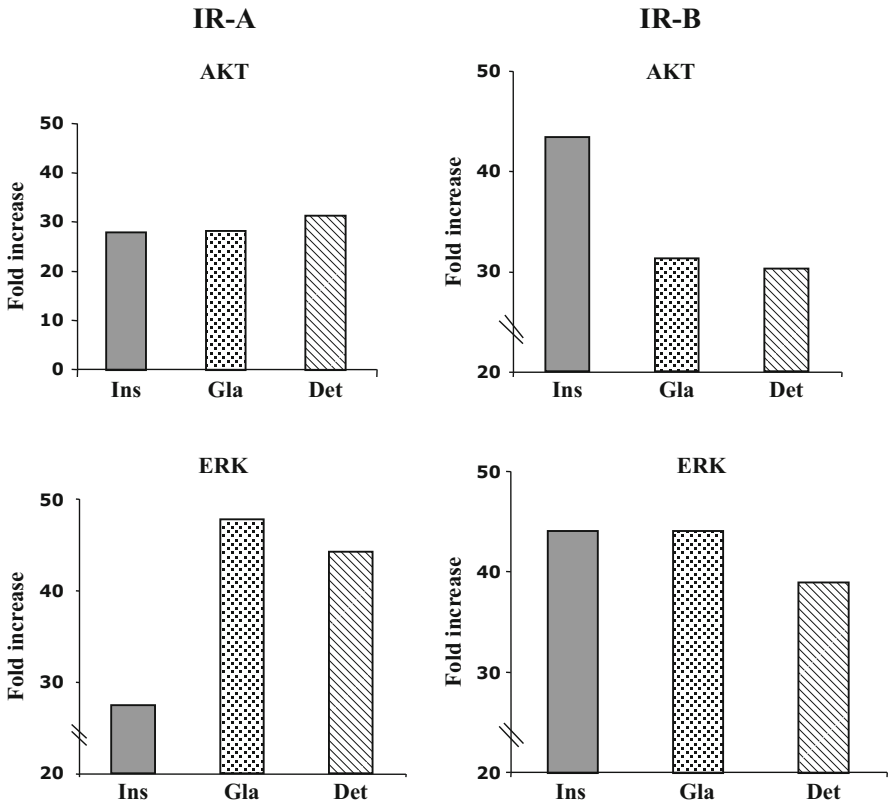

Fig. 2 Post-receptor pathway activation by long-acting insulin analogs. In engineered cells expressing only the IR-A isoform (left panel), the effects of insulin and long-acting analogs glargine and detemir are not different on post-receptor intracellular AKT pathway (mainly metabolic). In contrast, both long-acting analogs cause a markedly increased stimulation of the ERK pathway (mainly mitogenic) in comparison with insulin. In cells expressing only the IR-B isoform (right panel), the effect of the three ligands is similar on the ERK pathway, but the two long-acting analogs have a reduced effect on the AKT pathway. Therefore, long-acting analogs cause an increase of the ERK/AKT activation ratio in comparison with native insulin both in cells expressing only IR-A as well as in IR-B cells. The columns indicate the fold increase (area under the curve) of the phosphorylated effectors in the period 0–10 min of exposure to ligands (Vigneri et al. 2010)

than insulin (Kurtzhals et al. 2000). In an engineered cell model expressing only the human IGF-1R, the three short-acting analogs bound to IGF-1 receptor similarly to native insulin (Sciacca et al. 2010).

In vitro data demonstrated that the long-acting insulin glargine binds to the IGF-1R with a higher affinity than insulin, and some studies attributed to the increased IGF-1R activation the increased mitogenic effect of this analog (Kurtzhals et al. 2000). After glargine injection in patients, however, the proteolytic degradation of glargine produces two active metabolites, M1 and M2, which apparently have

reduced IGF-1R affinity and reduced mitogenic potency relative to insulin (Sommerfeld et al. 2010; Sciacca et al. 2014).

The other long-acting insulin analog, detemir, has been studied much less than glargine. The interaction of this analog with IGF-1R was calculated to be very low, approximately on sixth that of human insulin by Kurtzhals et al. (2000). But in a different model (engineered cells overexpressing IGF-1R and avoiding albumin interference), the two long-acting insulin analogs (detemir and glargine) showed a very similar IGF-1R binding affinity, higher than that of human insulin (Sciacca et al. 2010).

Insulin degludec has been only recently introduced, and, at present, the information on this analog interaction and activation of receptors is limited. Preliminary data indicate that its binding to the IR is similar to that of insulin and that binding to the IGF-1R is lower than the native hormone (Nasrallah and Reynolds 2012).

No data are available on insulin analogs' interactions with hybrid (IR/IGF-1R) receptors and on their post-receptor signaling after hybrid receptor activation.

The growth-promoting effect of insulin analogs was also studied directly in malignant cells. Also these models are only partially satisfactory. The growth rate is remarkably heterogeneous in different malignant cells, and very few studies have compared the proliferative effect of all insulin analogs in the same cell model. Moreover, the mitogenic effect of the analogs has been usually evaluated at concentrations higher than levels in the blood of treated patients (50–100 nM). In general, short-acting analogs stimulated cancer cell proliferation in a similar manner to human insulin (Kurtzhals et al. 2000; Sciacca et al. 2014; Mayer et al. 2008; Shukla et al. 2009; Weinstein et al. 2009), while long-acting analogs stimulated proliferation more than insulin. Although data are not homogeneous, in a variety of cell models, both glargine and detemir caused an increased mitogenic response (Sommerfeld et al. 2010; Kurtzhals et al. 2000; Sciacca et al. 2014). The proliferation of cancer cells was stimulated by these long-acting insulin analogs more than insulin but less than IGF-1 (Sciacca et al. 2014; Weinstein et al. 2009). However, when insulin glargine metabolites M1 and M2 were evaluated, their mitogenic effect was similar to that of human insulin (Sommerfeld et al. 2010; Sciacca et al. 2014).

For the clinical implications, it is remarkable to underline that the biological responses to insulin analogs of cancer cells expressing different levels of the IR and different prevalence of the isoforms IR-A and IR-B and of IGF-1R cannot be predicted on the basis of receptor expression levels (Sciacca et al. 2014). The cell proliferation, invasiveness, and foci formation responses to the analogs are not correlated to the malignant cell receptor content, implying that different factors other than IR expression influence these parameters.

Clinical Studies on Insulin Analogs and Cancer

In 2009 five retrospective observational studies using different diabetes registries were published and raised the issue of the possible increased cancer incidence in diabetic patients treated with insulin analogs (Hemkens et al. 2009; Jonasson et al. 2009; Colhoun 2009; Currie et al. 2009; Dejgaard et al. 2009). In these studies confounding factors and methodological flaws made the results interpretation

questionable and controversial. Nevertheless great concern was raised whether insulin analogs (and mainly insulin glargine) could promote cancer cell proliferation and tumor growth in diabetic patients.

