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Diabetes and cancer II: role of diabetes medications and influence of shared risk factors

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Abstract

An association between type 2 diabetes mellitus (DM) and cancer has long been postulated, but the biological mechanism responsible for this association has not been defined. In part one of this review, we discussed the epidemiological evidence for increased risk of cancer, decreased cancer survival, and decreased rates of cancer screening in diabetic patients. Here we review the risk factors shared by cancer and DM and how DM medications play a role in altering cancer risk. Hyperinsulinemia stands out as a major factor contributing to the association between DM and cancer, and modulation of circulating insulin levels by DM medications appears to play an important role in altering cancer risk. Drugs that increase circulating insulin, including exogenous insulin, insulin analogs, and insulin secretagogues, are generally associated with an increased cancer risk. In contrast, drugs that regulate insulin signaling without increasing levels, especially metformin, appear to be associated with a decreased cancer risk. In addition to hyperinsulinemia, the effect of DM medications on other shared risk factors including hyperglycemia, obesity, and oxidative stress as well as demographic factors that may influence the use of certain DM drugs in different populations are described. Further elucidation of the mechanisms behind the association between DM, cancer, and the role of DM medications in modulating cancer risk may aid in the development of better prevention and treatment options for both DM and cancer. Additionally,

incorporation of DM medication use into cancer prediction models may lead to the development of improved risk assessment tools for diabetic patients.

Keywords

Diabetes; Cancer; Review; Meta-analysis

Introduction

Type 2 diabetes mellitus (DM) and cancer are common conditions that are frequently diagnosed in the same individual. In the first part of this review, we discussed the epidemiological evidence for increased cancer risk, decreased cancer screening, and poorer prognosis upon cancer diagnosis in diabetic patients. Here we discuss the risk factors shared by cancer and DM and how DM medications play a role in altering risk.

Risk factors associated with DM are shared by many cancers due to common underlying pathophysiological mechanisms and include hyperinsulinemia and insulin resistance, metabolic syndrome, anthropometric factors such as obesity, hyperlipidemia, changes in glucose metabolism and presence of advanced glycosylation end products (AGE), alterations in microvascular endothelial function and hypertension, changes in mitochondrial function, subclinical inflammation, oxidative and hemodynamic stress, and family history. Common underlying environmental factors associated with DM, based largely on lifestyle, may also confound this relationship. These include socioeconomic status and demographic factors such as advancing age, sex, ethnicity, poor diet, sedentary lifestyle, smoking, and alcohol consumption. DM therapies are known to modulate or be modulated by many of these factors. Several associations between DM medications and cancer risk have been demonstrated [1] and are the focus of recent scientific debate and controversy. Recent epidemiological studies have reported an increased cancer risk associated with the use of insulin, insulin analogs, and insulin secretagogues [2, 3]. Conversely, metformin [4–6] and thiazolidinediones [7], which decrease insulin resistance and indirectly decrease circulating insulin levels, have been associated with a decreased cancer risk.

The exact mechanisms underlying the relationship between DM, medications for DM, and cancer have not been fully elucidated; however, hyperinsulinemia and insulin resistance are the most popular proposed links. Several confounding factors make it difficult to accurately assess these relationships including DM duration, varying metabolic profiles, and the possible presence of shared cancer-promoting factors. DM-related metabolic profiles include factors such as hyperglycemia, adipokines, growth factors, and epigenetic changes; while shared factors that may be influential in the pathogenesis of cancer include obesity, aging, and others. Any attempt to review cancer in relation to DM medications must, therefore, review these potential confounding factors in relation to cancer occurrence in diabetic individuals. Interestingly, many of these confounders are potentially modifiable by DM therapies and are also potential candidates for increased cancer risk in patients with DM [8] and, thus, may provide the biological basis for the modulation of cancer risk by DM medications. In this article, we explore the impact of pharmacotherapy for DM on shared

risk factors and the relationship of such changes with cancer risk in this population. Particular attention will be paid to the effect of DM medications on insulin resistance and hyperinsulinemia, hyperglycemia, obesity, and oxidative stress as well as demographic factors that may influence the use of certain DM drugs in different populations.

Diabetes medications

A wide array of treatment options is available for DM, and therapeutic regimens are quite heterogeneous among diabetic individuals. The major classes of drugs include insulin and insulin analogs, insulin secretagogues, insulin sensitizers, glucosidase inhibitors, and drugs to combat obesity. Endogenous insulin is produced by β -cells in the pancreas and reaches the body tissues through the circulation. As DM develops, insulin secretion is reduced leading to the progressive hyperglycemia characteristic of DM. The major classes of DM drugs function to replace circulating insulin and reduce hyperglycemia by different mechanisms or to reduce the associated obesity.

Insulin, insulin analogs, and insulin secretagogues increase levels of circulating insulin. Injectable insulin and insulin analogs, such as insulin glargine, act as an exogenous insulin replacement following loss of endogenous insulin production in DM. Sustained therapy with exogenous insulin to control hyperglycemia is needed in 40–80 % of diabetic patients [8, 9]. Insulin secretagogues, including sulphonylureas and glinides, augment insulin release by binding to pancreatic β -cells and stimulating the release of insulin from intracellular stores. The resultant effect is an increase in the circulating level of endogenous insulin.

The insulin sensitizers, including metformin and thiazolidinediones (TZDs), are oral anti-diabetic drugs that decrease insulin resistance by altering signaling through the AKT/mTOR pathway. The mechanism by which metformin exerts its effects is not completely understood, but activation of AMP-activated protein kinase (AMPK), which plays a role in insulin signaling, energy balance, and the metabolism of glucose and fats, is known to be involved. TZDs bind to peroxisome proliferator-activated receptors (PPARs) in the cell nucleus, altering the transcription of many genes. Despite differing mechanisms of action [10], the ultimate outcome of treatment with either metformin or TZDs is the same.

Glucosidase inhibitors are also oral anti-diabetic drugs, but work at the level of carbohydrate digestion to reduce hyperglycemia. Acarbose and other glucosidase inhibitors prevent post-prandial hyperglycemia in patients with DM by slowing digestion of carbohydrates, thereby slowing release of glucose into the bloodstream and preventing spikes in blood glucose after meals. In addition to traditional DM medications, drugs to promote weight loss are prescribed to treat the obesity that is generally associated with DM and include the lipase inhibitor orlistat and the appetite suppressants sibutramine and rimonabant. Sibutramine and rimonabant have both been removed from the market in the US due to a high risk of adverse side effects. Orlistat is FDA-approved for weight loss and used off-label for the treatment of DM.

