REVIEW

CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will neither overestimate nor underestimate the risk of cancer when prescribing diabetes therapy

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Diabetes therapy and cancer risk: Where do we stand when treating patients?

ABSTRACT

The pathophysiology of type 2 diabetes mellitus conveys increased cancer risk, and any antidiabetic drug may alter that risk in a favorable or unfavorable way. This article discusses the links between diabetes and cancer, the different agents available for treating diabetes, and the cancer risk associated with these therapies.

KEY POINTS

Exogenous insulin, insulin secretagogues, and incretin-based therapies are under scrutiny because of their potential influences on cancer development in a population already at risk.

At present, we lack adequate prospective data on the cancer risk from diabetes drugs.

Patients with a personal history of bladder cancer should avoid pioglitazone, and those who have had pancreatic cancer should avoid incretin therapies until definitive clinical data become available.

Patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 should not receive glucagon-like peptide-1 receptor agonists. These agents should also probably be avoided in patients with a personal history of differentiated thyroid carcinoma or a history of familial nonmedullary thyroid carcinoma.

Given the associations between diabetes and malignancy, cancer screening is especially important.

doi:10.3949/ccjm.81a.13140

In the last quarter century, many new drugs have become available for treating type 2 diabetes mellitus. The American Association of Clinical Endocrinologists incorporated these new agents in its updated glycemic control algorithm in 2013.[1] Because diabetes affects 25.8 million Americans and can lead to blindness, renal failure, cardiovascular disease, and amputation, agents that help us treat it more effectively are valuable.[2]

One of the barriers to effective treatment is the side effects of the agents. Because some of these drugs have been in use for only a short time, concerns of potential adverse effects have arisen. Cancer is one such concern, especially since type 2 diabetes mellitus by itself increases the risk of cancer by 20% to 50% compared with no diabetes.[3]

Type 2 diabetes has been linked to risk of cancers of the pancreas,[4] colorectum,[5,6] liver,[7] kidney,[8,9] breast,[10] bladder,[11] and endometrium,[12] as well as to hematologic malignancies such as non-Hodgkin lymphoma.[13] The risk of bladder cancer appears to depend on how long the patient has had type 2 diabetes. Newton et al,[14] in a prospective cohort study, found that those who had diabetes for more than 15 years and used insulin had the highest risk of bladder cancer. On the other hand, the risk of prostate cancer is actually lower in people with diabetes,[15] particularly in those who have had diabetes for longer than 4 years.[16]

Cancer and type 2 diabetes share many risk factors and underlying pathophysiologic mechanisms. Nonmodifiable risk factors for both diseases include advanced age, male

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sex, ethnicity (African American men appear to be most vulnerable to both cancer and diabetes),[17,18] and family history. Modifiable risk factors include lower socioeconomic status, obesity, and alcohol consumption. These common risk factors lead to hyperinsulinemia and insulin resistance, changes in mitochondrial function, low-grade inflammation, and oxidative stress,[3] which promote both diabetes and cancer. Diabetes therapy may influence several of these processes.

Several classes of diabetes drugs, including exogenous insulin,[19–22] insulin secretagogues,[23–25] and incretin-based therapies,[26–28] have been under scrutiny because of their potential influences on cancer development in a population already at risk (**TABLE 1**).

INSULIN ANALOGUES: MIXED EVIDENCE

Insulin promotes cell division by binding to insulin receptor isoform A and insulin-like growth factor 1 receptors.[29] Because endogenous hyperinsulinemia has been linked to cancer risk, growth, and proliferation, some speculate that exogenous insulin may also increase cancer risk.

In 2009, a retrospective study by Hemkens et al linked the long-acting insulin analogue glargine to risk of cancer.[19] This finding set off a tumult of controversy within the medical community and concern among patients. Several limitations of the study were brought to light, including a short duration of follow-up, and several other studies have refuted the study's findings.[20,21]

More recently, the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial[22] found no higher cancer risk with glargine use than with placebo. This study enrolled 12,537 participants from 573 sites in 40 countries. Specifically, risks with glargine use were as follows:

- Any cancer—hazard ratio 1.00, 95% confidence interval (CI) 0.88–1.13, $P = .97$
- Cancer death—hazard ratio 0.94, 95% CI 0.77–1.15, $P = .52$.