The first retrospective cohort study included more than 127,000 patients treated in Germany with either human insulin, lispro, aspart, or insulin glargine for a mean follow-up time of 1.63 years: a dose-dependent association was found between all insulin analogs and cancer incidence, but, after adjusting for the administered dose, only glargine was related to an increased cancer risk (HR 1.31 for 50 IU daily dose compared to human insulin) (Hemkens et al. 2009).

In the same journal, data from two additional retrospective observational studies, carried out in Sweden and Scotland, were published (Jonasson et al. 2009; Colhoun 2009).

In the Swedish cohort almost 115,000 patients treated with insulin were examined, and only the risk of developing breast cancer was increased among women receiving insulin glargine in monotherapy (RR 1.99, 95% C.I., 1.31–3.03). Other forms of cancer were not increased with insulin glargine (Jonasson et al. 2009).

In the Scottish study, analyzing the national registry, a higher risk of breast cancer was found in a small subset of 447 patients receiving only insulin glargine compared to patients receiving also other insulin analogs (RR 1.55, 95% C.I., 1.01–2.37). The authors explained this result as a possible bias because of the small number of events (Colhoun 2009).

In the same year, another retrospective cohort from the United Kingdom, studying 63,000 patients treated by general practitioners with either insulin or oral hypoglycemic agents, found no significant difference in cancer risk comparing users of insulin analogs versus users of human insulin (Currie et al. 2009).

A fifth study published in the same journal reported no increase of cancer in 3,983 diabetic patients treated with insulin detemir in comparison with 2,661 patients treated with NPH insulin (Dejgaard et al. 2009). Moreover, a small but more detailed retrospective case-control study found that cancer was increased in diabetic patients treated with a higher dose of insulin glargine (Mannucci et al. 2010).

Because of their retrospective nature, all these studies can be strongly criticized because patients were not randomized to treatment groups, and many potentially relevant confounders such as body mass index, duration of diabetes, smoking habit, and variable and not constant insulin dosage occurred in all series. Moreover, the follow-up time was very short in most cases (less than 3 years).

The issue of the possible pro-cancer effect of long-acting insulin analogs (especially at high dosage) was strongly debated until the data from a prospective study become available.

The ORIGIN trial was aimed at evaluating the cardiovascular risk in patients treated with glargine insulin. At the same time, the risk of cancer associated with insulin glargine treatment was also evaluated (Gerstein et al. 2012). A total of 12,537 participants were enrolled with an average follow-up of 6.2 years. The authors did not find an increased cancer incidence in the insulin glargine users (HR, 1.00; 95% C.I. 0.88–1.13).

The ORIGIN trial, much cited to exclude the risk of cancer associated with insulin glargine treatment (Gerstein et al. 2012), has several weaknesses. Among them are the average follow-up of only 6.2 years, definitely too short for a potential mild carcinogen to cause cancer, the inclusion of 62% of patients that discontinued glargine treatment temporarily or permanently, the low dose of insulin administered (median 0.3–0.4 units/kg body weight), and the possible interference of different medications such as sulfonylureas (that may favor cancer) and metformin (with an anticancer effect) (Vigneri et al. 2012).

Recently, a systematic review of observational studies, including 16 cohort and 3 case-control studies, examined the association between long-acting insulin analogs and cancer incidence. All studies evaluated insulin glargine and four studies evaluated also insulin detemir. Thirteen out of 15 studies reported no association between insulin glargine or insulin detemir and cancer. Four studies reported an increased risk of breast cancer with insulin glargine. In all these studies, the follow-up was very short (ranged from 0.9 to 7.0 years), and other important methodological shortcomings were present in all of them. For instance, reverse causality was an unexplored possibility: cancer often has a long preclinical period between the biological initiation and the clinical diagnosis. During this subclinical phase, insulin requirements might be affected by the undetected cancer and lead to increased dosage. To the unaware observer, this treatment change can appear as favoring cancer, while vice versa it is cancer that produces the treatment changes (Pocock and Smeeth 2009; Wu et al. 2016).

Moreover, although observational studies can usefully detect unexpected drug effects, they may also favor biased conclusions. In these retrospective studies, the clinical decision determining treatment was not random, and patients were prescribed additional therapies for health-related reasons. Therefore, despite adjustment for confounders, residual selection bias might distort true differences between treatments. For instance, patients with poor glycemic control are more frequently treated with insulin. The difference with patients in better control and receiving oral antidiabetic drugs might result in confounding factors: an increased cancer occurrence may be related not only to drug differences but also to the different metabolic control and general condition of the patient when the therapy is selected. Moreover, the higher doses of insulin required in diabetic patients with poor metabolic control and a cancer can produce an artifact: the higher mortality could be not a true consequence of treatment but rather the consequence of the advancement of the metabolic disease.

In conclusion, the available clinical evidence can neither demonstrate nor exclude an increased risk of cancer in diabetic patients when treated with long-term insulin analogs in comparison with normal insulin.

Oral Antidiabetic Drugs

The three major oral antidiabetic drug families (sulfonylureas, biguanides, and thiazolidinediones) have a different mechanism of action. Sulfonylureas stimulate endogenous insulin secretion (causing hyperinsulinemia), while the other two

categories of antidiabetic compounds are insulin sensitizers, i.e., they make tissues more responsive to insulin and, therefore, decrease insulin levels. If hyperinsulinemia plays a role in increasing cancer risk and progression in diabetic patients, it is reasonable to expect that these drugs will have a different effect on the association between diabetes and cancer.

The first group of drugs (sulfonylureas) is secretagogues, i.e., increase insulin secretion and cause hyperinsulinemia. As expected, therefore, they have been associated with an increased risk of cancer (Bowker et al. 2006). Different sulfonylureas may have different effects, with glyburide being more deleterious than gliclazide (Monami et al. 2007). The association between sulfonylureas' use in patients with breast cancer and all-cause mortality has been recently evaluated. In 1,057 patients with diabetes diagnosed before the occurrence of breast cancer, sulfonylurea use for less than 2 years was associated with increased breast cancer-specific mortality (adjusted HR 1.70; 95% C.I. 1.18–2.46), but longer use was not (adjusted HR 0.94; 95% C.I. 0.54–1.66). In 706 patients who developed diabetes after breast cancer, sulfonylurea treatment was strongly associated with cancer-specific mortality (adjusted HR 3.64; 95% C.I. 2.16–6.16) (Vissers et al. 2015). Although the sulfonylurea effect on cancer risk is usually attributed to the prolonged hyperinsulinemia that these drugs induce in patients, a direct effect on cancer (either positive or negative) cannot be excluded.

The biguanide metformin is of special interest because it is the recommended first-line treatment in type 2 DM patients and because of the attributed anticancer property.