Combination therapy and progression from one treatment plan to another is common in patients with DM. Studying the impact of DM medications on cancer risk is complicated by the potential for exposure to multiple pharmaceutical agents for differing durations. Despite

these difficulties, a growing body of literature suggests that therapeutic regimens for DM may alter cancer risk through modulation of shared risk factors (Table 1).

Insulin resistance and hyperinsulinemia

Type 2 DM is characterized by insulin resistance and hyperinsulinemia. There is a discernible trajectory of development from insulin resistance to full DM. The latter is then accompanied by a reduction in insulin secretion that leads to the progressive hyperglycemia characteristic of DM. In most diabetic patients, this status results in an increasing dependence on drug treatments over time to regulate blood sugar levels, and to the eventual need for sustained insulin therapy in 40–80 % of diabetic patients [8, 9]. It is important to recognize that cells with oncogenic potential found in patients with DM may be exposed to elevated levels of insulin within the body for many years before initiation of drug or insulin therapy. It is currently thought that prolonged exposure to excess insulin, either endogenous or via pharmacotherapy, might be implicated in the pathogenesis of increased cancer risk seen in DM [2, 4, 11].

Insulin is produced by β -cells in the pancreas and reaches neoplastic tissue through the circulation. Early in vitro studies demonstrated that breast cancer cells respond to physiologically relevant levels of insulin by upregulating DNA synthesis and that in vivo insulin deficiency is associated with a slower rate of cancer proliferation [12]. More recently, the impact of diabetogenic insulin concentrations on proliferation and migration of tumor cells was reported potentially explaining how hyperinsulinemia may trigger tumor cell proliferation and motility in humans [13]. Additionally, the receptors for insulin and insulin-like growth factor (IGF) 1 (IGF1R) are widely expressed on normal tissues and are expressed on many neoplastic cell lines and human cancers [14–18].

Like insulin, IGF pathways have also been implicated in the mechanism linking DM to cancer. Insulin is an important growth factor for body tissues and may stimulate cell proliferation and tumorigenesis through a variety of mechanisms including increasing the levels of potent IGFs. Stimulation of IGF1R by the increased levels of IGFs present in patients with hyperinsulinemia may lead to increased proliferation and decreased apoptosis [19–22]. In addition to promoting the production of IGFs, insulin can also increase the sensitivity of cells to these growth factors. In contrast to insulin, IGF1 and IGF2 are often expressed within neoplastic tissue in addition to the liver and, thus, may influence tumor growth through autocrine, paracrine, or endocrine pathways [23, 24]. Much evidence exists to suggest that IGFs play a role in tumor progression. Physiological concentrations of IGFs stimulate proliferation in many cancer cell lines in vitro [17]. Additionally, several prospective studies suggest that individuals with high levels of circulating IGF1 are at increased risk for the development of prostate, breast, colorectal, or other cancers [25–29], and it has been demonstrated that IGF1 [30, 31] and polymorphisms in IGF-related genes [32, 33] correlate with mammographic breast density, a risk factor for breast cancer. IGF function is regulated by IGF-binding proteins (IGFBPs), which can bind to both IGF1 and IGF2, thereby limiting access to IGF1R and decreasing bioactivity [34]. Consistent with the finding that high levels of IGF1 increase cancer risk, high levels of circulating IGFBP3,

which may correlate with reduced IGF1 bioactivity, have been associated with a reduced risk of cancer [28, 35].

A recent topic of particular interest is the differentiation of the effect of insulin and IGF1 on cancer prognosis versus cancer risk. Studies suggest that hyperinsulinemia is associated with prognosis and that IGF1 levels are less important as a prognostic factor [17, 29, 36–40]. It has been proposed that in established cancers, insulin receptor levels may be higher than IGF1R levels, but the reverse may be true in at-risk, untransformed cells [17, 29, 36–40]. Alternatively, measurements of circulating IGF1 may fail to accurately reflect the local effects of autocrine or paracrine production of IGF1 by aggressive cancers.

Finally, in addition to altering extracellular signaling molecules and cell surface receptors, DM may also result in altered intracellular signaling through the insulin and IGF receptors. The binding of insulin or IGFs to their receptors leads to activation of the PI3K and MAPK pathways via insulin receptor substrate 1 (IRS1) [41–43]. The IGFR pathways seem to be the stronger of the two pathways with regard to exerting mitogenic and anti-apoptotic effect [44]. Stimulation of IGFR results in signaling through the AKT/mTOR pathway. When the tumor suppressor gene PTEN is over-expressed in prostate cancer cells, proliferation decreases and apoptosis increases, while the levels of IGF1R on the surface of the cell decrease. PTEN is mutated in many cancers, which may lead to increased levels of IGF1R expression. Stimulation of IGF1R by the increased levels of IGFs present in patients with hyperinsulinemia may lead to increased proliferation and decreased apoptosis, and these pathways have been implicated in the complex mechanism of insulin and IGF mediated tumorigenesis [19–22].

Accumulating evidence suggests that hyperinsulinemia may not be only an important risk factor for cancer, but also the basis for increased risk of cancer in patients with DM as well as a target for cancer therapy [9]. Since most DM therapies have some effect on levels of circulating insulin, it follows that DM medications that alter insulin levels may also affect cancer risk in diabetic individuals. Several studies suggest this to be the case.

Impact of medications that increase insulin levels

In 2009, a large, retrospective cohort study of diabetic adults treated in UK general practice facilities compared the effects of different DM medications on cancer risk [45]. Insulin users were subdivided according to treatment with insulin glargine, long-acting human insulin, a biphasic insulin analog, or human biphasic insulin, and treatment was compared to metformin monotherapy, which carried the lowest risk of cancer. The risk for cancers of the breast, colon, pancreas, and prostate was examined. Insulin users had a 42 % greater risk of cancer than those who used metformin alone. Compared with metformin, insulin therapy of any type increased the risk of colorectal (HR = 1.69, 95 % CI 1.23–2.33) or pancreatic cancer (HR = 4.63, 95 % CI 2.64–8.10), but did not seem to influence the risk of breast or prostate cancer. Use of insulin analogs was not associated with increased cancer risk when compared to human insulin, but the risk of cancer was greater in individuals using human insulin alone compared to those using insulin glargine alone [45], and recent evidence suggests that there may be a dose–response relationship between the use of insulin analogs and cancer risk [46].

