Review of Associations Between Type 2 Diabetes and Cancer

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Debate is ongoing regarding the relationship between type 2 diabetes and cancer, and the pathways linking the two are incompletely understood. Some posit that the relationship hinges on a common predisposing factor such as obesity, insulin resistance, or chronic inflammation that increases the risk of cancer independently. Others speculate that diabetes acts as an independent risk factor for cancer because of other molecular pathways and interactions. Additionally, antidiabetic medications have been associated with changes in cancer risk. This review presents a summary of the latest studies and data concerning the relationships among type 2 diabetes, antidiabetic medications, cancer risk, and cancer prognosis.

KEY POINTS

- Type 2 diabetes is a common disease and appears to be a contributor to higher rates of some types of cancer.
- Rates of endometrial, liver, pancreatic, breast, and colorectal cancers are the types most closely associated with type 2 diabetes.
- Obesity and insulin resistance appear to be major mechanisms of this link; therefore, reduction of these factors should be a focus of treatment.

Type 2 diabetes has been strongly associated with comorbidities such as cardiovascular disease, diabetic nephropathy, retinopathy, neuropathy, and lower-limb amputations, among many others. However, cancer is less often mentioned as a comorbidity of diabetes. In the United States, cancer is the second leading cause of death, and diabetes is the seventh leading cause (1). According to the National Cancer Institute, 1,735,530 new cases of cancer were diagnosed in 2018 (2). There is growing evidence of a biological or physiological link between type 2 diabetes and cancer. Several studies have identified type 2 diabetes as an independent risk factor for certain types of cancer, including hepatic, pancreatic, endometrial, colorectal, bladder, and breast cancers; conversely, male patients with type 2 diabetes have a lower prevalence of prostate cancer than their counterparts without diabetes (3,4).

The potential link between type 2 diabetes and cancer have been the source of debate for decades. Some posit the association is purely based on risk factors such as obesity that coincidentally influence the risk of developing each disease separately. Others speculate that type 2 diabetes itself acts as a risk factor for developing cancer. A study using data from the National Health Interview Survey predicted that 39.7 million adults would be living with type 2 diabetes in 2030, up from 22.3 million adults in 2014, which was the starting point for the projection (5). Regardless of the specific mechanisms through which diabetes and cancer are linked, such an increase would be expected to lead to a corresponding increase in the relative risk (RR) of developing cancer, even if only by a small percentage. Additionally, several antidiabetic medications have been implicated in cancer pathogenesis or identified as protective against cancer. For example, a growing body of evidence supports the anticancer effects of the biguanide metformin (6). For other antidiabetic medications, however, the evidence to date is much more mixed and inconclusive.

Because type 2 diabetes is one of the most common chronic conditions in the United States, its associations with various forms of cancer has huge implications for the

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U.S. health care system in terms of both costs and mortality. The purpose of this article is to review the evidence with regard to these links and present a framework that primary care providers can use to discuss cancer risks with their patients with diabetes.

Literature Review Methods

This review is based on searches of PubMed conducted during the summer of 2018. Manuscripts were identified by searching various combinations of terms such as "cancer," "diabetes," "obesity," "breast cancer," "endometrial cancer," "pancreatic cancer," "colorectal cancer," "insulin," "metformin," "dipeptidyl peptidase-4 (DPP-4) inhibitor," "sodium–glucose cotransporter 2 (SGLT2) inhibitor," "glucagon-like peptide 1 (GLP-1) analogue/agonist" and "thiazolidinedione (TZD)." For example, search terms such as "diabetes and pancreatic cancer" or "metformin and cancer" were used. A detailed search strategy is included in the Supplementary Materials. The reference lists of potential articles were also checked to identify additional relevant publications.

Publications were included if they were relevant reviews, meta-analyses, case-control or cohort studies, or randomized controlled trials that investigated risk or mortality of cancer in association with type 2 diabetes or antidiabetic medications. Reviews and studies were included if they were fairly recent and most of the references were from the past 5–10 years. Large-scale trials were favored. Studies were excluded that were >20 years old, did not focus on type 2 diabetes (i.e., if they involved type 1 or gestational diabetes), or did not include cancer incidence or mortality as an outcome. The literature search was not focused on either cancer incidence or cancer mortality specifically and therefore included studies that reported outcomes for either or both.