Since the first observation in 2005 (Evans et al. 2005), many clinical studies have reported a lower prevalence of cancer in diabetic patients treated with metformin. In 10 years nearly 3,000 papers have been published on metformin and cancer, and most clinical studies suggest that in diabetic patients, metformin has a favorable anticancer effect on colon-rectal, breast, prostate, liver, pancreas, gastrointestinal, ovarian, and other cancers (Rizos and Elisaf 2013). Moreover, in vitro studies documented an antiproliferative effect of metformin in a variety of experimental models. Metformin has also been tested for cancer prevention in nondiabetic individuals and as an anticancer adjuvant drug in oncologic patients.

A large number of observational clinical studies suggest that treating diabetic patients with metformin reduces cancer incidence and cancer mortality in comparison with other glucose-lowering agents (Yin et al. 2013). This anticancer effect of metformin is not influenced by the additional treatment of diabetes with insulin and/or sulfonylureas and is more evident for some tumors (like liver and breast cancers) suggesting the possibility of a cancer-specific effect of the drug.

However, not all clinical studies found a decreased risk of cancer in patients treated with metformin, and, because of the retrospective design of the clinical studies, the nonrandom allocation of metformin, and the possibility of time-related biases (Suissa and Azoulay 2012), the presence and the relevance of the anticancer effect of metformin in clinical practice are still controversial.

The in vitro results consistently indicate that metformin reduces cancer cell proliferation, promotes apoptosis, and reduces the epithelial-mesenchymal transition.

In vitro studies, however, do not necessarily have a high translational value: metformin is usually added to cultured malignant cells at millimolar concentrations, hundred times higher than plasma concentrations reached during patient treatment (Dowling et al. 2012). Therefore, some of the direct effects of metformin reported in vitro may not be relevant in the clinical situation.

The positive effects observed in diabetic patients have suggested that the beneficial anticancer effects of metformin may occur also in nondiabetic patients. Metformin, therefore, has been studied for cancer prevention in both diabetic and nondiabetic individuals. Some evidences indicate that the anticancer action of metformin could be more effective in individuals with insulin resistance, but available data are insufficient to confirm this possibility. Finally, few reports indicate that metformin can potentiate the efficacy of chemotherapy in cancer patients, with prevention of relapse via a specific action on cancer stem cells. These data, however, are only preliminary.

How can metformin, the most used antidiabetes drug, exert such important effects in cancer? Two major mechanisms have been hypothesized.

First, metformin is an insulin sensitizer that reduces insulin resistance and, consequently, lowers the compensatory hyperinsulinemia that is considered a major risk factor for cancer initiation and progression. This indirect, insulin-mediated anticancer effect of metformin is believed to be of key importance in all individuals with hyperinsulinemia including, in addition to type 2 diabetes, obesity, metabolic syndrome, and polycystic ovary syndrome. Second, metformin is believed to have also direct, not insulin-mediated effects on cancer. This biguanide influences cell metabolism because it stimulates the AMP-activated protein kinase (AMPK), an intracellular sensor of nutrient availability, and, therefore, is a major regulator of cellular energy homeostasis. By inhibiting the respiratory chain complex I at mitochondrion level, metformin decreases ATP production with the consequent increase of AMT and ADP which activates the AMPK (Long and Zierath 2006). In the situation of energy deficiency, AMPK is the sensor that will decrease all energy-consuming processes. As already mentioned, cancer cells require more energy than normal cells to survive and grow: metformin, by reducing nutrient availability, will slow down growth for these hungry cells. In addition, AMPK phosphorylation will influence its major upstream activator, the liver kinase B1 (LKB1), a tumor suppressor that negatively regulates mTOR (mammalian target of rapamycin) signaling pathway, which is overactive in most cancers. Metformin, therefore, exerts its direct anticancer effect by stimulating the LKB1/AMPK signaling pathway, a tumor suppressor axis.

Additional anticancer mechanisms of metformin like p53 activation, cell cycle arrest, and promotion of malignant cell apoptosis have also been described in specific cancer cells and indicate that the antiproliferative effect of this drug may follow multiple molecular pathways and mechanisms in different cells (Fig. 3).

The issue of metformin and cancer is relevant for both scientific and socioeconomic aspects because metformin is the most used first-line drug in type 2 diabetes, with minor side effects and with a low cost. Overall the clinical evidences and the plausibility of its mechanisms of action support a favorable anticancer effect of this drug. Although the metformin effect in cancer may be variable, according to the variability of the metabolic and oncologic situation of the individual patient, its use

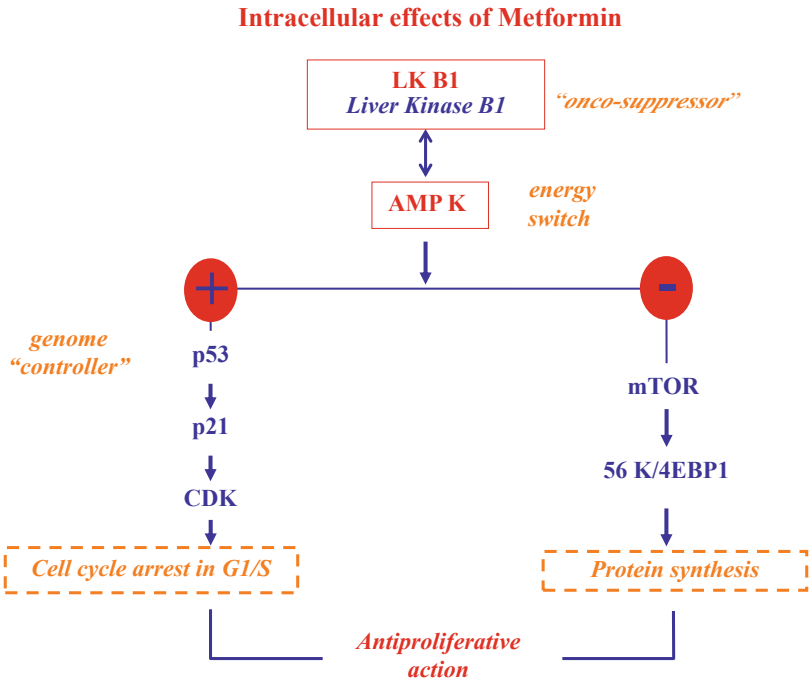

Fig. 3 Intracellular effects of metformin. In addition to its action as insulin sensitizer, reducing hyperglycemia due to insulin resistance, metformin also has multiple direct effects at intracellular level. These effects reduce cancer cell proliferation with multiple mechanisms that can be AMPK dependent but also independent

for opposing the pro-cancer effect of type 2 diabetes should be recommended because, at worst, metformin is beneficial for its metabolic activity and has no detrimental effect on cancer incidence or mortality when compared to other antidiabetes agents.

