

Diabetes and cancer

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Abstract

Diabetes and cancer are two heterogeneous, multifactorial, severe, and chronic diseases. Because of their frequency, reciprocal influences – even minor influences – may have a major impact. Epidemiological studies clearly indicate that the risk of several types of cancer (including pancreas, liver, breast, colorectal, urinary tract, and female reproductive organs) is increased in diabetic patients. Mortality is also moderately increased. Several confounding factors, having general or site-specific relevance, make it difficult to accurately assess cancer risk in diabetic patients. These factors include diabetes duration, varying levels of metabolic control, different drugs used for therapy, and the possible presence of chronic complications. Hyperinsulinemia most likely favors cancer in diabetic patients as insulin is a growth factor with pre-eminent metabolic but also mitogenic effects, and its action in malignant cells is favored by mechanisms acting at both the receptor and post-receptor level. Obesity, hyperglycemia, and increased oxidative stress may also contribute to increased cancer risk in diabetes. While anti-diabetic drugs have a minor influence on cancer risk (except perhaps the biguanide metformin that apparently reduces the risk), drugs used to treat cancer may either cause diabetes or worsen a pre-existing diabetes. In addition to the well-known diabetogenic effect of glucocorticoids and anti-androgens, an increasing number of targeted anti-cancer molecules may interfere with glucose metabolism acting at different levels on the signaling substrates shared by IGF-I and insulin receptors. In conclusion, diabetes and cancer have a complex relationship that requires more clinical attention and better-designed studies.

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Introduction

Diabetes mellitus (DM) is a serious and growing health problem worldwide and is associated with severe acute and chronic complications that negatively influence both the quality of life and survival of affected individuals. Today, 250 million people live with diabetes globally, with this figure expected to reach 380 million within 20 years. Therefore, if diabetes is associated even with a small increase in the risk of cancer, this may have important consequences at the population level.

The association between cancer and diabetes has been investigated extensively and most, but not all studies, found that DM is associated with an increased risk of several types of cancer. Most published data, however, requires reinterpretation because DM is not a

single disease, but rather a group of metabolic disorders characterized by hyperglycemia. Within this general context, each type of diabetes has additional metabolic and hormonal abnormalities that differently affect diabetic patients. It is therefore inappropriate to consider diabetic patients as a homogeneous cohort. In addition, a series of potential confounders directly related to the disease (obesity, quality of metabolic control, drugs employed for treatment, diet, etc.) and present in diabetic patients may influence the association between diabetes and cancer.

In the present review, we will discuss the available evidence concerning the association between diabetes and cancer, the different aspects of diabetes which may influence this association, and the possible mechanisms involved.

Cancer risk is increased in diabetic patients

A series of recent studies and meta-analyses confirm that the risk for several solid and hematologic malignancies (including liver, pancreas, colorectal, kidney, bladder, endometrial and breast cancers, and non-Hodgkin's lymphoma) is elevated in diabetic patients (Table 1). Evidence for the association of diabetes with other cancers is not available, while for prostate cancer, a reduced incidence has been reported in diabetic patients (Table 1). If we accept that cancer is more frequent in DM, the positive association between diabetes and cancer risk might actually be somewhat underestimated. Diabetes, in fact, is an underdiagnosed disease (3–5% of the adult population has undiagnosed diabetes; Harris *et al.* 1998) and thus the control population very likely includes individuals with diabetes, which will increase the cancer risk in the 'normal' population.

In diabetic patients, cancer may be favored by: i) general mechanisms that promote cancer initiation or progression in any organ because they are due to alterations (i.e. hyperglycemia or hyperinsulinemia or drugs) that affect all tissues; and ii) site-specific mechanisms affecting cancerogenesis of a particular organ.

The incidence of liver and pancreatic cancer is increased in diabetes

Several meta-analyses indicate that the strongest association between DM and increased cancer risk is with pancreatic and liver cancer (Table 1), i.e. two

key organs involved in the metabolic derangements typical of diabetes.

Because of the portal circulation, liver cells are exposed to higher insulin concentrations than other tissues, a condition that is exacerbated in insulin-resistant hyperinsulinemic type 2 diabetic individuals, but that is not present in insulin-deficient type 1 diabetic patients treated with exogenous insulin (see Fig. 1). It is unlikely, therefore, that insulin's mitogenic action is specifically involved in the higher incidence of liver cancer in diabetic patients since healthy liver cells are physiologically exposed to higher insulin concentrations than other tissues. Moreover, in diabetic patients injected with exogenous insulin, the liver is exposed to the same insulin levels as the other organs.

Since most epidemiologic studies indicate a two- to threefold increase in hepatocellular carcinomas (HCC) in diabetic patients, other conditions, specific to the liver, must favor liver cancerogenesis in diabetic patients. It has been questioned whether diabetes is a direct risk factor for liver cancer or whether diabetes-related diseases of the liver are also involved. Indeed, steatosis 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 obese-diabetic patients, occurring in over 80% of type 2 diabetic patients. Additional factors that may favor HCC in DM include hepatitis B and C virus (HBV and HCV) infections, both more frequent in diabetic subjects as compared with the nondiabetic population (Davila *et al.* 2005, Chen *et al.* 2006).

Table 1 Meta-analyses on the relative risk (RR) of cancer in different organs of diabetic patients

| Cancer | | RR (95% CI) |
|--|-------------------------|------------------|
| Liver (El-Serag <i>et al.</i> 2006) | 13 case-control studies | 2.50 (1.8–3.5) |
| | 7 cohort studies | 2.51 (1.9–3.2) |
| Pancreas (Huxley <i>et al.</i> 2005) | 17 case-control studies | 1.94 (1.53–2.46) |
| | 19 cohort studies | 1.73 (1.59–1.88) |
| Kidney ^a (Lindblad <i>et al.</i> 1999, Washio <i>et al.</i> 2007) | 1 cohort study | 1.50 (1.30–1.70) |
| | 1 cohort study | 2.22 (1.04–4.70) |
| Endometrium (Friberg <i>et al.</i> 2007) | 13 case-control studies | 2.22 (1.80–2.74) |
| | 3 cohort studies | 1.62 (1.21–2.16) |
| Colon-rectum (Larsson <i>et al.</i> 2005) | 6 case-control studies | 1.36 (1.23–1.50) |
| | 9 cohort studies | 1.29 (1.16–1.43) |
| Bladder (Larsson <i>et al.</i> 2006) | 7 case-control studies | 1.37 (1.04–1.80) |
| | 3 cohort studies | 1.43 (1.18–1.74) |
| Non-Hodgkin's lymphoma (Mitri <i>et al.</i> 2008) | 5 cohort studies | 1.41 (1.07–1.88) |
| | 11 case-control studies | 1.12 (0.95–1.31) |
| Breast (Larsson <i>et al.</i> 2007) | 5 case-control studies | 1.18 (1.05–1.32) |
| | 15 cohort studies | 1.20 (1.11–1.30) |
| Prostate (Kasper & Giovannucci 2006) | 9 case-control studies | 0.89 (0.72–1.11) |
| | 10 cohort studies | 0.81 (0.71–0.92) |

^aData on kidney cancer were not obtained from meta-analysis.