However, the study was designed to assess cardiovascular outcomes, not cancer risk. Furthermore, the participants were not typical of patients seen in clinical practice: their insulin doses were lower (the median insulin dose was 0.4 units/kg/day by year 6, whereas in clinical practice, those with type 2 diabetes mellitus often use more than 1 unit/kg/day, depending on duration of diabetes, diet, and exercise regimen), and their baseline median hemoglobin A_{1c} level was only 6.4%. And one may argue that the median follow-up of 6.2 years was too short for cancer to develop.[22]

In vitro studies indicate that long-acting analogue insulin therapy may promote cancer cell growth more than endogenous insulin,[30] but epidemiologic data have not unequivocally substantiated this.[20–22] There is no clear evidence that analogue insulin therapy raises cancer risk above that of human recombinant insulin, and starting insulin therapy should not be delayed because of concerns about cancer risk, particularly in uncontrolled diabetes.

INSULIN SECRETAGOGUES

Sulfonylureas: Higher risk

Before 1995, only two classes of diabetes drugs were approved by the US Food and Drug Administration (FDA)—insulin and sulfonylureas.

Type 2 diabetes by itself increases the risk of cancer by 20% to 50%

Sulfonylureas lower blood sugar levels by binding to sulfonylurea receptors and inhibiting adenosine triphosphate-dependent potassium channels. The resulting change in resting potential causes an influx of calcium, ultimately leading to insulin secretion.

Sulfonylureas are effective, and because of their low cost, physicians often pick them as a second-line agent after metformin.

The main disadvantage of sulfonylureas is the risk of hypoglycemia, particularly in patients with renal failure, the elderly, and diabetic patients who are unaware of when they are hypoglycemic. Other potential drawbacks are that they impair cardiac ischemic preconditioning[31] and possibly increase cancer risk.[21,32] (Ischemic preconditioning is the process in which transient episodes of ischemia "condition" the myocardium so that it better withstands future episodes with minimal anginal pain and tissue injury.[33]) Of the sulfonylureas, glyburide has been most implicated in cardiovascular risk.[32]

In a retrospective cohort study of 62,809 patients from a general-practice database in

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TABLE 1

Cancer risk from approved drugs for type 2 diabetes mellitus

Medication	Cancer risk	Types of studies	Notes
ORAL AGENTS			
Insulin sensitizers			
Metformin	Lower	Case-control Cohort Retrospective database	Decreased risk of cancer-related death
Thiazolidinediones	Higher risk of bladder cancer; lower risk of breast and lung cancer	Case-control Cohort	Slight dose-dependent increase in bladder cancer risk in cohort studies; no increased risk in randomized control trials
Insulin secretagogues			
Sulfonylureas	Higher	Case-control Cohort	Increased risk of cancer-related death compared with insulin sensitizers
Meglitinide	Higher	Case-control	Neutral to increased association of cancer risk (fewer available data compared with sulfonylurea)
Other oral agents			
Alpha glucosidase inhibitors	Neutral	Case-control Retrospective database	
Dipeptidyl peptidase-IV inhibitors	Possibly higher risk of pancreatic cancer	Expert opinion	Sitagliptin shows increased risk of acute pancreatitis, raising concerns about pancreatic cancer; to date, there is no evidence of increased risk of pancreatic cancer in humans
Sodium-glucose-linked cotransporter-2 inhibitors	Neutral	Randomized controlled clinical trials	
INJECTABLE AGENTS			
Glucagon-like peptide-1 receptor agonists	Higher risk of thyroid and pancreatic cancer	Adverse events reports Expert opinion Rodent studies	Medullary thyroid cancer and pancreatic cancer risk increased in rodents; potentially increased pancreatic cancer risk from adverse serious events reported for exenatide twice daily
Insulin glargine	Neutral	Case-control Randomized controlled	Median dose 0.4 U/kg/day at 6 years in the ORIGIN trial[20]
Insulin analogues	Higher	Case-control Cohort Retrospective database	

Do not delay starting insulin because of concerns about cancer risk, particularly in uncontrolled diabetes

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the United Kingdom, Currie et al[21] found that sulfonylurea monotherapy was associated with a 36% higher risk of cancer (95% CI 1.19–1.54, $P < .001$) than metformin monotherapy. Prescribing bias may have influenced the results: practitioners are more likely to prescribe sulfonylureas to leaner patients, who have a greater likelihood of occult cancer. However, other studies also found that the cancer death rate is higher in those who take a sulfonylurea alone than in those who use metformin alone.[23,24]

Some evidence indicates that long-acting sulfonylurea formulations (eg, glyburide) likely hold the most danger, certainly in regard to hypoglycemia, but it is less clear if this translates to cancer concerns.[31]

Meglitinides: Limited evidence

Meglitinides, the other class of insulin secretagogues, are less commonly used but are similar to sulfonylureas in the way they increase endogenous insulin levels. The data are limited regarding cancer risk and meglitinide therapy, but the magnitude of the association is similar to that with sulfonylurea therapy.[25]