Several recent publications in the journal *Diabetologia* [45–52] address the possibility that insulin analogs, notably the widely used insulin glargine, may lead to an increased cancer risk compared with other insulin-based treatments, particularly for breast cancer. Data from recent observational studies suggest that insulin analog therapy may confer an added risk of cancer, perhaps mediated by signaling through IGF1R. Signaling through IGF1R in DM has been implicated in tumor initiation and progression, and elevated levels of endogenous IGF1 have been linked to malignancies [25, 26, 28, 29, 35, 36]. However, in a large population-based study utilizing the Scottish national diabetes clinical database, Colhoun et al. [48] concluded that the excess cases of all cancers, and breast cancer in particular, that may have been due to the use of insulin glargine was more likely to reflect allocation bias than an effect of insulin glargine itself. Two studies have linked insulin glargine to cancer risk at high doses, suggesting that dose may also play a role in determining risk [46, 53].

In contrast to the above discussion, Yang et al. [54] reported that in Chinese patients with DM, insulin usage was associated with a reduced cancer risk. This may suggest a genetic difference in the metabolism of insulin by this particular study population or a methodological flaw in study design and analysis, as suggested by several others [55–58]. In light of such contradictory results, it is imperative that well-designed and, if possible, randomized studies be undertaken to determine the true association that may exist between treatments for DM and incident cancer risk. According to several recent reports, epidemiological evidence is insufficient to confirm or deny an increased risk of cancer associated with any particular DM therapy or combination of therapies. As suggested by Colhoun et al. [48], this may be due to biases inherent in observational studies and in unintentional selection for differing characteristics among patients who receive a particular diabetic treatment. Selection bias for a certain treatment can lead to untrue associations which may be easily misinterpreted [59].

Because increased insulin secretion ultimately results in increased levels of circulating insulin, it is not surprising that insulin secretagogues show an association with increased cancer risk, similar to the use of insulin or insulin analogs. With the exception of a largely criticized study [55–58] by Yang et al. [60], which reported the sulphonylureas glibenclamide and gliclazide to be associated with a reduced colon cancer risk in Chinese patients, most studies have shown an increased risk of cancer and cancer mortality in diabetic individuals treated with insulin secretagogues [3, 45, 61–63]. For example, the 2009 study of diabetic adults treated at UK general practice facilities found users of sulfonylurea therapy alone to have a 36 % greater risk of cancer than those who used metformin alone, similar to the users of insulin [45].

In addition to an increased risk of cancer, some studies suggest that exposure to drugs that increase insulin levels may also worsen cancer prognosis. Baur et al. [61] recently reported the results of a nationwide, cross-sectional, prospective, epidemiological study in Germany that examined the association between DM, medications for DM, cancer, and cancer-related mortality. In this analysis, diabetic patients on insulin had a similar prevalence of cancer compared to non-diabetic patients, but considerably higher cancer mortality [61]. Cancer mortality was also higher in patients treated with sulfonylurea compared to metformin monotherapy [61]. Similarly, in a population-based study using data from Saskatchewan

Health in Canada, Bowker et al. [3] examined insulin use in diabetic patients treated with either metformin or sulfonylurea and found that insulin users had an HR of cancer-related mortality of 1.9 (95 % CI 1.5–2.4, $p < 0.0001$), compared to diabetic patients who did not use insulin. Additionally, regardless of insulin use, patients treated with sulfonylurea had greater cancer-related mortality than those treated with metformin, with an HR of cancer-related mortality of 1.3 (95 % CI 1.1–1.6, $p = 0.012$) [3].

Impact of medications that decrease insulin levels

Given the evidence to suggest that medications that increase insulin levels increase the risk of cancer and worsen cancer prognosis, the opposite may be expected for insulin lowering drugs. Indeed, there is continually increasing evidence to suggest that insulin lowering drugs, especially metformin, may decrease the risk of cancer in diabetic individuals. Despite differing mechanisms of action [10], the ultimate outcome of treatment with either metformin or TZDs is decreased insulin resistance and lower levels of circulating insulin. It has been demonstrated that in certain cell types, metformin induces intracellular stress similar to metabolic stress, resulting in an inhibitory effect on anabolic pathways and apoptosis, autophagy, and cell cycle arrest [64, 65]. In in vitro studies, metformin and the TZD rosiglitazone both suppressed cancer cell growth and induced apoptosis [10], and preclinical studies have shown inhibition of growth in human cancer cell lines derived from cancers of the lung, colon, breast, stomach, ovaries, and prostate by TZD [66–69]. Additionally, a decrease in live cancer cells and increased apoptosis occurred with exposure to a combination of metformin or rosiglitazone with certain chemotherapy agents (gemcitabine or doxorubicin) [10].

Epidemiological data regarding metformin and cancer risk are less controversial than the data regarding the relationship between the use of insulin, insulin analogs, and insulin secretagogues and the risk of cancer. Metformin is a well-tolerated medication with a clinical advantage in that it does not induce hypoglycemia and is known to confer cardiovascular protection by its anti-glycemic effects, favorable effects on lipid metabolism, and obesity reduction properties [70, 71]. Several epidemiological studies reported a decrease in cancer risk in diabetic individuals treated with metformin [45, 61, 72, 73]. This decrease has been reported for several cancers, including cancer of the colon [45], pancreas [45, 63], and ovaries [74]. As an example, among all therapies examined, use of metformin alone resulted in the lowest risk of cancer in the 2009 study of diabetic adults treated at UK general practice facilities [45]. In this study, metformin use was associated with a lower risk of cancer of the colon or pancreas, but did not seem to affect the risk of breast or prostate cancer [45]. Importantly, adding metformin to insulin regimens reduced the risk of cancer by half [45]. In contrast, Bodmer et al. [75] reported a slight increase in risk of colorectal cancer, especially in men, associated with metformin use. Similarly, Azoulay et al. [76] found no association between risk of prostate cancer and metformin use. Overall, reports indicate that diabetic patients treated with metformin have anywhere from 25 to 40 % less cancer than those who are treated with drugs that increase insulin levels, including insulin, insulin analogs, and sulfonylureas [73].

In addition to the decreased risk of developing cancer, the use of metformin has also been associated with decreased cancer mortality [3, 6, 77] and improved cancer outcomes. In a population-based study using administrative data from Saskatchewan Health in Canada, Bowker et al. [3] demonstrated a decreased risk of cancer associated with metformin use when compared to sulfonylurea mono-therapy. Metformin was noted to have a similar effect on cancer mortality in the report by Baur et al. [61] from Germany. Currie et al. [62] found metformin use prior to cancer diagnosis to be associated with cancer-specific survival for all types of cancer in a retrospective cohort study conducted in UK primary care practices. When broken down by cancer type, metformin use before cancer diagnosis was associated with survival for liver and ovarian/endometrial cancer. There was some suggestion of an association between metformin and survival in prostate cancer, but no association was observed for bladder, breast, colorectal, lung, or pancreatic cancer [62]. Metformin use following cancer diagnosis was also associated with survival for all cancers together as well as by subtype for lung and ovarian/endometrial cancer [62]. Furthermore, diabetic patients with breast cancer who received metformin in addition to neoadjuvant chemotherapy had a higher pathologic complete response rate than diabetic patients who did not receive metformin [78].