Identified articles were then divided into those that evaluated type 2 diabetes and cancer and those that evaluated antidiabetic medications and cancer.

Obesity: A Common Link Between Diabetes and Cancer

As mentioned above, some believe that the association between type 2 diabetes and certain cancers is largely the result of the two sharing common risk factors such as obesity (7). Stated simply, there is credence to the notion that obesity increases the RR of developing both diseases, and there is evidence linking obesity to increasing rates of both diseases (7).

In the Cancer Prevention Study II, which followed >1 million patients from 1982 to 1996, researchers found that obese men and women had a 40–80% increased risk of dying from cancer (8). Another meta-analysis reported that for every 5 kg/m^2 increase in BMI, people had increased risks of multiple types of cancer, including colon, endometrial, pancreatic, and prostate cancers (9). Additionally, Birks et al. (10) conducted a meta-analysis that contained several studies noting a correlation between losing weight and decreased cancer risk. In this review, Birks et al. found that obese patients who underwent bariatric surgery had a 24–78% overall reduction in cancer incidence compared with an obese control group (10). Birks et al. also reviewed cohort studies focusing on nonsurgical weight loss and found reductions of 17–19% in cancer incidence in the populations that underwent intentional weight loss (10). Interestingly, a few of the studies examined by Birks et al. only noted a weight loss–associated decrease in cancer risk among women but not men (10).

Not surprisingly, with these sorts of correlations, there are several proposed mechanisms that independently link obesity to type 2 diabetes and to cancer. According to Berger (4), there are currently five major theories linking obesity and cancer. These include *1*) increased levels and bioavailability of growth factors such as insulin and insulin-like growth factor 1(IGF-1); *2*) increased sex steroid hormones such as estrogen and factors affecting their metabolism; *3*) altered adipocytokine levels such as leptin, adiponectin, and visfatin, all once believed to primarily affect energy balance but now known to have growth, immune, and tumor regulatory functions; *4*) low-grade inflammation and oxidative stress that affects growth-promoting cytokines and immune modulation; and *5*) altered microbiomes, and especially those composing intestinal flora (4).

Hyperinsulinemia, hyperglycemia, and resulting sequalae play important roles in cancer development. Hyperinsulinemia can increase tumor growth by stimulating mitogenesis and can increase serum IGF-1 levels by increasing production of IGF-1 and decreasing IGF-binding proteins (4). Alternatively, hyperinsulinemia has been proposed to lead to tumorigenesis by increasing cellular metabolic activity, which leads to DNA damage and mutagenesis (4). It is well known that tumor cells take up increased amounts of glucose compared with normal cells, so it is plausible that hyperglycemia stimulates tumorigenesis by providing the necessary fuel (4). Furthermore, hyperglycemia increases the production of advanced glycation end products, which, when interacting with

their receptors, increase oxidative stress and inflammation in cells (4).

Associations Between Diabetes and Specific Cancers

Endometrial Cancer

The association between endometrial cancer and type 2 diabetes is well established. Friberg et al. (11) studied the Swedish Mammography Cohort, a prospective cohort of 36,773 women, and found an RR of 1.94 (95% CI 1.23–3.08) for endometrial cancer in women with type 2 diabetes compared with those without diabetes. This RR was further increased when the women were also obese (RR 6.39, 95% CI 3.28–12.06) or had low levels of physical activity (RR 2.80, 95% CI 1.62–4.85). Like the study by Friberg et al., many of the studies in the meta-analyses included in this review adjusted for BMI, but unless specifically stated, the meta-analyses did not provide a measure adjusted for BMI or information regarding how BMI affected their measures. A meta-analysis of 29 cohort studies (12) found a summary RR of 1.89 (95% CI 1.46–2.45) and summary incidence rate ratio of 1.61 (95% CI 1.51–1.71) for endometrial cancer among women with type 2 diabetes versus those without type 2 diabetes. Saed et al. (13) performed a meta-analysis and identified an increased risk of endometrial cancer in patients with type 2 diabetes (RR 1.72, 95% CI 1.48–2.01). A subset of the studies included in this meta-analysis also controlled for BMI, and the meta-analysis identified an increased risk, albeit to a lesser extent, of endometrial cancer in the same population in this subset (RR 1.62, 95% CI 1.34–1.97). Likewise, a meta-analysis by Zhang et al. (14) found an increased incidence of endometrial cancer in patients with type 2 diabetes (RR 1.81, 95% CI 1.38–2.37). Supplementary Figure S1 shows a forest plot of endometrial cancer data, as well as data on other types of cancer included in this review.