INSULIN SENSITIZERS

There are currently two classes of insulin sensitizers: biguanides and thiazolidinediones (TZDs, also known as glitazones). These drugs show less risk of both cancer incidence and cancer death than insulin secretagogues such as sulfonylureas.[21,23,24] In fact, they may decrease cancer potential by alteration of signaling via the AKT/mTOR (v-akt murine thymoma viral oncogene homolog 1/mammalian target of rapamycin) pathway.[34]

Metformin, a biguanide, is the oral drug of choice

Metformin is the only biguanide currently available in the United States. It was approved by the FDA in 1995, although it had been in clinical use since the 1950s. Inexpensive and familiar, it is the oral antihyperglycemic of choice if there are no contraindications to it, such as renal dysfunction (creatinine ≥ 1.4 mg/dL in women and ≥ 1.5 mg/dL in men), acute decompensated heart failure, or pulmonary or hepatic insufficiency, all of which may lead to an increased risk of lactic acidosis.[1]

Metformin lowers blood sugar levels primarily by inhibiting hepatic glucose production (gluconeogenesis) and by improving peripheral insulin sensitivity. It directly activates AMP-activated protein kinase (AMPK), which affects insulin signaling and glucose and fat metabolism.[35] It may exert further beneficial effects by acutely increasing glucagon-like peptide-1 (GLP-1) levels and inducing islet incretin-receptor gene expression.[36] Although the exact mechanisms have not been fully elucidated, metformin's insulin-sensitizing properties are likely from favorable effects on insulin receptor expression, tyrosine kinase activity, and influences on the incretin pathway.[36,37] These effects also mitigate carcinogenesis, both directly (via AMPK and liver kinase B1, a tumor-suppressor gene) and indirectly (via reduction of hyperinsulinemia).[35]

Overall, biguanide therapy is associated with a lower cancer incidence or, at worst, no effect on cancer incidence. In vitro studies demonstrate that metformin both suppresses cancer cell growth and induces apoptosis, resulting in fewer live cancer cells.[34] Several retrospective studies found lower cancer risk in metformin users than in patients receiving antidiabetes drugs other than insulin-sensitizing agents,[21,23,25,38–40] while others have shown no effect.[41] Use of metformin was specifically associated with lower risk of cancers of the liver, colon and rectum, and lung.[42] Further, metformin users have a lower cancer mortality rate than nonusers.[24,43]

Metformin is associated with a lower cancer incidence or, at worst, no effect on cancer incidence

Thiazolidinediones

TZDs, such as pioglitazone, work by binding to peroxisome proliferator-activated gamma receptors in the cell nucleus, altering gene transcription.[44] They reduce insulin resistance and levels of endogenous insulin levels and free fatty acids.[44]

Concern over bladder cancer risk with TZD use, particularly with pioglitazone, has increased in the last few years, as various cohort studies found a statistically significant increased risk with this agent.[44] The risk appears to rise with cumulative dose.[45,46]

Randomized controlled trials also found an increased risk of bladder cancer with TZD therapy, although the difference was not statistically significant.[47–49] In a mean follow-up of

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8.7 years, the Prospective Pioglitazone Clinical Trial in Macrovascular Events reported 23 cases of bladder cancer in the pioglitazone group vs 22 cases in the placebo group, for rates of 0.9% vs 0.8% (relative risk [RR] 1.06, 95% CI 0.59–1.89).[49]

On the other hand, the risk of cancer of the breast, colon, and lung has been found to be lower with TZD use.[47] In vitro studies support the clinical data, showing that TZDs inhibit growth of human cancer cells derived from cancers of the lung, colon, breast, stomach, ovary, and prostate.[50–53]

Home et al[54] compared rosiglitazone against a sulfonylurea in patients already taking metformin in the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) trial. Malignancies developed in 6.7% of the sulfonylurea group compared with 5.1% of the rosiglitazone group, for a hazard ratio of 1.33 (95% CI 0.94–1.88).

Both ADOPT (A Diabetes Outcome Progression Trial) and the RECORD trial found rosiglitazone comparable to metformin in terms of cancer risk.[54]

Colmers et al[47] pooled data from four randomized controlled trials, seven cohort studies, and nine case-control studies to assess the risk of cancer with TZD use in type 2 diabetes. Both the randomized and observational data showed neutral overall cancer risk with TZDs. However, pooled data from observational studies showed significantly lower risk with TZD use in terms of:

- Colorectal cancer
  RR 0.93, 95% CI 0.87–1.00
- Lung cancer
  RR 0.91, 95% CI 0.84–0.98
- Breast cancer
  RR 0.89, 95% CI 0.81–0.98.