Some epidemiological studies of TZD and cancer risk have demonstrated results similar to those for metformin [7, 79]. For example, in a retrospective analysis of the impact of TZD treatment on cancer incidence in diabetic patients, Govindarajan et al. [79] reported a 33 % reduction in lung cancer risk in TZD users. Similarly, a large meta-analysis of randomized clinical trials of rosiglitazone use with a duration of >24 weeks showed that the incidence of malignancies was significantly lower in rosiglitazone-treated patients than in the control group [7]. The evidence for risk of cancer reduction with TZDs is not as clear as for metformin, however. Koro et al. [80] did not observe any association between TZD treatment and the risk of breast, colon, or prostate cancer in TZD users compared with users of other anti-diabetic medications; while Ramos-Nino et al. [81] reported that TZDs may actually increase the risk of cancer. Finally, in a recent study by Ferrera et al. [82], association between the TZD pioglitazone and ten different cancers was examined over the longest follow-up period to date, and no clear evidence of association was found, although there was some suggestion of increased risk of melanoma and non-Hodgkin's lymphoma (NHL) and decreased risk of kidney/renal pelvis cancers, but these associations were not significant. Based on the few epidemiological studies available at this time, a definite conclusion cannot be reached regarding TZD and the risk of cancer in individuals with DM. Similarly, there is very little evidence regarding the association between TZD use and cancer mortality. However, in a single study by He et al. [77], use of metformin or TZDs predicted longer survival time and decreased cancer-specific mortality in patients with HER2+ breast cancer.

As discussed, several studies suggest that drugs that increase levels of circulating insulin, including insulin, insulin analogs, and insulin secretagogues, increase the risk of certain types of cancer. However, results are not conclusive and deserve further attention. As Bowker et al. [3] point out, a gradient effect may be seen and both dose and duration of insulin therapy may have a risk modulating effect, as may length of exposure to hyperinsulinemia in the pre-diabetic state. There is more evidence to the contrary for drugs

that decrease levels of circulating insulin by increasing insulin sensitivity, especially metformin. Several studies demonstrate a decreased risk of cancer following treatment with metformin, and new insulin-suppressing drugs are being developed by the pharmaceutical industry [73]. There is less evidence regarding the relationship between TZDs and cancer, and results are mixed, suggesting that more research in this area is necessary, and that not all drugs that decrease circulating insulin levels will have the same effect on cancer risk.

Hyperglycemia

As DM develops, decline in pancreatic β -cell function results in decreased insulin production and progressive hyperglycemia in the absence of insulin-dependent regulation of blood glucose levels. Hyperglycemia defines the onset of DM and is progressive and present in varying severity. As previously mentioned, diabetogenic concentrations of glucose, as well as insulin, have been demonstrated to promote increased proliferation and migration of tumor cells [13], and it was long thought that the amount of glucose available to a tumor could be a factor in tumor development. However, more recent studies have demonstrated that tumors continue to burn high amounts of glucose, regardless of blood glucose levels [83]. Consistent with this finding, a recent meta-analysis reported a pooled risk ratio for cancer incidence of 0.91 (95 % CI 0.79–1.05) for subjects with improved glycemic control in three trials compared to those in the control arms of the studies, suggesting that improved glycemic control does not reduce risk of cancer in diabetic patients [84].

Most DM medications control hyperglycemia through modulation of circulating insulin levels, as previously discussed. Findings regarding the relationship between glycemic control and cancer risk suggest that modulation of cancer risk by drugs that alter circulating insulin levels is through modulation of insulin levels directly and not through consequent alterations in blood glucose concentrations. Consistent with this hypothesis, studies examining the effects of the glucosidase inhibitor acarbose on cancer risk have found no association [85, 86]. This result is expected, as acarbose alters blood glucose concentrations at the level of digestion rather than through insulin modulation. In contrast, there is no consistent pattern of cancer risk that can be discerned when several glucose-lowering agents that modulate glucose levels via insulin regulation, including exogenous insulin, sulfonylurea, and metformin, are compared [87].

Oxidative stress

Oxidative stress has been suggested to be an important, unifying, “common pathway” underlying the pathogenic mechanisms associated with the development of cancer and DM on a systemic scale by contributing to dysregulation of cellular metabolism and homeostasis within the cellular environment. Far-reaching effects of oxidative stress include establishment of an environment that contributes to the development of many conditions including insulin resistance, obesity, aging, hypertension, hyper-inflammatory states, cardiovascular disease, heart failure, and neurodegenerative diseases [88]. Several of the factors attributed to oxidative stress are themselves risk factors for both cancer and DM.

Oxidative stress is an imbalance between tissue oxidants, including free radicals, reactive oxygen species (ROS), and antioxidants. ROS are produced in response to human tissue or

organ injuries induced by xenobiotics, ischemia, activation of leukocytes, or other physiological processes [89]. Under normal conditions, ROS play a critical role in the regulation of many physiological processes including microorganism defense, cell signal transduction, cell growth, and cellular homeostasis as well as induction of apoptosis and senescence, two key mechanisms for cancer prevention [90, 91]. During oxidative stress, the production of ROS exceeds a biological system's ability to readily detoxify these reactive intermediates or easily repair the resulting damage causing dysregulation of nitric oxide production, which is a key regulator of oxidative stress [90, 92, 93]. Although ROS such as isoprostanes are detectable in healthy subjects [94], the production of too many ROS has been shown to have detrimental effects [95].

Chronic oxidative stress and inflammation lead to a self-perpetuating loop that exacerbates chronic disease states including cancer, DM, and cardiovascular, neurological, and pulmonary diseases [88, 96]. At the molecular level, oxidative stress causes cellular damage both directly and indirectly. ROS can result in DNA damage either by direct oxidation of DNA bases or by inhibition of cellular DNA repair mechanisms [97]. Additionally, oxidative stress can influence the expression of over 500 different genes, including those for growth factors, inflammatory cytokines, chemokines, cell cycle regulatory molecules, and anti-inflammatory molecules [90, 98, 99]. In patients with DM, oxidative stress is exacerbated by dysregulation of the enzymatic function of nicotinamide adenine dinucleotide phosphate-oxidase and xanthine oxidase, and uncoupling of nitric oxide synthase and superoxide production by mitochondria in response to micro-environmental changes and vascular injury induced by the hyperglycemic state [100].