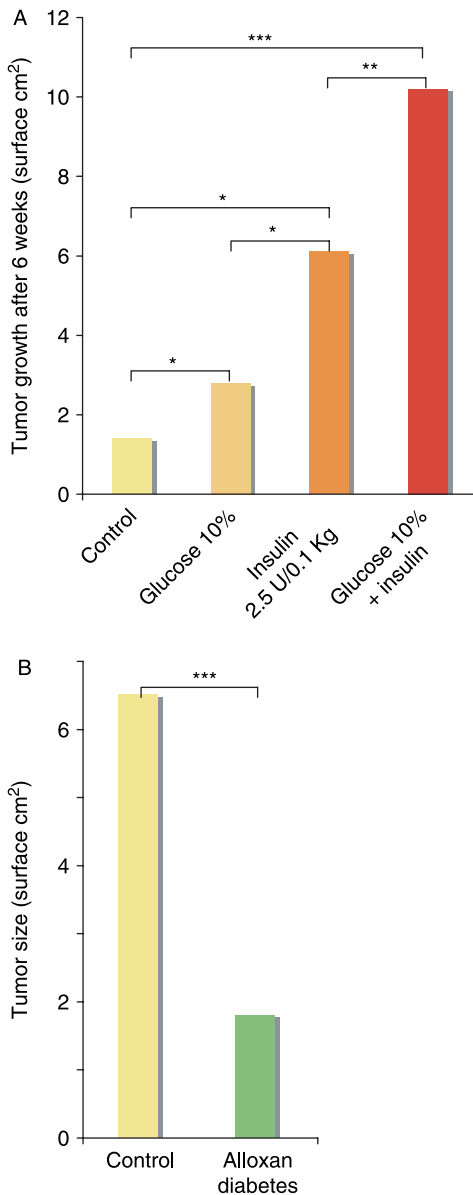


Figure 1 (A) Mammary tumor growth in four matched groups of rats, given either normal diet or with the addition of oral glucose or of insulin injections or both (significant differences: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.0005$; Heuson *et al.* 1972). (B) Mammary tumor regression after induction of alloxan diabetes in two groups of matched rats. Observation period = 6 weeks; $P < 0.001$ (Heuson & Legros 1972).

In conclusion, increased liver cancer incidence in diabetes is well documented and, although the exact mechanisms underlying this association are still unclear, liver inflammation, hepatocyte damage, and repair are likely to be involved in the higher frequency of HCC among diabetic patients.

Most earlier studies investigating the association between diabetes and pancreatic cancer are probably

misleading because they do not distinguish between pre-existing diabetes (a condition possibly favoring exocrine pancreatic cancer) and new-onset diabetes (a possible sign of pancreatic functional damage due to a still undiagnosed pancreatic cancer; Noy & Bilezikian 1994). The latter situation is so frequent that hyperglycemia and diabetes, when appearing after the age of 45–50 years, in a lean subject with no family history for diabetes, is considered sufficient to pose an indication for pancreatic cancer screening (Noy & 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 evidence suggest that diabetes caused by pancreatic cancer is due to cytokines produced by the tumor (Basso *et al.* 2002) rather than secondary to endocrine pancreatic tissue invasion and damage (Pannala *et al.* 2009). This conclusion is also supported 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). Epidemiological studies in subjects affected by DM at least 1 year prior to diagnosis or death from pancreatic cancer indicated a relative risk (RR) of 2.1 (95% confidence interval (CI) = 1.6–2.8). When the same analysis was carried out including only patients with 5 years of pre-diagnosed diabetes, their RR for pancreatic cancer was similar (RR = 2.0; Everhart & Wright 1995). Since all of these data exclude diabetes induced by pancreatic tumors, the reported findings support the possibility that diabetes is indeed a risk factor for pancreatic cancer.

The ‘pre-diabetes’ state should also be considered a risk factor for pancreatic cancer. Studies that evaluated the association between post-load glucose levels and pancreatic tumors in 35 658 individuals reported a higher RR with increasing glucose tolerance impairment. After adjusting for age, race, cigarette smoking, and body mass index (BMI), the risk progressively increased from normal subjects to subjects with slightly altered glycemia (RR = 1.65) and then to diabetes (RR = 2.15; Gapstur *et al.* 2000). These results did not change when patients who died of pancreatic cancer during the first 5 years after the assessment of post-load glucose levels were excluded, further suggesting that hyperglycemia and diabetes *per se* are predisposing factors for pancreatic cancer.

The biological mechanisms underlying the association between diabetes and pancreatic cancer are unclear. 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 & Goldfine 1985). Elevated insulin could act as a tumor growth-promoting factor in many different ways (covered later). This mechanism, however, does not justify the excess of pancreatic cancer in insulin-treated diabetic patients (Green & Jensen 1985) or in type 1 diabetes (Stevens *et al.* 2007) where 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 accrued, due to both the type of diabetes (type 1 diabetes accounts for <10% of all DM patients) and patient age (pancreatic cancer is rare before age 40).

Increased incidence of other cancers in diabetes

An increased frequency of malignancies of other organs has been reported in diabetic patients and has been ascribed to a variety of general and local mechanisms. In these cases, studies are not as numerous as for liver and pancreatic tumors, and the increases in RR are not as statistically significant. However, in many instances, the increased risk is clinically relevant, especially considering the prevalence of the two diseases in the general population.

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

Individuals with DM also display a modest increase in the risk of bladder cancer. In this case, in addition to general factors like hyperinsulinemia, the increased frequency of urinary tract infections is also likely to be involved.

The risk of cancers of the female reproductive organs is also increased in DM. Both breast and endometrial cancer risks are increased in diabetic women, and this risk is independent from obesity (a well-established factor promoting breast cancer) as it persists even 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 (Kaaks 1996) 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 nulliparity, irregular menses, and fertility disorders.

Type 2 diabetes has been associated with an increased risk of colorectal adenomas and carcinomas 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 cancer (Larsson *et al.* 2005). In addition to hyperinsulinemia, hypothesized mechanisms include slower bowel transit time and the elevated fecal bile acid concentrations often observed in DM (Stadler *et al.* 1988, Will *et al.* 1998).

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).

Decreased incidence of prostate cancer in diabetes

In contrast to the increased risk of numerous forms of neoplasia, most studies report a reduced risk of prostate cancer in men with diabetes. A recent meta-analysis (Kasper & Giovannucci 2006) including 14 studies carried out in the pre-PSA era (i.e. before the generalised use of prostate specific antigen screening for prostate cancer; Bonovas *et al.* 2004) and 5 additional studies carried out in the PSA era (and therefore, concerning cancers diagnosed earlier and smaller cancers) has found a significantly reduced risk in diabetic patients (Table 1). The 16% average decreased risk of developing prostate cancer must most likely be attributed to the decreased testosterone levels in diabetic patients (Barrett-Connor 1992, Betancourt-Albrecht & Cunningham 2003). However, other metabolic and hormonal factors, including altered insulin and leptin concentrations, the diffuse use of medications such as statins and metformin, and changes in diet and lifestyle in order to control diabetes, have also been hypothesized as elements potentially contributing to the inverse association between diabetes and prostate cancer (Kasper & Giovannucci 2006).

In conclusion, the epidemiological studies cited above may be partially biased by relevant heterogeneity due to different study design (inclusion criteria), incomplete characterization of DM, failure to consider potential confounders (obesity, diabetes duration, and treatment), and also variably defined control population. However, the overall increased risk

for the development of several types of cancer in diabetic patients must be considered well documented. In diabetes, there is a mild to moderate increase in the incidence of pancreas, liver, breast, colorectal, urinary tract, and female reproductive organ cancer and a mild reduction in prostate cancer risk.

Cancer mortality is increased in diabetic patients

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

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% CI=0.95–1.62; Larsson *et al.* 2007). In the largest study (cohort size 588 321 with 4346 deaths from breast cancer), after adjusting for age, race, BMI, physical activity, smoking, and alcohol, RR in diabetic women was 1.27 (1.11–1.45) when compared with the nondiabetic female population. In this cohort, as in most others, no stratification was performed for type of diabetes and different treatments. In addition, the menopausal status was not recorded (Coughlin *et al.* 2004). In a recent study aimed at evaluating whether diabetes could affect breast cancer prognosis, after a 5-year mean follow-up, mortality for breast cancer was significantly higher in women with diabetes (hazard ratio 1.39; 95% CI=1.22–1.59, $P<0.0001$) suggesting that early survival following breast cancer was reduced in women with diabetes (Lipscombe *et al.* 2008). This reduced survival might be a consequence of more aggressive breast cancer but also of diabetes-related comorbidities. In fact, in that study, the cause of death was not recorded and diabetic women without breast cancer had an increase in mortality similar to that of diabetic women with breast cancer, suggesting that diabetes, rather than breast cancer, was the major factor contributing to the raised mortality.