The mechanism that links type 2 diabetes and endometrial cancer is not very well understood. In vitro studies have shown that endometrial cancer cells show increased proliferation through activation of insulin, IGF-1, and estrogen signaling pathways (15). Estrogen, through activation of the IGF-1 receptors, can activate phosphoinositide 3-kinase signaling, leading to cellular proliferation (15). The chronic inflammation in type 2 diabetes may also play a role. C-reactive protein was increased by insulin resistance and associated with increased endometrial cancer risk in postmenopausal women (15). Polycystic ovary syndrome (PCOS) is an interesting mediating variable because it is known to be an independent risk factor for both endometrial cancer and type 2 diabetes. The authors of the current article believe that PCOS plays a role in the pathogenesis of type 2 diabetes and thus shares similar cancer risks.

Breast Cancer

A meta-analysis by De Bruijn et al. (16) found that women with type 2 diabetes had a 23% higher risk of developing breast cancer, and those with both type 2 diabetes and breast cancer had a 38% higher cancer-specific mortality. Larsson et al. (17) conducted a meta-analysis of 20 studies and found that women with diabetes had a 20% increased risk of developing breast cancer (RR 1.20, 95% CI 1.12–1.28). Although some studies included in that meta-analysis adjusted for BMI, the authors did not include a summary RR adjusted for BMI. Likewise, a meta-analysis by Liao et al. (18) stratified risk of breast cancer development by continent (America, Europe, or Asia) and found an increased risk in the American studies (RR 1.16, 95% CI 1.12–1.20). Liao et al. did not adjust for BMI in their meta-analysis because not all of the included studies adjusted for it. Another meta-analysis of 16 studies performed by Zhou et al. (19) found that women with breast cancer and preexisting diabetes had a 37% increase in all-cause mortality compared with those with breast cancer but without preexisting diabetes. The same meta-analysis found that, in 12 studies that measured breast cancer–specific mortality, women with preexisting diabetes had a 17% increase in breast cancer–related mortality. Additionally, a meta-analysis performed by Zhao et al. (20) found that preexisting diabetes correlated with lower overall survival (HR 1.51, 95% CI 1.34–1.71) and disease-free survival (HR 1.28, 95% CI 1.09–1.50) rates in patients with breast cancer. The researchers noted that the effect of diabetes on the relapse-free period was not statistically significant (HR 1.42, 95% CI 0.90–2.23).

There are several hypothesized mechanisms for the increased rate of breast cancer in people with type 2 diabetes. Hyperinsulinemia is believed to play a major role. Researchers have already shown that hyperinsulinemia reduces serum levels of sex hormone–binding protein, which in turn increases the bioavailability of estrogen (21). Additionally, insulin and IGF-1 directly enhance expression of aromatase, leading to increased serum levels of estrogen. Increased expression of aromatase has been found in breast tumor tissues and may fuel breast cancer growth (22). One study found that the interaction between IGF-1 and 17 β-estradiol can lead to the proliferation of breast carcinoma cells (23). In breast cancer cells, researchers have shown that insulin (via the insulin receptor substrate 1) and IGF-1 (via the IGF-1 receptor)

both act as mitogens and stimulate breast cancer cell growth and survival, with the IGF-1/IGF-1 receptor pathway having a stronger effect (24).