Chronic oxidative stress and chronic inflammation go hand-in-hand. Chronic inflammation is characterized by inflammatory cytokine expression, especially interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF α), C-reactive protein (CRP) production, and increased white blood cell count and activity. ROS can cause protein, lipid, and DNA damage, and malignant tumors often show increased levels of DNA base oxidation and mutations [89]. Additionally, chronic inflammation is associated with high levels of TNF α , which induces the development and progression of many tumors by strongly activating nuclear factor-kappa B (NF- κ B) and mediates many of the pro-tumoral effects of TNF α . In combination, long-term exposure to chronic oxidative stress and inflammation puts susceptible cells at risk of progression toward malignant transformation [8].

The oxidative stress and chronic inflammation characteristic of DM may be modulated by DM medications. In a recent double-blind, randomized controlled trial examining the effects of metformin on oxidative stress and inflammatory markers in patients with DM, Chakraborty et al. [101] found that metformin significantly decreased markers of oxidative stress and levels of CRP following 24 weeks of treatment, compared to subjects who did not receive metformin. TZDs appear to exert a similar effect, but are unique as a class of anti-oxidants in that they do not scavenge free radicals, but rather prevent generation of the mediators of oxidative stress through antagonism of intracellular pathways [102]. Furthermore, in a meta-analysis of 13 studies examining the effects of TZD treatment on serum CRP levels, TZDs were found to reduce CRP significantly in both diabetic and non-diabetic patients [103]. Reduction in oxidative stress and chronic inflammation may be a

mechanism besides insulin reduction by which metformin and TZDs exert anti-cancer effects. Conversely, administration of exogenous insulin appears to have a pro-oxidant effect. Monnier et al. [104] observed a positive correlation between insulin dose and oxidative stress as assessed by urinary excretion of isoprostanes, consistent with the doses of insulin glargine found by Mannucci et al. [46] to be related to cancer occurrence.

Environmental factors and oxidative stress

Environmental factors, particularly smoking and alcohol consumption, are known to modulate oxidative stress and to have a role in the development of DM and cancer. Smoking has long been associated with many negative health outcomes and is associated with worsening of inflammation, oxidative stress, and endothelial dysfunction [98]. Smoking accounts for as many as 71 % of all respiratory cancer deaths [105] and increases the risk of several other cancers including pancreatic, bladder, digestive, liver, and cervical cancers. Studies suggest that smoking is also an independent risk factor for the development of DM [106]. Because of the interactions between smoking, cardiovascular disease (CVD), and other complications of DM, smoking has a substantially negative effect on DM-related health outcomes [106, 107]. Smoking also impairs pancreatic β -cell function and worsens insulin resistance [98], reducing the efficacy of DM therapies.

The relationship between alcohol consumption, cancer, and DM is not as well understood. It has been demonstrated that even relatively moderate amounts of alcohol increase the risk of many cancers, including oral cavity, pharynx, esophageal, liver, colorectal, and female breast cancers. Excess alcohol consumption (>2 drinks per day for men, >1 drink per day for women) is a substantial risk factor for DM, although moderate alcohol consumption has been associated with reduced DM incidence in both men and women [108, 109]. The mechanisms by which ethanol induces oxidative stress and influences disease have been well described in vitro [110], and alcohol-induced oxidative stress has been observed in vivo following consumption of beer, wine, or spirits [111]. Alcohol consumption also promotes insulin resistance through modulation of oxidative stress [112] and can interact with sulfonylureas and lead to unpredictable fluctuations in serum glucose concentrations, especially in the elderly [113].

Overall, observations to date suggest that oxidative stress, chronic inflammation, and cancer are closely linked [90]. Obesity, metabolic syndrome, and DM are conditions that lead to chronic oxidative stress and chronic inflammation and are likely to play a major role in the development of cancer. Several studies support this concept and suggest that the effects of oxidative stress are exacerbated in patients with DM. Medications for DM that are suggested to decrease cancer risk, including metformin and TZDs, appear to decrease oxidative stress. Conversely, many studies suggest that administration of exogenous insulin increases cancer risk and also appears to increase oxidative stress. Further modulation of oxidative stress may occur as the result of environmental exposures, particularly smoking and alcohol consumption.

Obesity

Obesity is the most common comorbidity of type 2 diabetes and acts synergistically with DM to exacerbate oxidative stress and cause a permanent pro-inflammatory condition, which may persist for years, ultimately reducing intracellular antioxidant capacity [8]. Even the well-known association between obesity and cancer risk or mortality [114, 115] might be due at least in part to obesity-associated hyperinsulinemia [17]. Obesity in humans is considered a state of chronic inflammation and is a risk factor for many diseases including cancer [8, 90, 92]. Adipose tissue is not only a storage depot for lipid energy, but also functions as an active endocrine organ [98]. Adipocytes produce adipokines, secretory proteins that induce endothelial damage and functional dysregulation. Serum adipokines increase with fat mass, especially with visceral fat. Fat also expresses pro-inflammatory cytokines such as IL-6 and TNF α . Under normal conditions, the production of CRP by the liver is controlled by cytokines, including IL-6 and TNF α , which are elevated during acute infection [89, 99, 116]. Expansion of the adipose tissue depot in obese persons may increase IL-6 and TNF α levels [117], which activates CRP production. Reduction in fat mass is directly associated with reductions in inflammatory adipokines, depending on the degree of weight loss [8, 118].

Breast, colorectal, pancreatic, kidney, and liver cancers have all been associated with high body mass index (BMI) (>25 kg/m²). Overweight/obesity appears to impact especially strongly on cancers that affect women including endometrial, cervical, breast, and potentially ovarian cancer [119], and is estimated to directly impact on 5 % of all cancers [119]. La Vecchia et al. [120] discuss the relationship between overweight/obesity with DM and breast cancer. They suggest an association between diabetes and post-menopausal breast cancer that may be related to factors such as higher circulating estrogen and insulin levels as well as increased insulin resistance in overweight/obese women [120]. Obesity may also increase the risk of mortality from some cancers, such as prostate cancer [121]. It is not surprising, therefore, that overweight (BMI between 25 and 30 kg/m²) and obese (BMI ≥ 30 kg/m²) persons are at a higher risk of many cancers compared to persons with BMI in the normal range (18.5–25 kg/m²) [115]. Weight gain has been associated in particular with an increased risk of breast cancer [122]. Research has been consistent in finding a substantial and positive association between obesity, insulin resistance, and the development of DM, and the relative risk of DM increases incrementally with each unit of BMI gained [123]. In DM and some cancers, waist circumference, waist-to-hip ratio, or direct measures of central adiposity are associated with risk, independent of BMI [124].