The other insulin-sensitizing drugs (thiazolidinediones) are more controversial. Beneficial (Govindarajan et al. 2007), neutral (Koro et al. 2007), or even deleterious (Ramos-Nino et al. 2007) effects have been reported for different types of cancer. Recently thiazolidinediones have been shown to induce differentiation in solid tumors such as thyroid differentiated/anaplastic cancers (Ferrari et al. 2016). The biological mechanism of these compounds is to activate PPARgamma receptors which in several in vitro experimental models have shown a potential anticancer effect (Aiello et al. 2006). In addition to lowering hyperinsulinemia, this additional effect can explain an anticancer effect of glitazones.

New Antidiabetes Drugs

Glucagon-like peptide 1 receptor (GLP-1R) agonists and GLP-1 degradation inhibitors (dipeptidyl peptidase-4 inhibitor) are drugs that mimic the action of native GLP-1 and have become a common second line therapy for type 2 diabetes.

Incretin use is too recent to have reliable data on their association with cancer. The increased incidence of medullary thyroid cancer reported in rodents has not been confirmed in humans (Vangoitsenhoven et al. 2012). Their trophic effect on β-cells has raised some concerns for a possible pro-cancer effect in pancreatic target cells expressing the receptors (Labuzek et al. 2013). In two trials (SAVOR-TIMI and EXAMINE) (Raz et al. 2014; White et al. 2013) that have evaluated the cardiovascular effects of gliptins, the authors have examined also the risk of pancreatic cancer. The SAVOR-TIMI compared saxagliptin versus placebo with a median 2.1 years follow-up and evaluated pancreatic cancer as a safety outcome. No indication for an increased risk of pancreatic cancer was found (5 events with saxagliptin vs. 12 with placebo) (Raz et al. 2014). The EXAMINE trial, comparing alogliptin versus placebo, found no report of pancreatic cancer with 1.5 years of median follow-up in 5,380 patients (White et al. 2013). With regard to different cancers, other than pancreatic and thyroid cancers, available studies indicated no association between cancer and incretin drug use in humans. Based on the previous evidences, however, continuous monitoring of the cancer issue is required for incretin-based therapies, even though the benefits may outweigh the potential and minimal cancer risk in poorly controlled patients with T2DM.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a recently introduced new class of oral glucose-lowering drugs for treating type 2 diabetes. They decrease plasma glucose levels by selectively inhibiting renal glucose reabsorption and increasing urinary glucose excretion. In a recently published meta-analysis of 46 randomized controlled trials (RCTs), 580 incident cases of cancer were observed among 34,569 people with type 2 diabetes. SGLT2 inhibitors were not significantly associated with an increased risk of overall cancer (OR 1.14 [95% C.I. 0.96, 1.36]) when compared with placebo or other glucose-lowering treatments. Therefore, in the short-term (mean trial duration 61 weeks), current evidence does not support a significant association between SGLT2 inhibitors and an increased risk of cancer (Tang et al. 2017). Considering the exposure to increased glucose and the higher frequency of local infections of the genital and urinary excretion system (Rizzi and Trevisan 2016) in SGLT2 inhibitor-treated patients, their long-term effects on cancer remain uncertain.

Cancer Drugs Causing Hyperglycemia and Insulin Resistance

The cancer therapies are addressed to destroy malignant cells by interfering with their metabolic and survival mechanisms. At the same time, cancer drugs may also influence the function and survival of normal cells causing a variety of adverse events including changes in glucose metabolism. The most common consequence in this field is hyperglycemia, often accompanied by hyperinsulinemia. These changes can be of variable severity and duration: severity grade 1–4 of glucose derangement can be either reversible after therapy discontinuation or permanent (newly developed diabetes). At this regard it may be useful to remind diabetologists and

endocrinologists the criteria oncologists use to classify the severity of adverse events as far as glucose level abnormalities are concerned.

Grade	Hyperglycemia (fasting)	Hypoglycemia
1. Mild	126–160 mg/dL	70–55 mg/dL
2. Moderate	>160–250 mg/dL	<55–40 mg/dL
3. Severe	>250–500 mg/dL	<40–30 mg/dL
4. Life-threatening or disabling	>500 mg/dL	<30 mg/dL

The cutoff values for moderate fasting hyperglycemia according to the Common Terminology Criteria for Adverse Events (CTCAE), therefore, can already indicate a serious and urgent metabolic problem in a fragile and often old patient with systemic or organ-specific complications of diabetes and under multiple treatments.

Therefore, the adverse effects of drugs for treating cancer on glucose metabolism can complicate the patient treatment and reduce his/her well-being and also survival when hyperglycemia is severe, up to ketoacidosis or hyperosmolar coma. Moreover, there is considerable evidence that increased glucose and/or insulin levels will increase proliferation, survival, and migration of cancer cells. Therefore, even mild or moderate hyperglycemia and hyperinsulinemia can promote cancer progression and worsen treatment outcome (Brunello et al. 2011; Zeng et al. 2010) with the mechanisms previously indicated.

The most frequent cancer therapies that will affect glucose metabolism in an oncologic patient (and more so in a patient having both diabetes and cancer) are glucocorticoids, hormone therapies, and targeted therapies.

Glucocorticoids

Glucocorticoids are frequently used in cancer patients at a high dosage to both prevent and/or cure allergic reactions, inflammatory states, and edema and to alleviate fatigue, pain, and nausea. Moreover, glucocorticoids are a relevant component of chemotherapy treatment protocols. Glucocorticoids have a potent diabetogenic effect because at high doses, they cause severe insulin resistance which can be compensated by hyperinsulinemia only when the patient's pancreas is functioning well. Glucocorticoid administration may also result in the worsening of a condition of prediabetes or mild undiagnosed diabetes that can be transformed into a clinically severe illness, possibly leading to the deadly hyperosmolar coma (Clore and Thurby-Hay 2009; Kuo et al. 2015). Due to the high prevalence of diabetes and prediabetes in the aged population (over 15–20%, representing also the population category more prone to cancer), this is a real health risk. The risk level depends on the dose and duration of treatment and the metabolic condition of the patients. At higher risk of unknown diabetes are obese patients with familiarity for diabetes.

This diabetogenic complication of glucocorticoid administration may not be recognized when only fasting glycemia is measured because glucocorticoids mainly alter postprandial glucose, while fasting glucose may be only mildly affected.

Prandial insulin is the treatment of choice in these patients using short-acting analogs. When the patient is an already diagnosed diabetic patient under "basal-bolus" insulin treatment, prandial insulin dose should be increased (Ariaans et al. 2015).