Diabetes was also positively associated with colorectal cancer mortality. A statistically significant association was found in three out of six studies (Larsson *et al.* 2005), and a nonsignificant 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% CI=1.05–1.50), but heterogeneity issues partially compromise the significance of the results. Within these six articles, the two cohort studies that evaluated standardized mortality ratio both indicated a positive association between DM and colorectal

cancer death. However, only one study reported a statistically significant increased mortality from colorectal cancer in diabetic patients. A study aimed at evaluating the influence of diabetes on long-term outcome of patients resected for colon cancer (3759 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 (tumor, node, metastasis classification) category, 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 (DFS=48 vs 59% in nondiabetics, $P<0.0001$; OS=57 vs 66% in nondiabetics, $P<0.0001$). Median survival in diabetic patients was 6.0 years vs 11.3 in nondiabetic subjects. In this study, the role of DM comorbidities (that may negatively affect overall mortality among cancer patients because of adverse health conditions) was probably minor since cancer recurrence was also higher in diabetic patients (recurrence-free survival 56 vs 64% in nondiabetics, $P<0.012$).

A positive association was also found between diabetes and endometrial cancer mortality in two studies, but it was significant only in one of them (RR=2.38; 95% CI=1.05–5.37; Coughlin *et al.* 2004, Folsom *et al.* 2004).

It is interesting to note that, although diabetic patients have a reduced risk of prostate cancer, once an insulin-resistant, overweight man has been diagnosed with prostate cancer, his likelihood of dying from the disease is increased (Ma *et al.* 2008).

A recent study on the systematic assessment of long-term, all-cause mortality in cancer patients with or without diabetes has evaluated, at 1.41 (95% CI=1.28–1.55), the hazard ratio for death in cancer patients with diabetes compared to cancer patients without diabetes (Barone *et al.* 2008). Mortality was significantly increased for cancers of the breast, endometrium, colon, and rectum. In this study, the increase in mortality risk was not significantly increased for lung, gastric, liver, pancreatic or prostate cancers. Overall, however, the heterogeneity of the studies analyzed and the length of the observation period (1969–2008, during which treatment for both cancer and diabetes changed markedly) hamper, at least in part, the significance of the data.

Several possible explanations can be put forth to explain the increased risk of cancer death in DM. For instance, it is still unclear whether diabetes, through a number of mechanisms, makes the cancer more aggressive or whether the host organism is less

resistant to cancer progression. It is also possible that diabetic patients receive different cancer treatment (i.e. oncologists may employ lower chemotherapy doses in diabetic patients, concerned about their general health and their heart, liver, and kidney function). Of course, it is also possible that diabetic patients may have a worse response to chemotherapy compared with nondiabetic individuals.

In conclusion, epidemiologic studies provide evidence that cancer mortality is moderately increased in diabetic patients. Whether this is a consequence of hyperglycemia and hyperinsulinemia (growth-promoting effect on cancer cells), the impaired health conditions due to diabetes' comorbidities or a combination of the two is still unclear.

Type 1 and type 2 diabetes and cancer risk

DM is a group of metabolic disorders characterized by hyperglycemia. The two most frequent subtypes of DM differ in 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, hyperglycemia and hyperinsulinemia coexist for a long time because of insulin resistance in peripheral tissues. Only when β -cell function fails completely will the patient require insulin treatment because of endogenous insulin deficiency.

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 forms of diabetes.

For obvious epidemiological reasons, most studies on the association between cancer and diabetes have been carried out in patients with type 2 diabetes (90% of all diabetic patients). As these patients, unlike those with type 1 diabetes, have endogenous hyperinsulinemia and insulin resistance, it is questionable whether these data can be automatically extended to type 1 diabetic patients. This concern is particularly relevant for the older reports in which diabetes assessment was based on self-reported hyperglycemia, with no criteria aimed at distinguishing type 1 from type 2 diabetes. Although more recent studies have been based on medical records, the distinction between type 1 and type 2 diabetes was mostly based on surrogate indicators of diabetes type, like young patient age or insulin treatment (assumed as type 1) 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 oral hypoglycemic agents (OHA) are no longer effective (secondary failure to OHA), type 1 diabetes of the adult (~5% of adult subjects previously classified as type 2 diabetes; Buzzetti et al. 2007), and other less frequent conditions.

Because of the 10:1 ratio between type 2 and type 1 diabetes, and considering that cancer is mainly a disease of the older population (where type 1 diabetes is less frequent), it is reasonable to assume that the large majority of tumors observed in diabetic patients occurred in type 2 diabetics.

Thus, if cancer association with type 1 diabetes has specific characteristics, these have likely 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 poor diabetes type assessment. For example, a recent cohort study evaluating cancer incidence in nearly 30 000 Swedish type 1 diabetic patients diagnosed in the period 1965–1999 has identified 355 cases of cancer (standardized incidence ratio (SIR)=1.2; 95% CI=1.0–1.3, compared with the general Sweden population; Zendejdel et al. 2003). In contrast to type 2 diabetic patients, no increased risk of breast, pancreatic, colorectal, or kidney cancer was found in this cohort. However, type 1 diabetic patients had an increased RR for stomach (SIR=2.3; 95% CI=1.1–4.1), endometrial (SIR=2.7; 95% CI=1.4–4.7), and cervical cancer (1.6; 1.1–2.2). These positive associations have been attributed to the high prevalence of *Helicobacter pylori* infection or of pernicious anemia (for gastric carcinomas; Oldenburg et al. 1996, De Block et al. 1999) and to the higher incidence of nulliparity, irregular menses, and fertility disorders in type 1 diabetic women (for uterine malignancies). In contrast with this report, a recent meta-analysis including three cohort studies and six case–control studies has found that the RR for pancreatic cancer was doubled in type 1 diabetic patients and young-onset diabetics in comparison with nondiabetics (Stevens et al. 2007).

In conclusion, the large majority of the epidemiological data on cancer incidence and mortality has been obtained in type 2 diabetic patients. Because of the different biology between the two subtypes of diabetes, these findings cannot be acritically extended to type 1 diabetic subjects.

The role of hyperinsulinemia in favoring cancer incidence and progression in diabetic patients

A role for insulin in promoting cancer growth was first recognized by studies in experimental animals. Rats and mice made diabetic with streptozotocin or alloxan (therefore hyperglycemic and insulin deficient) developed less aggressive tumors as they display a longer latency period for cancer development, lower number of tumors, slower cancer progression, and smaller final tumor volume with respect to control animals (Heuson & Legros 1972; Fig. 1). Insulin treatment reversed these effects (Heuson *et al.* 1972). These results are in concert with the well-known mitogenic effect of insulin that has been extensively documented both *in vitro* and *in vivo*.

Most type 1 and type 2 diabetic patients are exposed for decades to increased insulin concentrations, although the physiologic and therapeutic conditions are very different in each individual with diabetes.

Type 1 diabetic patients have an absolute requirement for exogenous insulin because of autoimmune destruction of their pancreatic β -cells, which are therefore unable to produce endogenous insulin. In these patients, insulin administration cannot mimic the physiologic insulin secretion, not only in terms of temporal pattern and hormone serum levels but also in terms of compartment distribution. Indeed, pancreas-secreted insulin is first distributed to the liver (first passage insulin) where a relevant aliquot (up to 80%; Ferrannini & Cobelli 1987) is retained and degraded. The remaining hormone reaches the peripheral tissues through the systemic circulation. The liver/peripheral

tissue insulin concentration ratio, therefore, ranges from 3:1 up to 9:1 during insulin secretion bursts. Exogenously administered insulin, in contrast, will arrive to peripheral tissues and to the liver at the same time and at a similar concentration. Peripheral tissue hyperinsulinemia due to exogenous insulin (circulating levels may peak two- to fivefold higher than normal endogenous levels, depending on the dose injected and the type of insulin or analog used) and the ensuing relative liver hypoinsulinemia, therefore, are a common condition in type 1 diabetic patients (Fig. 2).