Obesity results in lower circulating adiponectin levels and elevated circulating levels of insulin and IGF, IL-6, TNF α , leptin, and IL-17 [125]. As discussed previously, insulin and IGF are potent growth factors, and IL-6 and TNF α are important in maintaining a state of chronic inflammation, suggesting a potential role in tumorigenesis. IL-17 is also associated with carcinogenesis through the activation of several kinases including Src/P13 K, MAPK, Stat3, and PKC, which are important for cell growth, movement, and differentiation [125]. Additionally, increased adipokine production by adipose tissue results in increased levels of leptin and PAI-1 and decreased levels of adiponectin, creating a stimulatory environment for cellular growth and angiogenesis [93]. Obesity also frequently leads to insulin resistance,

which is a central factor in promoting the diabetic state and also exacerbates hypertension while supporting cellular growth and inhibiting apoptosis [126].

Another related pathophysiological factor between DM and cancer at the molecular level is metabolic syndrome. Metabolic syndrome is a collection of risk factors that includes obesity, insulin resistance, hypertension, and dyslipidemia that is closely related to obesity and associated with a state of chronic oxidative stress [92, 98]. In metabolic syndrome, several metabolic regulators have been demonstrated to impact on molecular pathways that promote both DM and carcinogenic pathology, including AMP-activated protein kinases, peroxisome proliferator-activated receptors (PPARs), and the fatty acid synthetase complex [127]. Metabolic syndrome is related to obesity and DM and is also thought to play a role in oxidative stress. There is still some debate regarding the criteria and exact concept of metabolic syndrome; however, this clustering of risk factors is unequivocally linked to an increased risk of developing DM and CVD [128]. Metabolic syndrome is also suspected to have a role in cancer [129]. Metabolic syndrome is often associated with oxidative stress and the production of ROS, contributing to cellular dysfunction [92].

Weight loss has been shown to decrease the risk of both DM and cancer. In interventional trials, lifestyle and diet modifications have been shown to reduce the risk of DM, and in incident diabetic patients, to return to normal glycemic condition [130]. The association between weight loss and incident cancer is still undergoing further research. Observational studies of weight loss and cancer risk will require a very large sample size with long-term follow-up and careful monitoring of weight change [131, 132]. Confounding such studies is the fact that weight loss may be a symptom of latent cancer. Randomized trials are not feasible due to ethical concerns and would likely have to be stopped early because of the known protective effects of weight loss on DM and other related diseases.

It can be difficult to separate the effects of obesity from those of pharmaceutical exposures, because many diabetic treatments, such as insulin therapy, can lead to weight gain, and this in turn enhances insulin resistance and oxidative stress. Conversely, metformin often results in weight loss. The previously described increased risk of cancer with insulin use and decrease risk of cancer with metformin use is consistent with these patterns of weight alteration. Weight plays such an important role in DM and cancer that some weight loss drugs have been used off-label for the treatment of DM. The appetite suppressants rimonabant and sibutramine were prescribed for obesity, often in conjunction with DM, but have since been pulled from the market due to high risks for stroke and psychosis, respectively. In in vitro studies, rimonabant has been shown to have some anti-tumor activity [133], but is not safe for use in humans. Development of similar drugs is currently being explored [133]. Orlistat is a fatty acid synthase inhibitor with FDA approval for weight loss and has been shown to have some anti-tumoral effects in animal models of colorectal cancer [134], but there have been no epidemiological studies examining the effects of orlistat on cancer risk in patients with DM.

Diet and physical activity

Diet plays an important role in the development of both cancer and DM, as well as in the management of DM. Most research into diet and health suggests that low consumption of

red meats and high intake of vegetables and fruits leads to a lower risk of many types of cancer [135]. Similar diets that are high in monounsaturated fatty acids, fruits, vegetables, whole grain cereals, and dietary fiber may protect against DM by ameliorating insulin sensitivity and decreasing inflammation [136]. Low-carbohydrate diets including greater consumption of meats and animal fats are associated with weight loss and subsequent improvements in glycemic control. Several major health organizations such as the American Cancer Society and the American Institute for Cancer Research recommend limiting consumption of energy-rich and heavily processed foods [137]. Further research may reveal more conclusive evidence regarding dietary benefits in reducing DM and cancer risks [130].

Numerous observational studies have consistently demonstrated that higher levels of physical activity provide substantial health benefits and reduce risk of certain cancers including colon, post-menopausal breast, and endometrial cancer [138, 139]. It has also been suggested that physical activity post-diagnosis may improve cancer survival for some cancers, including breast and colorectal cancers [139]. Several large observational and randomized studies suggest that for DM, even moderately intense exercise such as walking for half an hour at least 5 days per week can reduce risk of DM by as much as 40 % [130]. The effects of physical activity on DM prevention are not only related to weight loss, as evidence suggests that subjects who met prescribed exercise goals significantly reduced their risk of DM regardless of weight loss goals [131].

Obesity is the most common comorbidity of DM and is a major contributor to oxidative stress and chronic inflammation. Weight loss is related to a decreased risk of cancer in diabetic patients. Consistent with this finding, drugs that tend to increase body weight are more commonly related to an increased risk of cancer, while drugs that tend to decrease body weight are not. However, there is little evidence regarding the relationship between specific weight loss drugs and cancer. Not surprisingly, a healthy diet and high levels of physical activity appear to play a role in decreasing the risk of cancer in patients with DM.

Demographic factors that affect use of DM medications

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes have issued consensus guidelines for the initiation and adjustment of therapy for the management of DM [140]. These guidelines recommend a three tier approach, recognizing that the progressive nature of DM will require additional medications and increased dosages over time. At diagnosis, lifestyle changes and metformin are recommended, followed by the addition of sulfonylurea and/or basal insulin, and finally intensive insulin [140]. However, these guidelines are not always followed, and the community of physicians that treat patients with DM are increasingly recognizing the need for personalized approaches to glycemic control that would optimally be based on randomized controlled trial subgroup analyses and specific goals and risks for the individual [141]. Studies suggest that certain demographic factors, including age, gender, race, and socioeconomic status, may affect the use of certain DM medications [142], and several of these factors are also related to the risk of DM and cancer.