Pancreatic Cancer

Song et al. (25) performed a meta-analysis of the association between type 2 diabetes and pancreatic cancer. Overall, patients with long-term diabetes (≥2 years) had a 1.5- to 1.7-fold increased risk of developing pancreatic cancer. RRs for subgroups with diabetes duration ≥2, ≥5, and ≥10 years were found to be 1.64 (95% CI 1.52–1.78), 1.58 (95% CI 1.42–1.75), and 1.50 (95% CI 1.28–1.75), respectively. This finding may have been the result of successful lifestyle changes or antidiabetic medications. A 3-year follow-up study (26) found that people with new-onset diabetes had an RR of 7.94 (95% CI 4.70–12.55) for developing pancreatic cancer compared with patients without diabetes. Additionally, they did not find significant differences in BMI between those diagnosed with pancreatic cancer and those not diagnosed with pancreatic cancer (26). Moreover, a large systematic review of 88 studies (27) found an increased risk of pancreatic ductal adenocarcinoma in patients with diabetes (RR 1.97, 95% CI 1.78–2.18). Likewise, a pooled analysis of three large-scale case-control studies (28) found a 1.8-fold increased risk (odds ratio [OR] 1.8, 95% CI 1.5–2.1) of developing pancreatic cancer in patients with type 2 diabetes. These authors did not find any statistically significant differences in risk when stratifying by BMI. More strong evidence comes from a meta-analysis conducted by the Pancreatic Cancer Case-Control Consortium (29). These researchers found a 1.9-fold increased risk (OR 1.9, 95% CI 1.72–2.09) of developing pancreatic cancer in patients with type 2 diabetes. Like the previous study, they did not find a statistically significant difference between BMI strata.

It should be noted that there is conflicting evidence about whether type 2 diabetes is an independent risk factor for pancreatic cancer or whether pancreatic cancer causes type 2 diabetes as a result of cancer-induced β-cell dysfunction, although the latter is thought to be less likely (3). The authors of the current article believe the former is more likely based on proposed mechanism of action; hyperinsulinemia is well known to induce tumorigenesis. Insulin is released into an intrapancreatic portal circulation that also provides blood to adjacent ductal and acinar cells, so high insulin levels can stimulate proliferation of tumor cells in the area (30). However, both hypotheses have credence. For example, exocrine pancreatic cells could become cancerous due to the high levels of insulin secreted from β-cells in type 2 diabetes (3). Alternatively, patients with pancreatic carcinoma have been shown to overproduce adrenomedullin, a peptide that inhibits insulin secretion from pancreatic β-cells compared with patients with benign or cystic pancreatic diseases. Expression of adrenomedullin was found to be higher in patients with both pancreatic cancer and diabetes than in those with pancreatic cancer but not diabetes (31).

Although there is a clear association between diabetes and pancreatic cancer, there seems to be no clear consensus with regard to causality. The precise physiological link is thought to involve insulin resistance, hyperinsulinemia, and high serum levels of IGF-1. Islet cell turnover is thought to play a major role because the hyperactivity and increased β-cell mass adds to insulin oversecretion and insulin resistance. In animal studies, stimulation of islet cell proliferation resulted in increased carcinogenesis of pancreatic ductal cells, and destruction of these same cells by streptozocin or alloxan resulted in reduced carcinogenesis of pancreatic cancer cells (32). Normalization of islet cell turnover with metformin in hamsters also reduced induction of pancreatic tumors (32). IGF-1 and IGF-1 receptors are also highly expressed in pancreatic tumor cells. Insulin oversecretion also increased the serum levels of IGF-1 by reducing hepatic production of IGF-binding proteins. This signal transduction pathway is central to the increased proliferation, invasion, and expression of angiogenesis mediators, as well decreased apoptosis in these cells (32).