Antiandrogens and Other Hormonal Therapies

Also *antiandrogens*, frequently used for the treatment of prostate cancer, may adversely affect glucose metabolism. Androgen deprivation therapy causes a variety of metabolic abnormalities that include decreased insulin sensitivity and altered lipid profile and, therefore, increased risk of diabetes and cardiovascular disease (Saylor and Smith 2009). Moreover, androgens are important determinants of body composition: their inhibition increases fat mass and decreases lean body mass. In patients treated with either gonadotropin-releasing hormone agonists (GnRH, whose chronic administration inhibits gonadotropins) and/or nonsteroidal antiandrogens (like flutamide and bicalutamide that compete at receptor level) or cyproterone acetate (a steroid antiandrogen and antigonadotropin), these anti-androgen treatments may cause "sarcopenic obesity," a combination of excess body weight and reduced muscle mass. Fat accumulation is primarily subcutaneous and is often associated with increased total cholesterol, triglycerides, and HDL. These changes result in insulin resistance, hyperglycemia, and, sometimes, diabetes. Among over 70,000 patients with locoregional prostate cancer, individuals treated with GnRH had a 44% increased risk of developing diabetes (Keating et al. 2006).

Glucose metabolism can also be altered by *somatostatin long-acting analogs*, in particular by pasireotide (Quinn et al. 2012), a novel multireceptor-targeted somatostatin analog (Grasso et al. 2015). These drugs are employed to treat advanced or metastatic neuroendocrine tumors (NET) and inhibit the release of numerous hormones, including insulin and incretins (like glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]). Hyperglycemia can appear particularly in the period following administration.

Cancer Drugs Targeting the Insulin Signaling Pathways

Because of the relevant role of insulin and IGF-1 in promoting cancer cell growth, numerous drugs have been developed to inhibit the receptors of these hormones and the intracellular signaling pathways. Due to the role of insulin signaling on glucose metabolism, the inhibition of these pathways may cause hyperglycemia, insulin resistance, and compensatory hyperinsulinemia (Yang et al. 2016; Vigneri et al. 2015).

Different inhibitors targeting different components of the signaling pathway may cause different effects on glucose homeostasis. Within a wide heterogeneity

due to differences in the drugs and also in the patients studied, it appears that PI3K/Akt, IR/IGF-1R, and mTOR inhibitors can cause mild to severe hyperglycemia (Ariaans et al. 2015; Verges and Cariou 2015). Everolimus, an inhibitor of mTOR (mammalian target of rapamycin) often used in breast and kidney cancer, can cause grade 1–2 hyperglycemia in up to 40–50% of patients and grade 3–4 hyperglycemia in up to 10–20% of cases. The use of this drug requires, therefore, glycemic surveillance.

Approach to Hyperglycemia Induced by Cancer Treatment

Early treatment of hyperglycemia and hyperinsulinemia induced by cancer drugs will not only ameliorate the patient clinical conditions but will also prevent the detrimental effects of the excess of glucose and insulin on cancer growth, recurrence, and resistance to treatment.

Intervention must be personalized to patient characteristics and to the mechanism of the cancer drug-inducing hyperglycemia.

Lifestyle intervention with appropriate diet and exercise is useful in all patients because it can reduce glucose and insulin levels and has been demonstrated to improve cancer survival rates (Pierce et al. 2007; Je et al. 2013). Metformin, a first-line and widely used insulin sensitizer, is a good option in all patients with insulin resistance induced by cancer treatment.

Insulin can be required when an absolute insulin deficiency is present or a short-term effect is necessary (like prandial insulin in glucocorticoid-induced hyperglycemia). In the case of newly diagnosed hyperglycemia due to cancer treatment and requiring insulin, it is important that physicians remember the psychological difficulties of the patient, often resistant to add a complicated treatment schedule with complicated, non-familiar devices (glucometer, glucose monitoring diary, pens, injection procedure and sites) since his/her major worry is the oncologic disease. Both the patient and the physician must not underestimate the deleterious effects of the altered metabolic condition. Hyperglycemia may show no evident signs at the beginning but can make the cancer more resistant to treatment and also cause severe life-threatening conditions like dehydration and hyperosmolar coma. Information and education are, therefore, of major importance for these patients.

The increased risk of cancer incidence and mortality in diabetic patients has become a clinically relevant issue. A very recent report in Australians registered in the National Diabetes Services Scheme indicates that in the years 2000–2011, age-standardized mortality rates in diabetic patients have decreased for all-cause and for cardiovascular diseases but not for cancer (Harding et al. 2016).

Cancer is a leading cause of death in diabetes, has progressively increased, and now accounts for 27% and 33% of all deaths in type 1 and type 2 diabetic patients, respectively (Harding et al. 2015).

This increasing burden of cancer in diabetic patients requires, therefore, attention from scientists, general physicians, and specialists and from health policy-makers.

References

Aiello A, Pandini G, Frasca F, Conte E, Murabito A, Sacco A, et al. Peroxisomal proliferator-activated receptor-gamma agonists induce partial reversion of epithelial-mesenchymal transition in anaplastic thyroid cancer cells. Endocrinology. 2006;147(9):4463–75.

Ariaans G, de Jong S, Gietema JA, Lefrandt JD, de Vries EG, Jalving M. Cancer-drug induced insulin resistance: innocent bystander or unusual suspect. Cancer Treat Rev. 2015; 41(4):376–84.

Bansal D, Bhansali A, Kapil G, Undela K, Tiwari P. Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. Prostate Cancer Prostatic Dis. 2013;16(2):151–8. S1

Bao C, Yang X, Xu W, Luo H, Xu Z, Su C, et al. Diabetes mellitus and incidence and mortality of kidney cancer: a meta-analysis. J Diabetes Complications. 2013;27(4):357–64.

Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA. 2008;300(23):2754–64.

Barone I, Catalano S, Gelsomino L, Marsico S, Giordano C, Panza S, et al. Leptin mediates tumor-stromal interactions that promote the invasive growth of breast cancer cells. Cancer Res. 2012;72(6):1416–27.

Barrett-Connor E. Lower endogenous androgen levels and dyslipidemia in men with non-insulin-dependent diabetes mellitus. Ann Intern Med. 1992;117(10):807–11.

Basso D, Valerio A, Seraglia R, Mazza S, Piva MG, Greco E, et al. Putative pancreatic cancer-associated diabetogenic factor: 2030 MW peptide. Pancreas. 2002;24(1):8–14.

Belfiore A, Frasca F, Pandini G, Sciacca L, Vigneri R. Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. Endocr Rev. 2009;30(6):586–623.

Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, et al. Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. Eur J Cancer. 2011;47(13):1928–37.

Betancourt-Albrecht M, Cunningham GR. Hypogonadism and diabetes. Int J Impot Res. 2003; 15(Suppl 4):S14–20.

Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. Diabetologia. 2004;47(6):1071–8.

Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care. 2006;29(2):254–8.

Brunello A, Kapoor R, Extermann M. Hyperglycemia during chemotherapy for hematologic and solid tumors is correlated with increased toxicity. Am J Clin Oncol. 2011;34(3):292–6.

Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625–38.

Carstensen B, Read SH, Friis S, Sund R, Keskimaki I, Svensson AM, et al. Cancer incidence in persons with type 1 diabetes: a five-country study of 9,000 cancers in type 1 diabetic individuals. Diabetologia. 2016;59(5):980–8.