The development of both cancer and DM appears to be age-related. The incidence of most cancers increases with age in both developed and developing countries [143]. In economically developed countries, most newly diagnosed cancers occur among individuals over 55 years of age [143]. DM also has a greater incidence with older age. The Centers for Disease Control and Prevention estimates that 10.2 % of individuals 20 years of age or older have DM, increasing to 23.1 % in those 60 years of age or older [144]. The factors influencing age-related diseases such as DM and cancer are not yet completely understood, although changes in metabolic processes and immune system function may play a role. Age also influences the use of certain DM medications. Desai et al. [142] examined first-line DM therapy in over 50 million patients ages 18–100 years in the US between 2006 and 2008. They found that patients diagnosed at ages >70 were most likely to receive the ADA-recommended first-line drug metformin [140]. Interestingly, adults ages 55–69 years were least likely to receive metformin as first-line therapy, with an OR of 0.27 (95 % CI 0.26–0.27, $p < 0.001$) compared to adults over age 70. Metformin is not recommended for patients with renal dysfunction [140], which may be related to age considerations. Consistent with this recommendation, patients with higher levels of comorbidity were less likely to receive metformin as first-line therapy ($p < 0.001$) [142].

Certain cancers are gender-specific, that is, cervical and uterine cancer in women and testicular and prostate cancer in men. However, in general, epidemiological evidence suggests that cancer occurs more frequently in men [144]. Similarly, men are at slightly higher risk of DM than women (11.2 % of men over age 20 versus 10.2 % of women) [143]. As with age, gender was also found by Desai et al. [142] to influence DM drug use, with women having an OR for receiving metformin as first-line therapy of 0.69 (95 % CI 0.68–0.70) compared to men.

After adjustment for age, the incidence of cancer and DM overall varies along racial and ethnic lines. Genetic factors, access to medical care, and other risk factors such as socioeconomic conditions may account for disparity among races. In the United States, African Americans are more likely to develop and die from cancer and to develop DM than any other race or ethnic group [143]. In contrast, Asian Americans/Pacific Islanders have among the lowest cancer incidence and mortality [143], despite DM being disproportionately higher in Asian Americans/Pacific Islanders compared with non-Hispanic whites [144]. There is some indication that socio-economic factors play a role in DM medication use. Desai et al. [142] found that patients living in zip code areas with lower median income levels were less likely to receive ADA-recommended first-line therapy ($p < 0.001$). However, the interaction between various risk factors related to health outcome disparities are not well understood and are likely to be multifactorial.

Several demographic factors are known to influence both DM and cancer risk. There is also some evidence to suggest that demographic factors influence the use of certain DM medications. However, at present, very little is known about the interplay between demographic factors, DM medication use, and modulation of cancer risk. Future studies focusing on subgroup analysis may help to shed more light on this issue.

Summary of the effect of DM drugs on cancer risk and importance in cancer prediction models

Attempts to use DM risk scores based on shared factors to model prediction for DM risk and that of subsequent associated comorbid conditions, including CVD and cancer, have met with some success. Candidate factors studied have included those occurring in physiological pathways, genetic/genomic markers, and proteomic and metabolomic markers. Important markers that have been targeted include identification of glycated hemoglobin (HbA1c), scoring of impaired fasting glucose (IFG), impaired glucose tolerance (IGT), blood pressure, and triglyceride levels. Evidence suggests that a longitudinal rise in either IFG or IGT has the ability to predict the development of DM, with a potential for predicting increased risk of certain cancers [145]. Because cancer and DM share so many risk factors, it seems logical that a joint prediction tool may be both feasible to develop and valuable as a diagnostic tool.

The evidence of an association between the drugs used to treat DM and the risk of cancer is increasing (Table 1). There is reasonably strong evidence to suggest that drugs that increase insulin levels, cause weight gain, and increase oxidative stress increase cancer risk. Conversely, drugs that decrease insulin levels, are associated with weight loss, and reduce oxidative stress appear to have a protective effect, especially metformin. Therefore, inclusion of DM medications in models for the prediction of cancer in diabetic patients may be a worthy goal. However, it should be noted that association between DM medications and cancer appear to vary widely by both medication and cancer type, as shown in Table 1. The majority of epidemiological studies lump all types of cancer together for analysis purposes. Studies that examined certain types of cancer individually highlight major inconsistencies in the evidence. As a particularly striking example, examinations of the association between colorectal cancer and metformin use have found evidence of reduced risk [45], increased risk [146], and no association [79]. Future research to better characterize how DM drugs modulate cancer risk that examines factors including drug combinations, treatment duration, dosage, and specific cancer types will be necessary to include DM drugs in models of cancer risk.

Conclusion

Evidence in the literature points toward hyperinsulinemia as a central player in the association between DM and cancer development and progression. Excessive endogenous production of insulin due to factors such as diet, obesity, age, metabolic syndrome, hyperglycemia, and smoking lead to a state of oxidative stress and chronic inflammation, which may be the common pathway leading to increased tumorigenesis and cancer promotion in patients with DM. The exact mechanism by which DM medications lead to cancer development has not been fully elucidated; however, hyperinsulinemia is again a likely mechanism. Exogenous insulin exposure has been linked to a higher risk of cancer, while metformin and TZDs, which reduce levels of circulating insulin, have been associated with a decreased risk of cancer. Many people with DM are treated with a multi-medication regimen. Therefore, determination of actual cancer risk related to any one medication is particularly difficult. Further exploration and explanation of the mechanisms behind the

association between DM, cancer, and the role of DM medications in modulating cancer risk may aid in the development of better prevention and treatment options for both DM and cancer.

Hyperinsulinemia stands out as a major contributing factor in the development of cancer. Therefore, the conflicting observations with respect to different DM medications are not particularly surprising. There is a clear correlation between hyperinsulinemia and an increased risk of cancer, as discussed previously. Consistent with this finding, drugs that increase circulating insulin including exogenous insulin, insulin analogs, and insulin secretagogues are generally associated with an increased risk of cancer. In contrast, the drugs that regulate insulin signaling without increasing the circulating levels of insulin by instead decreasing insulin resistance, particularly metformin, appear to be associated with a decreased risk of cancer. The decrease in insulin resistance and regulation of hyperinsulinemia achieved in diabetic patients using metformin presents a biologically plausible mechanism by which decreased signaling through the insulin and IGF pathways may lead to a reduction in cancer risk [6, 87, 88]. Furthermore, the insulin sensitizers metformin and TZDs have also been demonstrated to reduce oxidative stress and chronic inflammation, which may be an additional mechanism by which these drugs exert anti-cancer effects. Regarding the role of DM medications in cancer development, current clinical consensus is that data are not yet conclusive and, therefore, should not be the basis for changes in clinical practice. Continued study and increased surveillance for cancer in patients with DM are needed [72]. Until clear, prospective evidence from randomized clinical trials is available regarding increased cancer risk with insulin and insulin analog treatments, clinicians should continue to consider the benefits of optimal glycemic control over any presumed cancer risks in the management of DM [146]. Several important clinical trials are currently underway to examine the roles of metformin and TZDs in cancer prevention and treatment.