Colorectal Cancer

An observational, population-based cohort study by Peeters et al. (33) found that type 2 diabetes was associated with a 1.26-fold increased risk of developing colorectal cancer (HR 1.96, 95% CI 1.18–1.33). When risk was adjusted for obesity (BMI >30 kg/m^2), the risk estimate was slightly lower (HR 1.22, 95% CI 1.15–1.30) (26). A study by de Kort et al. (34) found that people with type 2 diabetes were 30% more likely to develop colorectal cancer and 70% were more likely to develop proximal colon cancer. Additionally, the effect of type 2 diabetes in developing colorectal cancer was much more pronounced in men under the age of 55 years. A meta-analysis by Mills et al. (35) reported a 17% increase in all-cause mortality (RR 1.17, 95% CI 1.09–1.25) and a 12% increase in cancer-specific mortality (RR 1.12, 95% CI 1.01–1.24) in colorectal cancer patients diagnosed with type 2 diabetes. Zhu et al. (36) found in a meta-analysis that patients with type 2 diabetes have a decrease in overall survival of 18, 19, and 16% with colorectal, colon, and rectal cancer, respectively. Cheng et al. (37) performed a case-control study

investigating whether 19 single-nucleotide polymorphisms (SNPs) associated with type 2 diabetes are associated with colorectal cancer. Of the four SNPs found to be associated with risk of colorectal cancer development, only one (KCNJ11) was associated with an increased risk of colorectal cancer (OR 1.18, 95% CI 1.05–1.32). When adjusted for BMI, the risk estimate remained essentially the same (OR 1.19, 95% CI 1.06–1.34).

Hyperglycemia associated with type 2 diabetes is thought to play a major role in the proliferation and expansion of colorectal cancer cells. Research has shown that high levels of glucose and advanced glycosylation end products increase proliferation and migration of cultured colon cells and also increase resistance to apoptosis via 5-fluorouracil. The strongest link between type 2 diabetes and colorectal cancer is that type 2 diabetes increases Wnt signaling, which leads to a signal transduction pathway mediated by β-catenin (38). Eventually, this pathway leads to increased transcription of genes involved in cell proliferation and other tumorigenesis genes. Supplementary Table S2 provides a comparison of the associations of various cancers with diabetes.

Associations Between Antidiabetic Medications and Cancer Risk

Metformin

The American Diabetes Association recommends metformin as the first-line agent to reduce blood glucose and lower A1C in type 2 diabetes (39). Metformin is nearly 100 years old and was approved for use in the United States in 1994. Recently, this relatively old drug has been garnering renewed interest because of its potential protective effects against cancer. Metformin is associated with a reduced risk of death from pancreatic cancer (HR 0.79, 95% CI 0.70–0.92) (40). It has also been associated with a 10% reduction in colorectal cancer among people with type 2 diabetes (OR 0.90, 95% CI 0.85–0.96) and with decreased rates of all-cause death (HR 0.68, 95% CI 0.58–0.81) and colorectal cancer–specific mortality (HR 0.66, 95% CI 0.50–0.87) (41). A small observational trial (42) found that people with colon polyps who took metformin were less likely to progress to colon adenocarcinoma. A higher overall survival rate in patients with endometrial cancer was reported among those taking metformin (HR 0.82, 95% CI 0.70–0.95) (43). Although not associated with a reduced incidence of breast cancer in people with type 2 diabetes, metformin was associated with a reduction in all-cause mortality in the setting of breast cancer (RR 0.652, 95% CI 0.488–0.873) (44). Thus, based on these meta-analyses, metformin seems to have a protective effect against some types of cancer (40–44).

Researchers have hypothesized several potential mechanisms. First, metformin could decrease cancer incidence simply through its reduction of serum insulin (45). Other possible mechanisms include reduction of hepatic glucose output through activation of the LKB1/AMPK tumor suppressor pathway, induction of cell cycle arrest/apoptosis, inhibition of protein synthesis, inhibition of unfolded protein response, and possible eradication of cancer stem cells. The LKB1/AMPK pathway specifically inhibits the mTOR kinase, which would reduce protein synthesis (46). Additionally, metformin has been shown to reduce tumorigenesis through inhibition of mitochondrial complex I and hypoxic activation of hypoxia-inducible factor in human cancer cells (47). In colorectal cancer cells, metformin has been shown to reduce reactive oxygenation species, NF-κB activity, and interleukin (IL)-8 activity induced by lithocholic acid, a known endogenous colorectal cancer promoter (45). Metformin also reduces STAT3 protein and its phosphorylated version, both of which are elevated in endometrial cancers (43).