On the contrary, in most type 2 diabetic patients, hyperglycemia is associated with endogenous hyperinsulinemia, a compensatory state caused by insulin resistance. This condition often persists for many years (decades when including the pre-diabetes period before clinically evident diabetes is diagnosed). Hence, in these patients, the liver/peripheral tissue insulin concentration ratio reflects that of nondiabetic patients, but at a higher level. However, in contrast to normal individuals, in these diabetic patients, increased insulin secretion fails to replete body fuel storages in response to feeding because of insulin resistance. Therefore, in these patients, excess unused substrates (i.e. glucose) are present concomitantly with hyperinsulinemia. This abnormal situation is accompanied by a series of other abnormalities involving other hormones like glucagon, incretins, leptin, etc.

As DM persists for many years, this scenario is often subject to changes, with most type 2 diabetic patients progressively presenting decreased insulin secretion following the failure of β -cells, due to increased apoptosis rates that are not balanced by neogenesis. At this stage, patients with type 2 diabetes may

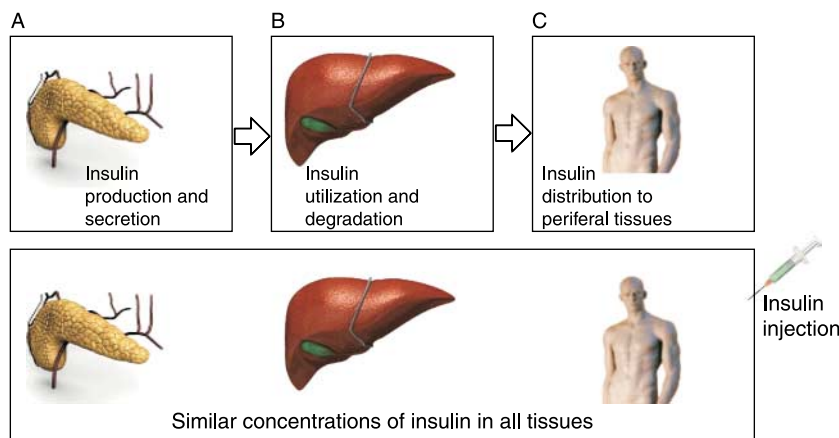


Figure 2 Endogenous insulin is distributed according to a three compartment model: (A) produced by pancreas β -cells, insulin arrives to the liver (B) where most is used and degraded and, therefore, (C) peripheral tissues receive 1/3–1/10 the amount received by the liver. Exogenous insulin is distributed according to a single compartment model: once injected, all tissues are exposed to the same dose.

become similar to type 1 diabetic individuals, with endogenous hypoinsulinemia and exogenous insulin requirement.

When studying type 2 diabetic patients, therefore, diabetes duration and insulin requirement may affect tissue exposure to insulin in different ways. If hyperinsulinemia has a role in promoting cancer initiation and/or progression, these aspects should be considered when determining the individual risk of a diabetic patient to develop cancer. Most studies on the diabetes–cancer association overlooked these different biological conditions.

In conclusion, diabetes is generally characterized by hyperglycemia and hyperinsulinemia, often coupled with a reduced metabolic effect of insulin (insulin resistance) in peripheral tissues. Chronic hyperinsulinemia, however, is a possible factor favoring cancer initiation and/or progression in diabetic patients due to the mitogenic effect of insulin. The heterogeneity and complexity of different tissue exposure to hyperinsulinemia in diabetic individuals does not allow the quantification of the role of insulin in promoting cancer risk in the different organs of different diabetic patients.

One example is the potentially increased risk of lung cancer in diabetic patients using the recently introduced inhaled insulin (von Kriegstein & von Kriegstein 2007). The long-term effects of this form of therapy are unknown. Although short-term studies in animals have shown no substantial effect on cell proliferation indices, the high insulin concentration at alveolar and bronchiolar epithelia (due to the fact that only 10–25% of inhaled insulin is absorbed) has raised safety concerns about the possibility that it may promote lung cancer. These concerns have been recently reinforced by the long-time surveillance analysis, indicating that 6 out of 4740 (0.13%) diabetic patients treated with inhaled insulin but only 1 out of 4292 comparator-treated patients (0.02%) developed lung cancer (Mitri & Pittas 2009).

There are multiple and complex mechanisms potentially responsible for the mitogenic effects of insulin.

First, when insulin levels increase (as in the post-prandial surge in insulin-resistant subjects or after insulin injection), insulin may bind and activate the related insulin-like growth factor-I (IGF-I) receptor, which shares ~80% homology with the insulin receptor (IR), but has a more potent mitogenic and transforming activity. Moreover, insulin decreases IGF-I-binding proteins (IGF-BP1 and, perhaps, IGF-BP2; Kaaks & Lukanova 2001): this will result in increased free IGF-I, the biologically active form of the growth factor.

Secondly, many cancer cells have an increased IR content (Papa *et al.* 1990; Fig. 3A). The IR may be expressed in two different isoforms, A and B, produced by an alternative splicing of the IR gene transcript (Moller *et al.* 1989). In malignant cells, the A isoform (IR-A) expression is predominant (Frasca *et al.* 1999, Sciacca *et al.* 1999, Kalli *et al.* 2002; Fig. 3B), and its activation, at variance with the IR-B isoform, elicits more mitogenic than metabolic effects (Frasca *et al.* 1999). By binding to the overexpressed IR-A, insulin may favor cancer progression and facilitate the growth of tumors that would otherwise have likely remained clinically irrelevant for an undetermined length of time.

Finally, insulin mitogenic activity might be enhanced at the cellular level by post-receptor molecular mechanisms, including insulin (or its synthetic analogs) residence time on the receptor (De Meyts *et al.* 1995) and the intracellular up-regulation of the insulin mitogenic pathway. Experimental data indicate that this pathway, unlike the insulin metabolic pathway, may not be blunted in the condition of insulin resistance typical of diabetes (Fig. 4). The AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), and insulin-signaling pathway

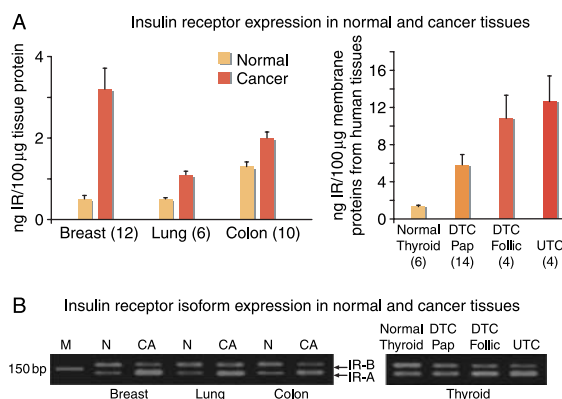


Figure 3 Total IR content and IR isoforms expression in paired normal and cancer specimens from human breast, lung, and colon. Cancer specimens were obtained together with specimens of normal tissue from the same individuals, and IR content was determined by ELISA. (A) The average total IR content was significantly higher in the malignant tissues than in the corresponding normal tissues. Number of examined specimens is indicated within brackets (Frasca *et al.* 1999). DTC, differentiated thyroid cancer; UTC, undifferentiated thyroid cancer. (B) IR-A and IR-B expression in different normal or malignant human tissues. IR isoform expression was determined by RT-PCR. Relative abundance of IR-A (median value) was significantly higher in cancer tissue than in normal tissue. Breast, 73 vs 43; lung, 53 vs 39; colon, 68 vs 35; thyroid: normal tissue = 44; papillary DTC = 53; follicular DTC = 56; UTC = 70.5 (Frasca *et al.* 1999, Vella *et al.* 2002).