Castillo JJ, Mull N, Reagan JL, Nemr S, Mitri J. Increased incidence of non-Hodgkin lymphoma, leukemia, and myeloma in patients with diabetes mellitus type 2: a meta-analysis of observational studies. Blood. 2012;119(21):4845–50.

Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. Gastroenterology. 2005;129(2):504–11.

Chari ST, Leibson CL, Rabe KG, Timmons LJ, Ransom J, de Andrade M, et al. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. Gastroenterology. 2008;134(1):95–101.

Chen HF, Li CY, Chen P, See TT, Lee HY. Seroprevalence of hepatitis B and C in type 2 diabetic patients. J Chin Med Assoc. 2006;69(4):146–52.

Chow WH, Gridley G, Fraumeni JF Jr, Jarvholm B. Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med. 2000;343(18):1305–11.

Clore JN, Thurby-Hay L. Glucocorticoid-induced hyperglycemia. Endocr Pract. 2009;15(5): 469–74.

Colhoun HM. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. Diabetologia. 2009;52(9):1755–65.
Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol. 2004;159(12):1160–7.
Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia. 2009;52(9):1766–77.
Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. Gut. 2005;54(4):533–9.
De Block CE, De Leeuw IH, Van Gaal LF. High prevalence of manifestations of gastric autoimmunity in parietal cell antibody-positive type 1 (insulin-dependent) diabetic patients. The Belgian Diabetes Registry. J Clin Endocrinol Metab. 1999;84(11):4062–7.
De Bruijn KM, Arends LR, Hansen BE, Leeflang S, Ruiter R, van Eijck CH. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. Br J Surg. 2013;100(11):1421–9.
Dejgaard A, Lynggaard H, Rastam J, Krogsgaard Thomsen M. No evidence of increased risk of malignancies in patients with diabetes treated with insulin detemir: a meta-analysis. Diabetologia. 2009;52(12):2507–12.
Dibble CC, Cantley LC. Regulation of mTORC1 by PI3K signaling. Trends Cell Biol. 2015; 25(9):545–55.
Dowling RJ, Niraula S, Stambolic V, Goodwin PJ. Metformin in cancer: translational challenges. J Mol Endocrinol. 2012;48(3):R31–43.
El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol. 2006;4(3):369–80.
Elwing JE, Gao F, Davidson NO, Early DS. Type 2 diabetes mellitus: the impact on colorectal adenoma risk in women. Am J Gastroenterol. 2006;101(8):1866–71.
Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ. 2005;330(7503):1304–5.
Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA. 1995;273(20):1605–9.
Ferrari SM, Materazzi G, Baldini E, Ulisse S, Miccoli P, Antonelli A, et al. Antineoplastic effects of PPARgamma agonists, with a special focus on thyroid cancer. Curr Med Chem. 2016;23:636.
Folsom AR, Anderson KE, Sweeney C, Jacobs DR Jr. Diabetes as a risk factor for death following endometrial cancer. Gynecol Oncol. 2004;94(3):740–5.
Frasca F, Pandini G, Scalia P, Sciacca L, Mineo R, Costantino A, et al. Insulin receptor isoform A, a newly recognized, high-affinity insulin-like growth factor II receptor in fetal and cancer cells. Mol Cell Biol. 1999;19(5):3278–88.
Frasca F, Pandini G, Sciacca L, Pezzino V, Squatrito S, Belfiore A, et al. The role of insulin receptors and IGF-I receptors in cancer and other diseases. Arch Physiol Biochem. 2008; 114(1):23–37.
Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia. 2007;50(7):1365–74.
Furstenberger G, Senn HJ. Insulin-like growth factors and cancer. Lancet Oncol. 2002;3(5): 298–302.
Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. JAMA. 2000;283(19):2552–8.
Garofalo C, Surmacz E. Leptin and cancer. J Cell Physiol. 2006;207(1):12–22.
Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, Maggioni AP, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012;367(4):319–28.
Govindarajan R, Ratnasinghe L, Simmons DL, Siegel ER, Midathada MV, Kim L, et al. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. J Clin Oncol. 2007;25(12):1476–81.
Grasso LF, Auriemma RS, Pivonello R, Colao A. Adverse events associated with somatostatin analogs in acromegaly. Expert Opin Drug Saf. 2015;14(8):1213–26.

Green A, Jensen OM. Frequency of cancer among insulin-treated diabetic patients in Denmark. Diabetologia. 1985;28(3):128–30.

Guraya SY. Association of type 2 diabetes mellitus and the risk of colorectal cancer: a meta-analysis and systematic review. World J Gastroenterol. 2015;21(19):6026–31.

Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation. Diabetes Care. 2015;38(2):264–70.

Harding JL, Shaw JE, Peeters A, Davidson S, Magliano DJ. Age-specific trends from 2000–2011 in all-cause and cause-specific mortality in type 1 and type 2 diabetes: a cohort study of more than one million people. Diabetes Care. 2016;39(6):1018–26.

Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994. Diabetes Care. 1998;21 (4):518–24.

Hassan MM, Curley SA, Li D, Kaseb A, Davila M, Abdalla EK, et al. Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer. 2010; 116(8):1938–46.

Hemkens LG, Grouven U, Bender R, Gunster C, Gutschmidt S, Selke GW, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia. 2009;52(9):1732–44.

Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. Association between physical activity and mortality in colorectal cancer: a meta-analysis of prospective cohort studies. Int J Cancer. 2013; 133(8):1905–13.

Jonasson JM, Ljung R, Talback M, Haglund B, Gudbjornsdottir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. Diabetologia. 2009;52(9):1745–54.

Kaaks R. Nutrition, hormones, and breast cancer: is insulin the missing link? Cancer Causes Control. 1996;7(6):605–25.

Kalli KR, Falowo OI, Bale LK, Zschunke MA, Roche PC, Conover CA. Functional insulin receptors on human epithelial ovarian carcinoma cells: implications for IGF-II mitogenic signaling. Endocrinology. 2002;143(9):3259–67.

Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2006;15(11):2056–62.

Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006;24(27):4448–56.

Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab. 2001;280(5):E745–51.

Kido Y, Nakae J, Accili D. Clinical review 125: the insulin receptor and its cellular targets. J Clin Endocrinol Metab. 2001;86(3):972–9.

Koro C, Barrett S, Qizilbash N. Cancer risks in thiazolidinedione users compared to other anti-diabetic agents. Pharmacoepidemiol Drug Saf. 2007;16(5):485–92.

Kuo T, McQueen A, Chen TC, Wang JC. Regulation of glucose homeostasis by glucocorticoids. Adv Exp Med Biol. 2015;872:99–126.

Kurtzhals P, Schaffer L, Sorensen A, Kristensen C, Jonassen I, Schmid C, et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. Diabetes. 2000;49(6):999–1005.

Labuzek K, Kozlowski M, Szkudlapski D, Sikorska P, Kozlowska M, Okopien B. Incretin-based therapies in the treatment of type 2 diabetes – more than meets the eye? Eur J Intern Med. 2013;24(3):207–12.

Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97(22):1679–87.

Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer. 2007;121(4):856–62.

Lee JY, Jeon I, Lee JM, Yoon JM, Park SM. Diabetes mellitus as an independent risk factor for lung cancer: a meta-analysis of observational studies. Eur J Cancer. 2013;49(10):2411–23.
LeRoith D, Roberts CT Jr. The insulin-like growth factor system and cancer. Cancer Lett. 2003; 195(2):127–37.
LeRoith D, Yakar S. Mechanisms of disease: metabolic effects of growth hormone and insulin-like growth factor 1. Nat Clin Pract Endocrinol Metab. 2007;3(3):302–10.
Liao C, Zhang D, Mungo C, Tompkins DA, Zeidan AM. Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. Gynecol Oncol. 2014;135(1):163–71.
Limburg PJ, Vierkant RA, Fredericksen ZS, Leibson CL, Rizza RA, Gupta AK, et al. Clinically confirmed type 2 diabetes mellitus and colorectal cancer risk: a population-based, retrospective cohort study. Am J Gastroenterol. 2006;101(8):1872–9.
Lindblad P, Adami HO. Kidney cancer. In: Adami HO, Hunter D, Trichopoulos D, editors. Textbook of cancer epidemiology. New York: Oxford University Press; 2002. p. 467–85.
Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE. The impact of diabetes on survival following breast cancer. Breast Cancer Res Treat. 2008;109(2):389–95.
Long YC, Zierath JR. AMP-activated protein kinase signaling in metabolic regulation. J Clin Invest. 2006;116(7):1776–83.
Luo W, Cao Y, Liao C, Gao F. Diabetes mellitus and the incidence and mortality of colorectal cancer: a meta-analysis of 24 cohort studies. Colorectal Dis. 2012;14(11):1307–12.
Ma J, Li H, Giovannucci E, Mucci L, Qiu W, Nguyen PL, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. Lancet Oncol. 2008;9(11):1039–47.
Macheda ML, Rogers S, Best JD. Molecular and cellular regulation of glucose transporter (GLUT) proteins in cancer. J Cell Physiol. 2005;202(3):654–62.
Mannucci E, Monami M, Balzi D, Cresci B, Pala L, Melani C, et al. Doses of insulin and its analogues and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care. 2010;33(9):1997–2003.
Markussen J, Havelund S, Kurtzhals P, Andersen AS, Halstrom J, Hasselager E, et al. Soluble, fatty acid acylated insulins bind to albumin and show protracted action in pigs. Diabetologia. 1996; 39(3):281–8.
Mayer D, Shukla A, Enzmann H. Proliferative effects of insulin analogues on mammary epithelial cells. Arch Physiol Biochem. 2008;114(1):38–44.
Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB 3rd, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol. 2003;21(3):433–40.
Mitri J, Castillo J, Pittas AG. Diabetes and risk of non-Hodgkin's lymphoma: a meta-analysis of observational studies. Diabetes Care. 2008;31(12):2391–7.
Monami M, Balzi D, Lamanna C, Barchielli A, Masotti G, Buiatti E, et al. Are sulphonylureas all the same? A cohort study on cardiovascular and cancer-related mortality. Diabetes Metab Res Rev. 2007;23(6):479–84.
Muti P, Quattrin T, Grant BJ, Krogh V, Micheli A, Schunemann HJ, et al. Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev. 2002; 11(11):1361–8.
Nasrallah SN, Reynolds LR. Insulin degludec, the new generation basal insulin or just another basal insulin? Clin Med Insights Endocrinol Diabetes. 2012;5:31–7.
Noy A, Bilezikian JP. Clinical review 63: diabetes and pancreatic cancer: clues to the early diagnosis of pancreatic malignancy. J Clin Endocrinol Metab. 1994;79(5):1223–31.
Oldenburg B, Diepersloot RJ, Hoekstra JB. High seroprevalence of *Helicobacter pylori* in diabetes mellitus patients. Dig Dis Sci. 1996;41(3):458–61.
Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology. 2008;134(4):981–7.
Pannala R, Basu A, Petersen GM, Chari ST. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. Lancet Oncol. 2009;10(1):88–95.
Papa V, Pezzino V, Costantino A, Belfiore A, Giuffrida D, Frittitta L, et al. Elevated insulin receptor content in human breast cancer. J Clin Invest. 1990;86(5):1503–10.

Pierce JP, Stefanick ML, Flatt SW, Natarajan L, Sternfeld B, Madlensky L, et al. Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. J Clin Oncol. 2007;25(17):2345–51.

Pocock SJ, Smeeth L. Insulin glargine and malignancy: an unwarranted alarm. Lancet. 2009; 374(9689):511–3.

Quinn TJ, Yuan Z, Adem A, Geha R, Vrikshajanani C, Koba W, et al. Pasireotide (SOM230) is effective for the treatment of pancreatic neuroendocrine tumors (PNETs) in a multiple endocrine neoplasia type 1 (MEN1) conditional knockout mouse model. Surgery. 2012;152(6):1068–77.

Ramos-Nino ME, MacLean CD, Littenberg B. Association between cancer prevalence and use of thiazolidinediones: results from the Vermont Diabetes Information System. BMC Med. 2007;5:17.

Raz I, Bhatt DL, Hirshberg B, Mosenzon O, Scirica BM, Umez-Eronini A, et al. Incidence of pancreatitis and pancreatic cancer in a randomized controlled multicenter trial (SAVOR-TIMI 53) of the dipeptidyl peptidase-4 inhibitor saxagliptin. Diabetes Care. 2014;37(9):2435–41.

Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet. 2004;363(9418):1346–53.

Rizos CV, Elisaf MS. Metformin and cancer. Eur J Pharmacol. 2013;705(1–3):96–108.

Rizzi M, Trevisan R. Genitourinary infections in diabetic patients in the new era of diabetes therapy with sodium-glucose cotransporter-2 inhibitors. Nutr Metab Cardiovasc Dis. 2016;26(11):963–70.

Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. J Urol. 2009;181:1998.

Sciacca L, Costantino A, Pandini G, Mineo R, Frasca F, Scalia P, et al. Insulin receptor activation by IGF-II in breast cancers: evidence for a new autocrine/paracrine mechanism. Oncogene. 1999;18(15):2471–9.

Sciacca L, Cassarino MF, Genua M, Pandini G, Le Moli R, Squatrito S, et al. Insulin analogues differently activate insulin receptor isoforms and post-receptor signalling. Diabetologia. 2010;53(8):1743–53.

Sciacca L, Vigneri R, Tumminia A, Frasca F, Squatrito S, Frittitta L, et al. Clinical and molecular mechanisms favoring cancer initiation and progression in diabetic patients. Nutr Metab Cardiovasc Dis. 2013;23(9):808–15.