TZDs

Unlike metformin, TZDs demonstrate mixed effects on cancer risk. One meta-analysis found no association between TZD use and cancer overall but found interesting trends when analyzing subgroups (48). Pioglitazone has been linked to a modest increased risk of bladder cancer (RR 1.20, 95% CI 1.07–1.34), but not rosiglitazone (48). On the contrary, a slight inverse relationship was found for colorectal cancer (RR 0.93, 95% CI 0.90–0.97) and a stronger inverse relationship was found for liver cancer (RR 0.65, 95% CI 0.48–0.89) for both TZD agents (48). In contradiction to this meta-analysis, Lewis et al. (49) conducted a large-scale prospective cohort study and found no association of pioglitazone with an increased risk of bladder cancer (HR 1.06, 95% CI 0.89–1.26). In a previous interim study with the same cohort (49), the authors reported an increased risk of bladder cancer at >2 years, but that increased risk disappeared after >4 years of pioglitazone use. The authors adjusted their analyses for bladder risk factors and proteinuria, which could have acted as a bladder cancer screening test.

The mechanism underlying this relationship is not completely known. One hypothesis centers on the induction of peroxisome proliferator–activated receptor γ (PPAR-γ). It has been shown that PPAR-γ increases tumor

growth and progression and is also highly expressed in bladder cells (50).

Insulin Analogs

The relationship between insulin analogs and cancer has been historically controversial. Observational trials and preclinical trials have raised concerns about a link between cancer and insulin. A meta-analysis performed by Karlstad et al. (51) found that insulin was associated with some cancers. They found an RR of 1.52 (95% CI 1.16–2.00) when comparing insulin to noninsulin antidiabetic drugs for overall cancer incidence. Additionally, this association was stronger for colorectal and pancreatic cancers, with RRs of 1.79 (95% CI 1.36–2.36) and 3.83 (95% CI 1.43–10.23), respectively. Interestingly, shorter durations of insulin exposure were associated with a higher risk than longer duration. The RR for overall cancer for insulin compared with no insulin was much lower though, at 1.04 (95% CI 0.75–1.45). Karlstad et al. used the Newcastle Ottawa Score (NOS) to assess risk of bias. Although most studies included scored fair to high quality based on NOS, some argue that NOS is a crude measure of bias because it does not fully take into account important issues such as definition of drug exposure or time-related biases (51). Furthermore, Karlstad et al. observed selective reporting bias and inadequate accounting for confounding variables in several studies. They cautioned that data quality and study designs should be reviewed because they may have been flawed in several studies.

Although many reviews point out that any associations between insulin analogs and cancer should be made with caution, there is research pointing to mechanisms that may lend credence to this association. In an experiment by Weinstein et al. (52), HCT-116 (colorectal cancer), PC-3 (pancreatic cancer), and MCF-7 (breast adenocarcinoma) cell lines were treated with insulin, IGF-1, and insulin analogs. The authors found that the insulin analogs demonstrated IGF-1–like anti-apoptoic properties unlike human insulin. IGF-1 has been associated with cancer initiation and progression. Glargine also stimulated insulin and IGF-1 receptor phosphorylation (52).

Another in vitro study found that insulin glargine, specifically, activated IGF-1 receptors and the mitogen-activated protein kinase (MAPK) pathway in MCF-7 cells and acted as a mitogen in cells with a high IGF-1 receptor/insulin receptor ratio, which MCF-7 cells have (53). However, in humans, glargine is quickly converted to a nonmitogenic metabolite, and this theoretical risk does not appear to be present.

A meta-analysis evaluating analog basal insulin and cancer (54) found that the quality and conclusions of included studies were too inconsistent to definitively determine risk. The meta-analysis included 16 cohort and 3 case-control studies. Participant follow-up ranged from 0.9 to 7.0 years. Of the 19 included studies, only 15 had a measurement for any cancer. The great majority (13 of 15 studies) found no associations between insulin glargine and detemir and any cancer. Additionally, only 13 of the 19 studies had a measurement for breast cancer. However, 4 of 13 studies found an increased risk of breast cancer with insulin glargine. In the quality assessment, human randomized controlled trials did not find an increased risk of cancer with the use of insulin (54).