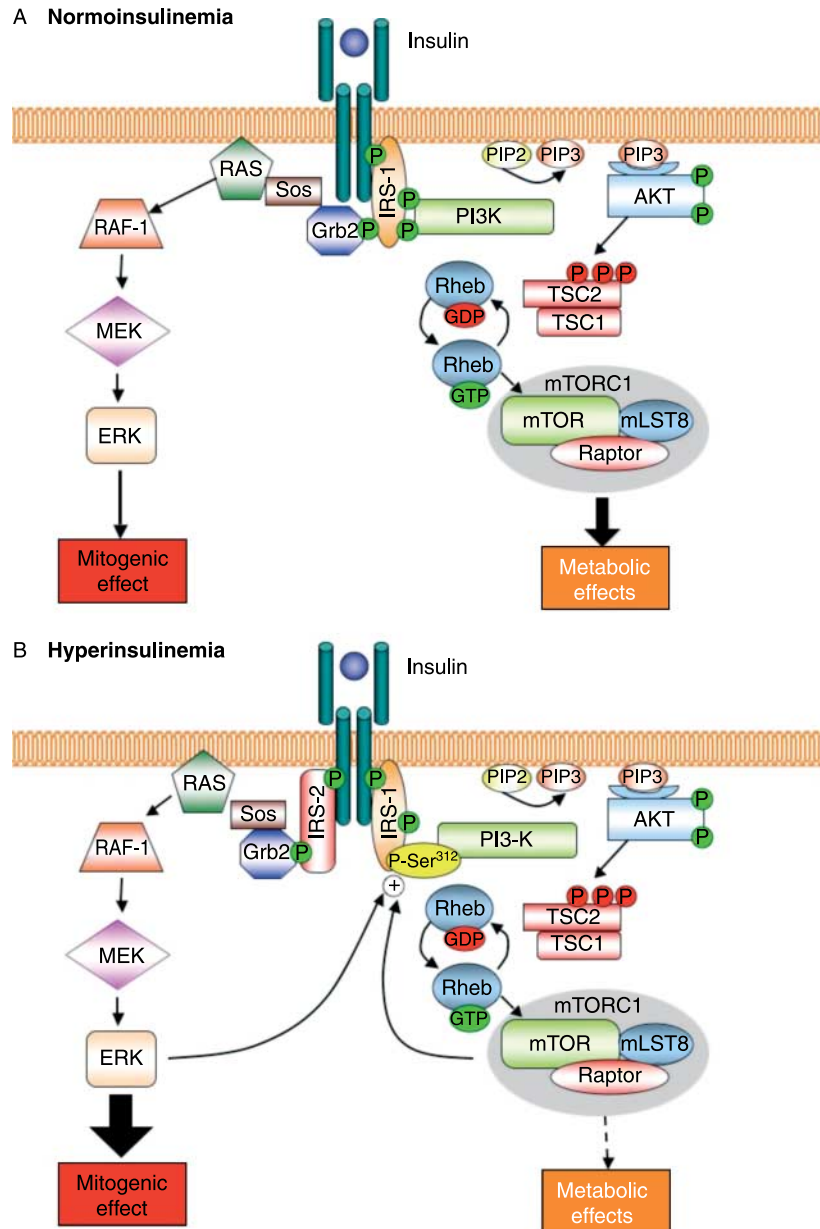


Figure 4 The ‘paradox’ of insulin resistance. In normoinsulinemic subjects (A), typical target tissues respond to insulin mainly with metabolic effects via the activation of the PI3 kinase pathway. In contrast, in hyperinsulinemic subjects (B), IR signaling may be attenuated for the metabolic branch, but not for the mitogenic branch. Indeed, studies in insulin-resistant PCO subjects described several insulin-signaling abnormalities, including IRS-1 phosphorylation in serine 312 (yellow) leading to inhibition of PI3 kinase recruitment and activation. This abnormal IRS-1 phosphorylation represents a negative feedback loop for attenuating metabolic activity in response to hyperinsulinemia and is consequent to mTOR overactivation. In contrast to the metabolic attenuation, ERK activation is not attenuated, but rather increased by hyperinsulinemia. The mitogenic branch overactivation has been ascribed to increased IRS-2 expression leading to unaffected or increased Grb2 recruitment, increased RAF-1 expression, and, as a consequence, increased ERK activation. This, in turn, further increases Serine-312 IRS-1 phosphorylation (Corbould *et al.* 2006). This implies that insulin resistance mainly involves the metabolic but not mitogenic effects of insulin. This unbalanced IR signaling may have different effects in different tissues, depending on the cell predominant enzymatic machinery: it may cause impaired glucose homeostasis in typical insulin target tissue like liver, muscle, and adipose tissue, while it will result in increased cell proliferation in other tissues, including ovary and cancer cells.

represent three interrelated components of a complex mechanism controlling cell responses to nutrient availability, and their dysregulation may favor malignant cell proliferation in response to hyperinsulinemia.

In conclusion, strong but circumstantial evidence indicates a role for endogenous hyperinsulinemia and of exogenous insulin or analogs in promoting cancer growth in diabetic patients. However, the clinical relevance of this pro-cancer effect of insulin in diabetic patients is still unclear.

Anti-diabetic drugs that may influence cancer risk in diabetic patients

Most diabetic patients are treated for years or decades with a variety of drugs (Table 2). The potential role of these drugs in favoring cancer is unclear but most likely minor, if any. Data are not conclusive because the large majority of diabetic patients change the drug dosage and/or the type many times during the course of the disease. Moreover, many are treated with more than one drug. Epidemiological studies on this issue, therefore, are difficult to interpret and often inconclusive.

The three major oral anti-diabetic drug families (sulphonylureas, biguanides, and thiazolidinediones) have a different mechanism of action. Sulphonylureas stimulate endogenous insulin secretion, while the other two categories of compounds are insulin sensitizers, i.e. they make tissues more responsive to insulin and, therefore, decrease hyperinsulinemia. 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 biguanide metformin, widely used for more than 30 years and currently suggested as first-line therapy in type 2 diabetic patients, has been recently reported to reduce cancer risk (odds ratio=0.86) when compared with untreated patients (Evans et al. 2005). In addition to lowering the amount of circulating insulin, another possible mechanism for the anti-cancer effect of metformin is the stimulation of AMPK (an enzyme inducing glucose uptake by muscles) and its upstream regulator LKB1, a well-recognized tumor suppressor protein (Luo et al. 2005). AMPK activators act as anti-proliferative agents because they reduce insulin (and IGF-I)-signaling downstream of the receptor and, therefore, inhibit insulin-stimulated proliferation (McCarty 2004, Ruderman & Prentki 2004). Hence, the anti-cancer effect of metformin can be explained by this dual mechanism.

Recent studies in MCF-7, BT-474, and SKBR-3 human breast cancer cells showed that *in vitro* metformin inhibited cell proliferation, reduced colony formation, and caused partial cell cycle arrest (Alimova et al. 2009). These effects mainly occurred via MAPK, AKT, and mTOR inhibition and were replicated also in *erbB2*-overexpressing cells. On the basis of both epidemiological data and *in vitro* studies, a clinical trial for evaluating metformin activity on breast cancer cell proliferation (Ki67 index) is currently undergoing in 100 breast cancer patients (Cazzaniga et al. 2009).

Data on the other insulin-sensitizing drug (thiazolidinediones) are more controversial. A beneficial (Govindarajan et al. 2007), neutral (Koro et al. 2007), or even deleterious (Ramos-Nino et al. 2007)

Table 2 Oral hypoglycemic agents used to treat type 2 diabetes mellitus

| Pharmacological class | Pharmacological compound | Mechanism of action |
|----------------------------------|--|---|
| Biguanides | Metformin | Insulin sensitizer (reduces insulin resistance pre-eminently at hepatic level) |
| Thiazolidinediones (glitazones) | Rosiglitazone Pioglitazone | Insulin sensitizers (reduce insulin resistance pre-eminently at muscle and fat level) |
| Sulphonylureas | Glipizide Gliclazide Glyburide Gliquidone Glycypyramide Glimepiride | Secretagogues (stimulate insulin secretion) |
| Meglitinides | Repaglinide Nateglinide | Short-term secretagogues (stimulate insulin secretion) |
| α -Glucosidase inhibitors | Acarbose | Reduces carbohydrate absorption |

GLP-1 analogs and gliptines (Dpp-4 inhibitors) have been introduced recently for diabetes treatment and no data are available on their potential influence on the cancer risk in diabetic patients.

effect has been reported for different types of cancer. The biological mechanism of these compounds is to activate PPAR γ receptors, which, in several *in vitro* experimental models, has shown a potential anti-cancer effect (Aiello *et al.* 2006). In addition to lowering hyperinsulinemia, this effect can explain the described anti-cancer effect of glitazones. In any case, the use of these compounds is too recent and too limited to consider the present meager epidemiologic observations reliable.