GLP-1 receptor agonists are injected; DPP-IV inhibitors are oral agents

INCRETIN-BASED THERAPIES

Incretins are hormones released from the gut in response to food ingestion, triggering release of insulin before blood glucose levels rise. Their action explains why insulin secretion increases more after an oral glucose load than after an intravenous glucose load, a phenomenon called the incretin effect.[55]

There are two incretin hormones: glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1). They have short a half-life because they are rapidly degraded by dipeptidyl peptidase-IV (DPP-IV).[55] Available incretin-based therapies are GLP-1 receptor agonists and DPP-IV inhibitors.

When used as monotherapy, incretin-based therapies do not cause hypoglycemia because their effect is glucose-dependent.[55] GLP-1 receptor antagonists have the added benefit of inducing weight loss, but DPP-IV inhibitors are considered to be weight-neutral.

GLP-1 receptor agonists

Exenatide, the first of the GLP-1 receptor agonists, was approved in 2005. The original formulation (Byetta) is taken by injection twice daily, and timing in conjunction with food intake is important: it should be taken within 60 minutes before the morning and evening meals. Extended-release exenatide (Bydureon) is a once-weekly formulation taken without regard to timing of food intake. Exenatide (either twice-daily Byetta or once-weekly Bydureon) should not be used in those with creatinine clearance less than 30 mL/min or end-stage renal disease and should be used with caution in patients with renal transplantation.

Liraglutide (Victoza), a once-daily formulation, can be injected irrespective of food intake. The dose does not have to be adjusted for renal function, although it should be used with caution in those with renal impairment, including end-stage renal disease. Approval for a 3-mg formulation is pending with the FDA as a weight-loss drug on the basis of promising results in a randomized phase 3 trial.[56]

Albiglutide (Tanzeum), a once-weekly GLP-1 receptor antagonist, was recently approved by the FDA.

DPP-IV inhibitors

Whereas GLP-1 receptor agonists are injected, the DPP-IV inhibitors have the advantage of being oral agents.

Sitagliptin (Januvia), the first DPP-IV inhibitor, became available in the United States in 2006. Since then, three more have become available: saxagliptin (Onglyza), linagliptin (Tradjenta), and alogliptin (Nesina).

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Concerns about thyroid cancer with incretin drugs

Concerns of increased risk of cancer, particularly of the thyroid and pancreas, have been raised since GLP-1 receptor agonists and DPP-IV inhibitors became available.

Studies in rodents have shown C-cell hyperplasia, sometimes resulting in increased incidence of thyroid carcinoma, and dose-dependent rises in serum calcitonin, particularly with liraglutide.[26] This has raised concern about an increased risk of medullary thyroid carcinoma in humans. However, the density of C cells in rodents is up to 45 times greater than in humans, and C cells also express functional GLP-1 receptors.[26]

Gier et al[27] assessed the expression of calcitonin and human GLP-1 receptors in normal C cells, C cell hyperplasia, and medullary cancer. In this study, calcitonin and GLP-1 receptor were co-expressed in medullary thyroid cancer (10 of 12 cases) and C-cell hyperplasia (9 of 9 cases) more commonly than in normal C cells (5 of 15 cases). Further, GLP-1 receptor was expressed in 3 of 17 cases of papillary thyroid cancer.

Calcitonin, a polypeptide hormone produced by thyroid C cells and used as a medullary thyroid cancer biomarker, was increased in a slightly higher percentage of patients treated with liraglutide than in controls, without an increase above the normal range.[57]

A meta-analysis by Alves et al[58] of 25 studies found that neither exenatide (no cases reported) nor liraglutide (odds ratio 1.54, 95% CI 0.40–6.02) was associated with increased thyroid cancer risk.

MacConell et al[59] pooled the results of 19 placebo-controlled trials of twice-daily exenatide and found a thyroid cancer incidence rate of 0.3 per 100 patient-years (< 0.1%) vs 0 per 100 patient-years in pooled comparators.

Concerns about pancreatic cancer with incretin drugs

Increased risk of acute pancreatitis is a potential side effect of both DPP-IV inhibitors and GLP-1 receptor agonists and has led to speculation that this translates to an increased risk of pancreatic cancer.

In a point-counterpoint debate, Butler et al[28] argued that incretin-based medications have questionable safety, with increased rates of pancreatitis possibly leading to pancreatic cancer. In counterpoint, Nauck[60] argued that the risk of pancreatitis or cancer is extremely low, and clinical cases are unsubstantiated.