Researchers in the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial (55) tested the effect of titrated basal insulin glargine versus standard care. This study randomized 12,537 people with hyperglycemia and cardiovascular risk to insulin glargine or standard care. Although ORIGIN was a cardiovascular outcomes trial, cancer was a prespecified end point. They did not find an increase in incidence of cancer (HR 1.00, 95% CI 0.88–1.13, $P = 0.97$), death from cancer (HR 0.94, 95% CI 0.77–1.15, $P = 0.52$), or cancer at specific sites.

The DEVOTE (Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes) trial (56) randomized 7,637 patients with type 2 diabetes to either insulin degludec or insulin glargine U100. This, too, was a cardiovascular outcomes trial, but it also prespecified cancer as an outcome. There were no differences in benign or malignant neoplasms.

A recent review (57) noted that, to date, a conclusion about the risk of cancer in patients using a long-acting insulin analog cannot be made because all of the relevant studies have had methodological problems that limited researchers' ability to draw conclusions. The authors suggested that longer trials that document insulin dose, length of treatment, and duration of disease would improve the generalizability of results.

Newer Antidiabetic Drug Classes

DPP-4 Inhibitors

Research to date has been inconclusive regarding associations between newer classes of antidiabetic medications and cancer risk. One meta-analysis (58) that included 38 studies and 59,000 patients found that DPP-4 inhibitors did not increase the risk of pancreatic cancer (Peto OR 0.65, 95% CI 0.35–1.21). Using the Mantel-Haenzel risk ratio (MH-RR), another meta-analysis (59)

of 72 trials and 69,087 patients found no statistically significant association between DPP-4 inhibitors and cancer when compared with active drugs or placebo (MH-RR 1.01, 95% CI 0.91–1.12). Additionally, no individual DPP-4 inhibitor was found to have a significant association with overall cancer risk or site-specific cancer risk.

SGLT2 Inhibitors

Similarly, Tang et al. (60) conducted a meta-analysis of 46 independent randomized controlled trials and 34,659 individuals and found no statistically significant association between overall cancer risk and SGLT2 inhibitor use (OR 1.14, 95% CI 0.96–1.36). They also found that canagliflozin may be protective against gastrointestinal cancers (OR 0.15, 95% CI 0.04–0.60). For bladder cancer, the risk may be increased (OR 3.87, 95% CI 1.48–10.08), with empagliflozin having the strongest association (OR 4.49, 95% CI 1.21–16.73). Although Tang et al. found an increased risk of bladder cancer association for empagliflozin, Kohler et al. (61) reviewed the same data from the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial, but instead conducted an analysis factoring in length of drug exposure. In patients with >6 months of exposure to empagliflozin, they found that bladder cancer was reported in 0.1 and 0.3% of the 10- and 25-mg empagliflozin groups, respectively, compared with 0.2% in the placebo group. They concluded that there was no association between empagliflozin and bladder cancer.

GLP-1 Receptor Agonists

In 2011, it was reported that GLP-1 receptor agonists could potentially cause pancreatitis and pancreatic cancer (62), resulting in the U.S. Food and Drug Administration (FDA) requiring a warning for this association in prescribing information. Subsequent systemic reviews and meta-analyses were mixed with some showing an association and not others. Most recently though, the FDA reported there was insufficient evidence that GLP-1 receptor agonists cause pancreatic cancer based on rodent models (63). Recent systematic reviews and meta-analyses support this finding. Pinto et al. (64) found that GLP-1 receptor agonists did not increase pancreatic cancer risk compared with other treatments (OR 1.06, 95% CI 0.67–1.67) at an average follow-up of 1.76 years. Similarly, a pooled analysis by Liu et al. (65) found no increased risk of developing pancreatic cancer (OR 0.84, 95% CI 0.53–1.53) when comparing GLP-1 receptor agonists and standard care to placebo and standard care at a mean follow-up of 2.1–3.8 years.