The third group of drugs (sulphonylureas) are 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 sulphonylureas may have different effects, with glyburide being more deleterious than gliclazide (Monami *et al.* 2007). Although their effect on cancer risk is attributed to the prolonged hyperinsulinemia that they induce in patients, a direct effect on cancer (either positive or negative) cannot be excluded.

In conclusion, some evidence suggests that the biguanide metformin may reduce cancer risk in diabetic patients but, in general, the influence of anti-diabetic drugs on the risk of cancer is not well studied and evidence is weak, indirect, and controversial.

Other factors that may influence the risk of cancer in diabetes

Obesity

Over 80% of type 2 diabetic patients are obese. Obesity is associated with a higher incidence and a higher mortality in cancer (Adami & Trichopoulos 2003, Vigneri *et al.* 2006). Moreover, cancer mortality significantly increases with increasing patient BMI (Calle *et al.* 2003). Fat distribution in the body is also important: central (upper body or android) obesity is more harmful than gynoid obesity in terms of increased risk and worst cancer outcome. Given these observations, it is evident that studies on the diabetes–cancer association are influenced by the high prevalence of obesity in DM patients. Since both DM and obesity are characterized by hyperinsulinemia and higher cancer incidence, it is difficult to identify the contribution of each of the two conditions.

Among the many possible mechanisms involved, hyperinsulinemia (which is typical of central obesity), diet and nutritional factors causing a positive energy balance, and other hormone abnormalities have been indicated as causal factors.

A tight correlation has been observed between obesity, circulating estrogen levels, and increased breast cancer risk (Key *et al.* 2003, Cleary & Grossmann 2009) especially in post-menopausal women. Obese post-menopausal women usually present an increase in both estrone and estradiol, a likely consequence of the increased aromatase activity of the adipose tissue (Reed & Purohit 2001). Considering the growing prevalence of obesity and diabetes in both developed and developing countries, these data might explain the reported rise in estrogen receptor-positive breast cancers (Glass *et al.* 2007). Several other molecular alterations associated with obesity might also be responsible for the higher incidence of breast cancer found in obese (and obese-diabetic) pre- and post-menopausal women. Preclinical evidence has suggested that leptin, an adipocyte-derived cytokine, highly expressed in obese subjects, promotes breast cancer cell proliferation (Hu *et al.* 2002), an observation that has not yet been confirmed in the clinical setting since an association between leptin levels and breast cancer outcome has not been demonstrated (Goodwin *et al.* 2005). Another adipokine produced by the adipose tissue, adiponectin, which is inversely correlated with body fat, might exert a protective effect on breast epithelial cells since its addition to different breast cancer cell lines inhibited proliferation and enhanced apoptosis (Cleary *et al.* 2009).

Hyperglycemia

Most diabetic patients present both hyperglycemia and hyperinsulinemia. Thus, it is difficult to distinguish the specific role of each abnormality in increasing cancer risk.

It is known that a high intake of sugar and refined carbohydrates and elevated blood glucose levels are strongly associated with the risk of cancer (Krone & Ely 2005). It is also known that impaired glucose tolerance without diabetes is associated with increased cancer risk (Dankner *et al.* 2007). Both these conditions, however, are also characterized by hyperinsulinemia. Although much convincing evidence demonstrates an association between hyperglycemia and cancer, it has yet to be demonstrated that hyperglycemia *per se* is an independent risk factor.

Possible mechanisms implicated include the role of an abnormal energy balance and the effect of hyperglycemia in impairing the effect of ascorbic acid on the intracellular metabolism and reducing the effectiveness of the immune system. Further evidence suggests a role for the oxidative stress-responsive

genes (like thioredoxin-interacting protein) that are sensitive to hyperglycemia and regulate the level of reactive oxygen species (ROS; Turturro *et al.* 2007).

Free fatty acids

Deregulation of fatty acid synthase (FASN) activity, which catalyzes *de novo* fatty acids biogenesis (Hillgartner *et al.* 1995, Semenkovich *et al.* 1995), could also play a role in the pathogenesis of insulin resistance, diabetes, and cancer. FASN activity is important for *de novo* fatty acid synthesis in the liver and is stimulated by a low-fat/high-carbohydrate diet (Hudgins 2000, Hudgins *et al.* 2000). Interestingly, FASN expression is increased in insulin-resistant/hyperinsulinemic patients (Moustaid *et al.* 1996, Claycombe *et al.* 1998), and its increased activity further worsens insulin resistance and may result in NAFLD (Postic & Girard 2008), which is associated with an increased risk of hepatocarcinoma (Caldwell & Lazo 2009). FASN activity is also increased in cancer cells, where *de novo* fatty acid synthesis is crucial for membrane remodeling during cell migration and proliferation, as well as for lipid-based post-translational modifications of intracellular proteins in highly proliferating cell populations (i.e. myristylation of RAS). The concept that FASN is directly involved in affecting tumor progression derives also from studies with the FASN blocker cerulenin (Lupu & Menendez 2006a,b). Indeed, cell exposure to this inhibitor results in cytostatic, cytotoxic, and apoptotic effects *in vitro* and retards the growth of tumor in xenograft models (Menendez *et al.* 2009).

Therefore, FASN activity and fatty acid production are another possible link between diabetes and cancer as indicated by the hypothesis that insulin-resistant conditions such as obesity, type 2 diabetes, and cancer are favored by common FASN-driven 'lipogenic state' (Menendez *et al.* 2009).

Chronic inflammation and oxidative stress

The metabolic abnormalities that characterize diabetes, especially under conditions of poor metabolic control, increase oxidative stress and cause a permanent pro-inflammatory condition. This chronic pro-inflammatory state (which persists for years or decades) reduces intracellular anti-oxidant capacity, predisposing susceptible cells to malignant transformation. In fact, high concentrations of diverse free radicals and oxidants generate a potent ROS that can damage cell DNA by direct oxidation or by interfering with the mechanisms of DNA repair

(Federico *et al.* 2007). ROS may also react with proteins and lipids, forming derivative products that may alter intracellular homeostasis favoring the accumulation of mutations that, in turn, contribute to the multistage carcinogenesis process (Ohshima *et al.* 2003).

A possible additional mechanism is related to mitochondrial dysfunction, a well-recognized abnormality in diabetes. DNA repair is a high energy consuming process that requires increased mitochondrial activity: stimulating malfunctioning mitochondria will not only provide low, insufficient energy supply, but also increase ROS production (Cebioglu *et al.* 2008).

Moreover, an additional factor correlated with insulin resistance is the pro-inflammatory cytokine tumor necrosis factor α (TNF α) produced by the adipose tissue (Kern *et al.* 2001). TNF α induces development and progression of many tumors (Szlosarek *et al.* 2006) by strongly activating nuclear factor-kappa B (NF- κ B), which mediates many of the pro-tumoral effects of TNF α .

In conclusion, DM, by mechanisms both specific to diabetes and common with other chronic degenerative diseases, might accelerate the aging biological processes that favor cancerogenesis.

Drugs used to treat cancer may favor diabetes

A recently emerging issue is the possible adverse effect on glucose metabolism of anti-cancer therapies. Cancer patients can exhibit temporary hyperglycemic states or full-blown diabetes following steroid-based medication (administered before and during chemotherapy), or because of the specific mechanism of action of an anti-cancer drugs. Glucocorticoids are frequently used at a high dosage both to prevent and/or cure allergic reactions, inflammatory states caused by anti-cancer treatment, for their anti-edema effect and to alleviate fatigue. Glucocorticoids, however, 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. Otherwise, glucocorticoid administration may result in the worsening of a condition of pre-diabetes or undiagnosed diabetes and may transform mild diabetes into a clinically severe illness, possibly leading to a deadly hyperosmolar coma. Owing to the high prevalence of diabetes and pre-diabetes (over 15–20% in the aged population, which is more prone to cancer), this is a real health risk.