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Table 1

Epidemiological studies of cancer and DM medication use

Medication	Effect on shared risk factors	Reference	Cancer type	Effect on cancer incidence/outcomes
Insulin, insulin analogs, insulin secretagogues				
Insulin (any)	Increases insulin levels	Bowker [3]	All types	Increased risk of cancer-related mortality compared to insulin nonuse
	Reduces hyperglycemia	Currie [45]	All types	Increased risk compared to metformin use
	Increases oxidative stress		Colorectal	Increased risk compared to metformin use
	Associated with weight gain		Pancreatic	Increased risk compared to metformin use
			Breast	No association with incidence
			Prostate	No association with incidence
		Hemkens [97]	All types	Positive association between cancer incidence and insulin dose
		Yang [54]	All types	Reduced risk compared to insulin nonuse
		Baur [61]	All types	Increased risk of cancer-related mortality compared to insulin nonuse
		Bodmer [74]	Ovarian	Increase risk compared to insulin nonuse
		Currie [62]	All types	Increased risk of cancer-related mortality compared to non-diabetes
		Bodmer [75]	Colorectal	No association with incidence
		Bodmer [63]	Pancreatic	Increased risk compared to insulin nonuse
		Dehal [147]	Colorectal	No association with survival
Insulin analogs	Increases insulin levels	Currie [45]	All types	Increased risk compared to metformin use, not different from human insulin
	Reduced hyperglycemia	Hemkens [47]	All types	Increased risk with insulin glargine compared to human insulin, dose-dependent
	Increases oxidative stress	Dejgaard [50]	All types	No difference in risk with NPH insulin, insulin glargine, or insulin detemir
	Associated with weight gain	Home [51]	All types	No difference in risk of insulin glargine compared to other insulins
		Colhoun [48]	All types	No difference in risk of insulin glargine compared to other insulins
		Jonasson [49]	Breast	Increased risk of insulin glargine compared to all other insulins
			Gastrointestinal	No difference in risk of insulin glargine compared to other insulins
			Prostate	No difference in risk of insulin glargine compared to other insulins
			All types	No difference in risk of insulin glargine compared to other insulins
		Ljung [52]	Breast	Follow-up of Jonasson [94], no difference in 2008
		Mannucci [46]	All types	Increased risk at high insulin glargine doses compared to other insulins
		Lind [53]	Prostate	Increased risk with higher doses of insulin glargine
			Breast	Increased risk with higher doses of insulin glargine
Sulfonylurea	Increases insulin levels	Bowker [3]	All types	Increased risk of cancer-related mortality compared to metformin use

Medication	Effect on shared risk factors	Reference	Cancer type	Effect on cancer incidence/outcomes	
	Reduces hyperglycemia	Currie [45]	All types	Increased risk compared to metformin use	
	Associated with weight gain		Colorectal	Increased risk compared to metformin use	
			Pancreatic	Increased risk compared to metformin use	
			Breast	No association with incidence	
			Prostate	No association with incidence	
			Yang [60]	All types	Glibenclamide and gliclazide associated with reduced risk, dose-dependent
	Baur [61]	All types	Increased risk of cancer-related mortality compared to metformin use		
	Bodmer [74]	Ovarian	No association with incidence		
	Currie [62]	All types	Increased risk of cancer-related mortality compared to non-diabetes		
	Bodmer [75]	Colorectal	No association with incidence		
Bodmer [63]	Pancreatic	Increased risk compared to sulfonylurea nonuse			
Insulin sensitizers					
Metformin	Reduces insulin resistance	Bowker [3]	All types	Reduced risk of cancer-related mortality compared to sulfonylurea use	
	Reduces insulin levels	Libby [5]	All types	Reduced risk compared to metformin nonuse	
	Reduces hyperglycemia	Currie [45]	All types	Reduced risk compared to any other treatment	
	Reduces oxidative stress		All types	Addition to insulin regimens reduced cancer risk by half	
	Associated with weight loss		Colorectal	Reduced risk compared to any other treatment	
			Pancreatic	Reduced risk compared to any other treatment	
			Breast	No association with incidence	
			Prostate	No association with incidence	
			Jiralerspong [78]	Breast	Increased rate of pathologic complete response compared to metformin nonuse
			Landman [6]	All types	Reduced risk of cancer-related mortality compared to metformin nonuse
			Baur [61]	All types	Reduced risk compared to any other treatment
			Azoulay [76]	Prostate	No association with incidence
			Bodmer [74]	Ovarian	Reduced risk compared to metformin nonuse
			He [77]	Breast	Increased length of survival and decreased mortality
	Taubes [73]	All types	25–40 % less cancer than treatment with drugs that increase insulin levels		
	Currie [62]		All types	Reduced risk of cancer-related mortality compared to non-diabetes	
			All types	Reduced risk of cancer-related mortality compared to insulin or sulfonylurea	
			Liver	Reduced cancer-related mortality compared to metformin nonuse	
			Ovarian	Reduced cancer-related mortality compared to metformin nonuse	
			Prostate	Suggestion of reduced cancer-related mortality, not significant	
			Bladder	No association with mortality	

Medication	Effect on shared risk factors	Reference	Cancer type	Effect on cancer incidence/outcomes
Thiazolidinediones	Reduces insulin resistance Reduces insulin levels Reduces hyperglycemia Reduces oxidative stress		Breast	No association with mortality
			Colorectal	No association with mortality
			Lung	No association with mortality
			Pancreatic	No association with mortality
		Bodmer [75]	Colorectal	Slight increase in risk compared to metformin nonuse
		Bodmer [63]	Pancreatic	Reduced risk compared to metformin nonuse, in women only
		Govindarajan [79]	Lung	Reduced risk compared to thiazolidinedione nonuse
		Koro [80]	Colorectal	No association with incidence
			Prostate	No association with incidence
			Breast	No association with incidence
			Colon	No association with incidence
		Ramos-Nino [81]	Prostate	No association with incidence
			All types	Increased risk compared to thiazolidinedione nonuse, especially rosiglitazone
			All types	Reduced incidence with rosiglitazone use compared to nonuse
		Ferrara [82]	All types	No clear association of pioglitazone and cancer
Glucosidase inhibitors	Acarbose Reduces hyperglycemia	Monami [85] Tseng [86]	Melanoma	Suggestion of increased risk with pioglitazone use, not significant
			NHL	Suggestion of increased risk with pioglitazone use, not significant
			Kidney/renal	Suggestion of decreased risk with pioglitazone use, not significant
			Breast	Increased length of survival and decreased mortality

NHL non-Hodgkin lymphoma