Additionally, there is some evidence that GLP-1 receptor agonists could be associated with an increased breast cancer risk. One randomized controlled trial (66) found an increased absolute number (10 vs. 3 cases) in the liraglutide group (n = 2,487) versus the placebo group (n = 1,244). Women in the liraglutide group experienced significant weight loss, which the authors hypothesized led to increased screening via mammography. They postulated that this imbalance was thus a result of chance instead of a result of liraglutide treatment. Another study (67) found a similar imbalance in a trial of patients with type 2 diabetes taking liraglutide versus placebo (9 vs. 1 case). These studies raised concerns for European and American regulatory agencies. These findings are at odds, though, with the results of the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial (68), which found no imbalance in the number of breast cancer cases in the liraglutide group (21 of 1,657 patients) and the placebo group (20 of 1,680 patients). Furthermore, Hicks et al. (67) performed a large-scale observational study comparing the incidence of breast cancer in patients taking either a GLP-1 receptor agonist or a DPP-4 inhibitor and found no increased risk with GLP-1 receptor analogs (HR 1.40, 95% CI 0.91–2.16). Interestingly in secondary analyses, these authors found increased risks at 3.1–4 years after initial use (HR 2.62, 95% CI 1.37–4.99) and 2.1–3 years of total use (HR 2.66, 95% CI 1.32–5.38). Both risks returned to closer to null at 4 years after initial use (HR 1.14, 95% CI 0.49–2.66) and >3 years of total use (HR 0.98, 95% CI 0.24–4.03), which supported only a transient increase in breast cancer risk. Hicks et al. postulated that this finding was the result of an increased detection bias and not a result of GLP-1 receptor agonist treatment. More research will be needed to provide greater clarity regarding this relationship.

GLP-1 receptor agonists have also been associated with medullary thyroid carcinomas in mice models. Rats treated with long-term liraglutide (104 weeks) had significantly more medullary thyroid carcinomas and adenomas, with a corresponding increase in calcitonin release (69). However, this increase in calcitonin release was not seen in studies of liraglutide use in humans, probably because GLP-1 receptors do not seem to be present at appreciable levels in human thyroid cells (69). The LEADER and EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trials, looked at the effect of liraglutide and exenatide, respectively, on serum calcitonin levels, as well as the incidence of medullary thyroid carcinoma. The former trial (70) found no difference in serum calcitonin levels between treatment

and placebo groups and reported no cases of C-cell hyperplasia or medullary thyroid carcinoma. The latter trial (71) reported three cases of medullary thyroid carcinoma, but all had significantly elevated calcitonin levels at baseline. Supplementary Table S1 provides a quick comparison of antidiabetic medications and their associated risks.

Implications for Patient Care

As stated above, patients with type 2 diabetes have a higher risk of developing and dying from cancer. It is important that patients are aware of this association so they may make lifestyle changes and control their diabetes. This association also raises the question of cancer screening in patients with type 2 diabetes. Physicians already screen for the microvascular (i.e., retinopathy, nephropathy, and neuropathy) and macrovascular complications (i.e., cerebrovascular and cardiovascular disease). The findings summarized here warrant earlier cancer screenings, as well. However, at present, the authors are not aware of any cancer screening recommendations specific to patients with type 2 diabetes, so physicians should follow existing general guidelines. Physicians should be aware of these associations, though, because it may raise their index of suspicion when a patient does present with concerning symptoms outside of screening protocols.

Conclusion

Undoubtedly, there are links among specific types of cancer, obesity, and type 2 diabetes. This fact is important for providers to recognize and explain to patients. The relationships and exact mechanisms between various diabetes medications and cancer are less clear. Several classes of antidiabetic drugs have been shown to have promising anticancer effects, whereas others may increase cancer risks. When these relationships are fully understood, health care providers can individualize treatment even more specifically to address each patient's risks and needs. Medical research has greatly expanded our understanding of these diseases, but we still have a long way to go to fully understand the relationships among them. Thus, this topic remains an exciting area of research with potentially huge implications for the future of medicine.

DUALITY OF INTEREST

J.H.S. has served as an advisor to Bayer, Lilly Diabetes, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

P.R.B. completed the research and wrote the manuscript. J.H.S. supervised the research and edited the manuscript. P.R.B. is the guarantor of this work and, as such, had full access to all the data presented and takes responsibility for the integrity of the data reported and the accuracy of the review.

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