Bailey[61] outlined the complexities and difficulties in drawing firm conclusions from individual clinical trials regarding possible adverse effects of diabetes drugs. The trials are typically designed to assess hemoglobin A_{1c} reduction at varying doses and are typically restricted in patient selection, patient numbers, and drug-exposure duration, which may introduce allocation and ascertainment biases. The attempt to draw firm conclusions from such trials can be problematic and can lead to increased alarm, warranted or not.

Type 2 diabetes mellitus itself is associated with an increased incidence of pancreatic cancer, and whether incretin therapy enhances this risk is still controversial. Whether more episodes of acute pancreatitis without chronic pancreatitis can be extrapolated to an increased incidence of pancreatic cancer is doubtful. A normal pancreatic duct cell may take up to 12 years to become a tumor cell from which pancreatic carcinoma develops, another 7 years to develop metastatic capacity, and another 3 years before a diagnosis is made from clinical symptoms (which are usually accompanied by metastases).[62]

The risks and benefits of incretin therapies remain a contentious issue, and there are no clear prospective data at this time on increased pancreatic cancer incidence. Long-term prospective studies designed to analyze these specific outcomes (pancreatitis, pancreatic cancer, and medullary thyroid cancer) need to be undertaken.[63]

The risks and benefits of incretin therapies are contentious, with unclear data on the risk of pancreatic cancer

OTHER DIABETES THERAPIES

Alpha glucosidase inhibitors

Oral glucosidase inhibitors ameliorate hyperglycemia by inhibiting alpha glucosidase enzymes in the brush border of the small intestines, preventing conversion of polysaccharides to monosaccharides.[64] This slows digestion of carbohydrates and glucose release into the bloodstream and blunts the postprandial hyperglycemic excursion.

The two alpha glucosidase inhibitors currently available in the United States are acar-

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bose and miglitol, and although data are limited, they do not appear to increase the risk of cancer.[65,66]

Sodium-glucose-linked cotransporter 2 inhibitors

The newest class of oral diabetes agents to be approved are the sodium-glucose-linked cotransporter 2 (SGLT2) inhibitors canagliflozin (Invokana) and dapagliflozin (Farxiga).

SGLT2 is a protein in the S1 segment of the proximal renal tubules responsible for over 90% of renal glucose reabsorption. SGLT2 inhibitors lower serum glucose levels by promoting glycosuria and have also been shown to have favorable effects on blood pressure and weight.[67,68]

Canagliflozin was the first of its class to gain FDA approval in the United States. It has not been found to be associated with increased cancer risk.[68]

Dapagliflozin, originally approved in Europe, was approved in the United States on January 8, 2014. Because of a possible increased incidence of breast and bladder malignancies, the FDA advisory committee initially recommended against approval and required further data. In those who were treated, nine cases of bladder cancer and nine cases of breast cancer were reported, compared with one case of bladder cancer and no cases of breast cancer in the control group; however, the difference was not statistically significant.[68]

Since SGLT2 inhibitors are still new, data on long-term outcomes are lacking. Early clinical data do not show a significant increase in cancer risk.

Since SGLT2 inhibitors are still new, data on long-term outcomes are lacking

WHAT THIS MEANS IN PRACTICE

Many studies have found associations between diabetes, obesity, hyperinsulinemia, and cancer risk. In the last decade, concerns implicating antihyperglycemic agents in cancer development have arisen but have not been well substantiated. At this time, there are no definitive prospective data indicating that the currently available type 2 diabetes therapies increase the incidence of cancer beyond the inherent increased risk in this population. What, then, is one to do?

Educate. Lifestyle modification, including weight management, should continue to be emphasized in diabetes education, as no therapy is completely effective without adjunct modifications in diet and physical activity. Epidemiologic studies have shown the benefits of lifestyle modifications, which ameliorate many of the adverse metabolic conditions that coexist in type 2 diabetes and cancer.

Screen for cancer. Given the associations between diabetes and malignancy, cancer screening is especially important in this high-risk population.

Customize therapy to individual patients. Those with a personal history of bladder cancer should avoid pioglitazone, and those who have had pancreatic cancer should avoid sitagliptin until definitive clinical data become available.

Moreover, patients with a personal or family history of medullary thyroid cancer should not receive GLP-1 receptor agonists. These agents should also probably be avoided in patients with a personal history of differentiated thyroid carcinoma or a history of familial nonmedullary thyroid carcinoma. Until we have further elucidating data, it is not possible to say whether a family history of any of the other types of cancer should represent a contraindication to the use of any of these agents.

Discuss. The multitude of diabetes therapies warrants physician-patient discussions that carefully weigh the risks and benefits of additional agents to optimize glycemic control and metabolic factors in individual patients.

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