Sciacca L, Cassarino MF, Genua M, Vigneri P, Giovanna Pennisi M, Malandrino P, et al. Biological effects of insulin and its analogs on cancer cells with different insulin family receptor expression. J Cell Physiol. 2014;229(11):1817–21.

Shin HY, Jung KJ, Linton JA, Jee SH. Association between fasting serum glucose levels and incidence of colorectal cancer in Korean men: the Korean Cancer Prevention Study-II. Metabolism. 2014;63(10):1250–6.

Shukla A, Grisouard J, Ehemann V, Hermani A, Enzmann H, Mayer D. Analysis of signaling pathways related to cell proliferation stimulated by insulin analogs in human mammary epithelial cell lines. Endocr Relat Cancer. 2009;16(2):429–41.

Sommerfeld MR, Muller G, Tschank G, Seipke G, Habermann P, Kurrle R, et al. In vitro metabolic and mitogenic signaling of insulin glargine and its metabolites. PLoS One. 2010;5(3):e9540.

Stadler J, Yeung KS, Furrer R, Marcon N, Himal HS, Bruce WR. Proliferative activity of rectal mucosa and soluble fecal bile acids in patients with normal colons and in patients with colonic polyps or cancer. Cancer Lett. 1988;38(3):315–20.

Stevens RJ, Roddam AW, Beral V. Pancreatic cancer in type 1 and young-onset diabetes: systematic review and meta-analysis. Br J Cancer. 2007;96(3):507–9.

Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care. 2012;35(12):2665–73.

Szlosarek P, Charles KA, Balkwill FR. Tumour necrosis factor-alpha as a tumour promoter. Eur J Cancer. 2006;42(6):745–50.

Tang H, Dai Q, Shi W, Zhai S, Song Y, Han J. SGLT2 inhibitors and risk of cancer in type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Diabetologia. 2017;60:1862.

Vangoitsenhoven R, Mathieu C, Van der Schueren B. GLP1 and cancer: friend or foe? Endocr Relat Cancer. 2012;19(5):F77–88.
Vella V, Sciacca L, Pandini G, Mineo R, Squatrito S, Vigneri R, et al. The IGF system in thyroid cancer: new concepts. Mol Pathol. 2001;54(3):121–4.
Vella V, Pandini G, Sciacca L, Mineo R, Vigneri R, Pezzino V, et al. A novel autocrine loop involving IGF-II and the insulin receptor isoform-A stimulates growth of thyroid cancer. J Clin Endocrinol Metab. 2002;87(1):245–54.
Verges B, Cariou B. mTOR inhibitors and diabetes. Diabetes Res Clin Pract. 2015;110(2):101–8.
Vigneri R, Squatrito S, Sciacca L. Insulin and its analogs: actions via insulin and IGF receptors. Acta Diabetol. 2010;47(4):271–8.
Vigneri R, Vigneri P, Frittitta L. Basal insulin and cardiovascular and other outcomes. N Engl J Med. 2012;367(18):1761–2; author reply 3–4
Vigneri PG, Tirro E, Pennisi MS, Massimino M, Stella S, Romano C, et al. The insulin/IGF system in colorectal cancer development and resistance to therapy. Front Oncol. 2015;5:230.
Vissers PA, Cardwell CR, van de Poll-Franse LV, Young IS, Pouwer F, Murray LJ. The association between glucose-lowering drug use and mortality among breast cancer patients with type 2 diabetes. Breast Cancer Res Treat. 2015;150(2):427–37.
Wang C, Wang X, Gong G, Ben Q, Qiu W, Chen Y, et al. Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. Int J Cancer. 2012;130(7):1639–48.
Warburg O. On the origin of cancer cells. Science. 1956;123(3191):309–14.
Weinstein D, Simon M, Yehezkel E, Laron Z, Werner H. Insulin analogues display IGF-I-like mitogenic and anti-apoptotic activities in cultured cancer cells. Diabetes Metab Res Rev. 2009;25(1):41–9.
White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14): 1327–35.
Will JC, Galuska DA, Vinicor F, Calle EE. Colorectal cancer: another complication of diabetes mellitus? Am J Epidemiol. 1998;147(9):816–25.
Williams JA, Goldfine ID. The insulin-pancreatic acinar axis. Diabetes. 1985;34(10):980–6.
Wu JW, Filion KB, Azoulay L, Doll MK, Suissa S. The effect of long-acting insulin analogs on the risk of cancer: a systematic review of observational studies. Diabetes Care. 2016;39:486.
Xu H, Jiang HW, Ding GX, Zhang H, Zhang LM, Mao SH, et al. Diabetes mellitus and prostate cancer risk of different grade or stage: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2013a;99(3):241–9.
Xu X, Wu J, Mao Y, Zhu Y, Hu Z, Lin Y, et al. Diabetes mellitus and risk of bladder cancer: a meta-analysis of cohort studies. PLoS One. 2013b;8(3):e58079.
Yang X, Ko GT, So WY, Ma RC, Yu LW, Kong AP, et al. Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry. Diabetes. 2010;59(5):1254–60.
Yang IP, Tsai HL, Huang CW, Lu CY, Miao ZF, Chang SF, et al. High blood sugar levels significantly impact the prognosis of colorectal cancer patients through down-regulation of microRNA-16 by targeting Myb and VEGFR2. Oncotarget. 2016;7(14):18837–50.
Yin M, Zhou J, Gorak EJ, Quddus F. Metformin is associated with survival benefit in cancer patients with concurrent type 2 diabetes: a systematic review and meta-analysis. Oncologist. 2013; 18(12):1248–55.
Yuan JM, Castelao JE, Gago-Dominguez M, Ross RK, Yu MC. Hypertension, obesity and their medications in relation to renal cell carcinoma. Br J Cancer. 1998;77(9):1508–13.
Zendehdel K, Nyren O, Ostenson CG, Adami HO, Ekbom A, Ye W. Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. J Natl Cancer Inst. 2003;95(23):1797–800.
Zeng L, Biernacka KM, Holly JM, Jarrett C, Morrison AA, Morgan A, et al. Hyperglycaemia confers resistance to chemotherapy on breast cancer cells: the role of fatty acid synthase. Endocr Relat Cancer. 2010;17(2):539–51.

Zhang ZH, Su PY, Hao JH, Sun YH. The role of preexisting diabetes mellitus on incidence and mortality of endometrial cancer: a meta-analysis of prospective cohort studies. Int J Gynecol Cancer. 2013;23(2):294–303.

Zhu Z, Wang X, Shen Z, Lu Y, Zhong S, Xu C. Risk of bladder cancer in patients with diabetes mellitus: an updated meta-analysis of 36 observational studies. BMC Cancer. 2013;13:310.

Zucchetto A, Dal Maso L, Tavani A, Montella M, Ramazzotti V, Talamini R, et al. History of treated hypertension and diabetes mellitus and risk of renal cell cancer. Ann Oncol. 2007; 18(3):596–600.