Apart from corticosteroids, anti-androgens may also adversely affect glucose metabolism. Androgen deprivation therapy is the fundamental treatment of

prostate cancer. This therapy causes a variety of metabolic abnormalities that include decreased insulin sensitivity and altered lipid profile. It therefore, increases risk of diabetes and cardiovascular disease (Saylor & Smith 2009).

Androgens are important determinants of body composition: their inhibition increases fat mass and decreases lean body mass. In patients treated with GnRH agonists and/or nonsteroidal anti-androgens, such as flutamide, bicalutamide, and nilutamide, or with the steroidal anti-androgen cyproterone acetate, 'sarcopenic obesity' is favored, 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 high-density lipoprotein (HDL). These changes result in insulin resistance and, sometimes, diabetes. In a recent study in over 70 000 subjects with locoregional prostate cancer, those who were treated with GnRH had a 44% increased risk of developing diabetes (Keating *et al.* 2006). Diet and lifestyle interventions with a 5–10% weight loss and statin drugs are the main strategies for preventing or treating the metabolic complications of androgen deprivation therapy in prostate cancer patients.

The other most currently employed targeted anti-cancer molecules do not significantly affect glucose homeostasis. However, an increasing number of compounds are being tested for therapeutic use which alter the IGF-I system and its intracellular pathways. The increasing use of these compounds may amplify the frequency of anti-cancer drug-related diabetes. Since IGF-I signaling plays a key role in both tumor progression and glucose homeostasis, therapies targeting the IGF system for its pro-cancer effect may at the same time cause hyperglycemia. In this paragraph, we will examine drugs and mechanisms responsible for hyperglycemia induced by novel anti-cancer therapies that may alter the insulin–glucose balance.

IGF-I system targeting anti-cancer treatments

IGF-I and insulin, their receptors and their intracellular signaling pathways share large similarities. Likewise, the biological (metabolic and mitogenic) effects of the two hormones partially overlap. Because of the well-known role of IGF-I as a cancer-promoting factor, many efforts have been made to block its function in cancer patients. However, these efforts may have a detrimental effect on glucose metabolism through three different mechanisms: i) the inhibition of the IGF-I insulin-mimetic effect (Kuzuya *et al.* 1993, Fernandez *et al.* 2001, Pennisi *et al.* 2006);

ii) the increase in circulating GH levels due to the lack of IGF-I feedback (GH is a potent diabetogenic hormone; Yakar *et al.* 2004); and iii) the possibility that agents that block IGF-I signaling might also cross inhibit the insulin-signaling pathway.

Currently, anti-cancer strategies inhibiting the IGF system include both direct targeting of the IGF-I receptor (IGF-IR) with both monoclonal antibodies and suppression of the IGF-IR-signaling pathway by protein kinase inhibitors (Fig. 5).

Several antibodies targeting the IGF-I peptide or the IGF-IR have been tested, but only the latter are currently undergoing preclinical testing or are in phase I–II trials for the treatment of both hematological (multiple myeloma, and leukemia) and solid (sarcomas, carcinomas of the lung, breast, colon, and prostate) tumors (Haluska *et al.* 2007, Lacy *et al.* 2008).

Hyperglycemia has been observed in a few patients enrolled in studies with the anti-IGF-IR antibody (Haluska *et al.* 2007, Lacy *et al.* 2008). This is likely to be a consequence of a compensatory increase in the circulating concentration of GH after IGF-I blockade, with the consequent insulin resistance (del Rincon *et al.* 2007) that may cause or worsen diabetes.

A second approach to IGF-I inhibition is to block IGF-IR signaling at the enzymatic level. Since IGF-IR is a transmembrane tyrosine kinase (TK) receptor, several TK inhibitors targeting IGF-IR have been developed and found to be active in preclinical models and in phase I clinical trials (Hofmann & Garcia-Echeverria 2005, Gable *et al.* 2006, Haluska *et al.* 2006, Ji *et al.* 2007, Mulvihill *et al.* 2008, Vasilcanu *et al.* 2008, Zimmermann *et al.* 2008). These small molecules may cause more serious toxicity than that observed with the IGF-IR-specific antibodies, as they cross the blood–brain barrier with the possibility of neurotoxicity for the inhibition of the neuroprotective effect of IGF-I. Unexpectedly, these TK inhibitors are associated with less hyperglycemia than IGF-IR-blocking antibodies. One possible explanation for this difference is that the TK inhibitors do not accumulate in muscle, leaving unaffected IR function on the metabolic process of this tissue (Pollak 2008). More research is needed to clarify this point.

Downstream of the receptor, IGF-I signaling occurs via the activation of enzymes and substrates like phosphatidylinositol 3-kinase (PI3K), AKT, and mTOR. When activated via IGF-IR, these substrates play a role in tumor cell proliferation and survival, but they are also activated via the IR and heavily contribute to glucose homeostasis. Several compounds targeting different signaling molecules downstream of the IGF-IR have been tested, as anti-cancer therapies

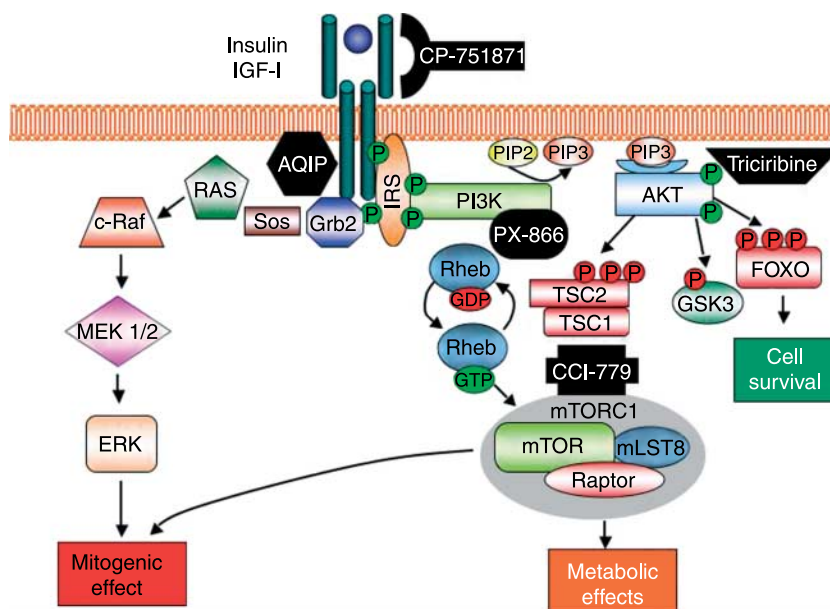


Figure 5 Schematic representation of insulin and IGF-1R signaling and inhibition steps. IR and IGF-1R share a very similar signaling pathway, which can be schematically represented by two main branches: the mitogenic pathway (RAS/RAF/MEK/ERK) and the metabolic pathway (PI3K/AKT). The metabolic pathway can be further subdivided into two subpathways: the mTOR pathway, which, although mainly metabolic, is also in part mitogenic; and the Foxo pathway, which is mainly involved in cell survival in response to nutrient availability. Given the complexity of this signaling, it is very difficult to target a specific pathway and function. Indeed, inhibitors aimed at targeting the mitogenic and survival pathways have also got effects on the metabolic pathways, resulting in insulin resistance and hyperglycemia. Inhibitors are represented in black: CP-751871, humanized anti-IGF-1R antibody; AQIP, IGF-1R and IR tyrosine kinase inhibitor; PX-866, PI3K kinase inhibitor; triciribine, AKT inhibitor; CCI-779, mTOR inhibitor.

are able to inhibit the mitogenic and anti-apoptotic effects of IGF-I in cancer cells (Fig. 5).

Targeting PI3K, the most proximal pathway component, has the advantage of providing a broader inhibition of downstream signaling compared with distal component inhibition (such as AKT and mTOR). Inhibitors like LY294002 and wortmannin effectively inhibit PI3K, but poor solubility and high toxicity have prevented their clinical application. New compounds (like PX-866) are now being tested in xenograft models and in phase I clinical trials (Ihle *et al.* 2004, 2009a,b, LoPiccolo *et al.* 2008). In xenograft models, PX-866 increases glucose and insulin levels as well as glucose intolerance. While metformin is not effective in counteracting this effect and lowering glucose levels, glitazones (e.g. pioglitazone) ameliorate glucose balance in these patients, without affecting the anti-tumor activity of the compound (Ihle *et al.* 2004, 2009a,b, LoPiccolo *et al.* 2008).

A variety of AKT inhibitors have been developed (including perifosine, phosphatidylinositol ether lipid analogs PIAs, and triciribine phosphate; Ihle *et al.* 2004, 2009a,b, LoPiccolo *et al.* 2008; Fig. 5). Clinical data concerning the anti-tumor activity of AKT inhibitors as well as their effect on glucose homeostasis

are insufficient. Recent preliminary data obtained in a xenograft model with GSK690693, a novel ATP-competitive/pan-AKT kinase inhibitor, indicate that abrogating AKT activity results in increased glucose and insulin levels. Interestingly, the diabetogenic effect of GSK690693 is not reverted by either metformin or pioglitazone or GLP-I agonist exendin-4, but only by a low-carbohydrate diet (Rhodes *et al.* 2008, Crouthamel *et al.* 2009).

A further class of targeted drugs that may interfere with blood glucose levels is the inhibitors of the mTOR kinase. This mTOR serine/threonine kinase and the mTOR-raptor complex (TORC1) regulate cell cycle progression (i.e. G1-S phase transition) and increase the expression of angiogenic factors. When dysregulated, mTOR plays a key role in cell proliferation and neoplastic transformation favoring the development of resistance to several types of cancer therapy (Bjornsti & Houghton 2004, Panwalkar *et al.* 2004).

Several mTOR inhibitors have been developed *in vitro* (Fig. 5). Some of them have been used in clinical trials. The most important, everolimus (RAD001; 40-O-2-hydroxyethyl-rapamycin), an orally available ester derivative of the anti-fungal antibiotic sirolimus (rapamycin), is currently used as an

immunosuppressive agent to prevent rejection in transplant recipients (Eisen *et al.* 2003, Lorber *et al.* 2005). Immunosuppression maintenance with everolimus has been associated with a significantly reduced risk of developing *de novo* malignancies after renal transplant (Kauffman *et al.* 2005). Everolimus forms a complex with the immunophilin FKBP-12, which then binds to and disrupts TORC1, leading to mTOR inhibition and G1 phase cell cycle arrest, apoptosis (Aguirre *et al.* 2004, Majumder *et al.* 2004), and angiogenesis suppression (Majumder *et al.* 2004). Temozolimumab is a further novel mTOR inhibitor of the same family, recently approved for the treatment of renal cell carcinoma with unfavorable clinical characteristics. As expected from mTOR inhibition, hyperglycemia, hypertriglyceridemia, and hypercholesterolemia have been observed in ~20% of patients treated with these inhibitors. In particular, recent data have reported increased blood glucose levels in 26% of temsirolimus-treated patients with 11% displaying G3/G4 hyperglycemia (Bellmunt *et al.* 2008, Malizzia & Hsu 2008). Most diabetic patients treated with temsirolimus required an increase in their hypoglycemic treatment, and roughly 30% of nondiabetic patients had to begin a specific therapy to lower their blood glucose (Bellmunt *et al.* 2008, Malizzia & Hsu 2008). Treatment of mTOR inhibition-related hyperglycemia has not yet been studied.

Finally, inhibitors of the ABL TK may also affect glucose homeostasis. *In vitro* results indicate that ABL is involved in IR signaling and upon insulin stimulation enhances IR-dependent metabolic effects while attenuating the nonmetabolic ones (Frasca *et al.* 2007, Genua *et al.* 2009). Therefore, treatment with an ABL inhibitor was expected to impair glucose homeostasis (Fig. 6). However, adult patients with chronic and accelerated phase chronic myelogenous leukemia (CML), treated with the ABL inhibitor imatinib mesylate, have actually shown a consistent reduction in their blood glucose levels (Veneri *et al.* 2005). Interestingly, a recent report has described hyperglycemia in ~10% of CML patients treated with nilotinib, a second-generation ABL kinase inhibitor currently used for individuals resistant or intolerant to imatinib (Kantarjian *et al.* 2006). The increase in fasting glucose registered after nilotinib therapy is predictive of drug response and apparently does not require administration of hypoglycemic drugs (Deremer *et al.* 2008). However, the follow-up of the study is too short to yield conclusive evidence, especially considering that patients responding to nilotinib will have to continue drug treatment indefinitely until disease progression.

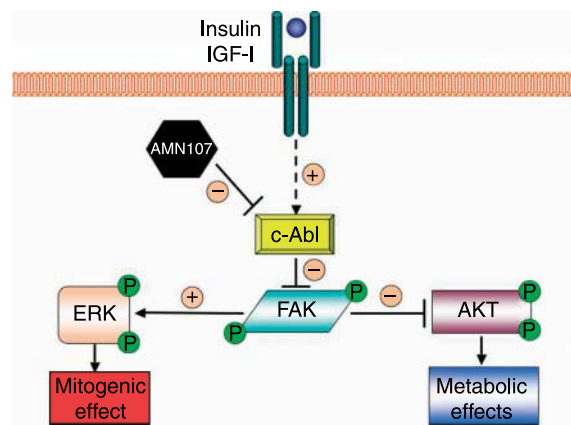


Figure 6 Schematic representation of a possible hypothesis explaining the effect of nilotinib (Abl inhibitor AMN107) on IR signaling and glucose homeostasis. c-Abl tyrosine kinase is activated in response to insulin stimulation. Activation of c-Abl results in decreased FAK phosphorylation and, as a consequence, increased AKT phosphorylation and decreased ERK phosphorylation, thus enhancing insulin metabolic effects and decreasing insulin mitogenic effect. In the presence of the c-Abl inhibitor AMN107, the opposite occurs: insulin stimulation results in increased ERK activation and decreased AKT phosphorylation and, as a consequence, decreased metabolic activity. The reasons why different Abl inhibitors (imatinib mesylate and nilotinib) have different metabolic effects are not understood. (↓) stimulation, (⊥) inhibition.

In conclusion, in addition to glucocorticoid- and anti-androgen-dependent hyperglycemia, the use of molecular inhibitors of IGF-I, pro-mitogenic and anti-apoptotic signaling will likely become more diffuse in cancer patients, possibly causing hyperglycemia. Since diabetes and pre-diabetes have a high prevalence in the general population and patients treated with these novel anti-cancer compounds often have a considerable life expectancy, careful monitoring of glycemia is a requirement in all patients treated with agents that may interfere, at different levels, with glucose metabolism.

Conclusions

The complexity of the various diabetic conditions, the diversities in the biology of different forms of cancer, and the multiplicity of the possible mechanisms involved prevent a comprehensive and definite answer to many questions regarding the association of diabetes with an increased risk of cancer initiation and progression. Most epidemiologic studies have not carefully considered a series of confounding factors, and diabetic patients have not been adequately characterized for the type of diabetes, the duration of the disease, the drugs used for therapy, the quality of the metabolic control, or the presence of comorbidities.

Because of the intrinsic heterogeneity of both diabetes and cancer, studies on the association of the two diseases are not easy to carry out. Indeed, considering the wide array of possible mechanisms causing increased cancer incidence and mortality in diabetic patients, it is difficult to accurately define the aims, the recruitment criteria, and the appropriate design for such studies.

The available evidence indicates that the level of cancer risk related to diabetes will probably differ for each diabetic patient, on the basis of the cancer type and many other diabetes-related factors. Our present knowledge provides good evidence for a mild increase of cancer risk (and cancer mortality) in diabetic patients, more evident for some site-specific cancers. Present evidence, however, does not allow us to accurately define the general and the specific organ cancer risks in the individual diabetic patient. Because of the growing worldwide frequency of diabetes, this question needs to be properly addressed, in order to acquire a more rational approach to cancer prevention and treatment in diabetic patients.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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