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Diabetes drugs and the incidence of solid cancers: a survey of the current evidence

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Abstract

Introduction: The evaluation of the relationship between the use of antidiabetic drug and the occurrence of cancer is extremely challenging, both from the clinical and pharmacoepidemiological standpoint. This narrative review described the current evidence supporting a relationship between the use of antidiabetic drugs and the incidence of solid cancers.

Areas Covered: Data from pharmacoepidemiological studies on cancer incidence were presented for the main antidiabetic drugs and drug classes, including human insulin and insulin analogues, metformin, sulfonylureas, glinides, alpha-glucosidase inhibitors, thiazolidinediones, incretin mimetics, and sodium glucose co-transporter 2 inhibitors. The relationship between the use of antidiabetics and the incidence of solid cancer was described in strata by any cancer and by organ-specific cancer and by drug and by drug classes. Information supporting biological evidence and putative mechanisms were also provided.

Expert Opinion: The history of exploration of the relationship between antidiabetic drugs and the risk of solid cancers has showed several issues. Unrecognized biases and misinterpretations of study results have had important consequences that delayed the identification of actual risk and benefits of the use of antidiabetic drugs associated with cancer occurrence or progression. The lesson learned from the past should address the future research in this area, since in the majority of cases findings are controversial and confirmatory studies are warranted.

Keywords: diabetes, antidiabetic drugs, solid cancer, pharmacoepidemiological studies, chemoprevention

Article highlights

- The relationship between the exposure to antidiabetic drugs and the incidence of solid cancer was explored in many observational studies. Unfortunately, these studies are easily subjected to bias and often provided misleading results.
- In the majority of cases, the current evidence is controversial and good quality observational studies are required. With very few exceptions, a cancerogenic effect of antidiabetic drugs seems unlikely as well as a chemopreventive activity, and the benefit-risk profile of these drugs remained favorable.
- Caution should be recommended in the conduction of future studies, particularly when designing the study, interpreting their results, and taking consequent regulatory decision.

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1. Introduction

Exploring the relationship between the use of a drug and the occurrence of any cancer is extremely challenging, both from the clinical and pharmacoepidemiological standpoint. This is particularly true for antidiabetic medications, for several reasons. First, there is a biological and epidemiological intimate link between type 2 diabetes (T2DM) and related-factors (e.g. obesity, hyperinsulinemia, hyperglycemia, hyperlipidemia, increased oxidative stress and inflammation) and the initiation, promotion, and progression of several kinds of malignancies. T2DM per se is independently associated with the risk of cancer and cancer-related mortality. Therefore, weighting the contribution of disease-related factors to cancer occurrence during an antidiabetic treatment can be complicated.^{1,2} Second, antidiabetic medications are prescribed sequentially and often in response to T2DM progression. As a consequence, a potential causal role of previous and combined antidiabetic medications should be always taken into account, particularly for long term outcomes, such as cancer. Furthermore, since T2DM severity has been suggested as a potential risk factor for the onset of several neoplasms,³ comparisons among patients exposed to different lines of antidiabetic medications could be misleading, and the choice of the comparator group as well as the definition of exposure may heavily affect the results of the analysis.⁴ Finally, even assuming that investigating putative associations of antidiabetic drugs with cancer using healthcare administrative databases could be easy, it is important to remark that these observational studies are subject to important methodological pitfalls, including prevalent-users bias, detection bias and reverse causality, immortal time bias, time-lag bias, confounding by indication, and residual confoundings.²

The immediate consequence of the above-mentioned issues is that studies investigating associations of antidiabetic drugs with several kinds of cancer have provided conflicting results. In this review, to cope with the very large amount of published data in the field, we have

summarized the results of studies that evaluated associations of each category of antidiabetic drugs with any cancer and site-specific cancers. When the evidence was robust, studies investigating the association of a specific drug and a specific kind of malignancy have been also introduced and commented in detail. Finally, a summary of the available biological evidence supporting a cancer-inducing or a cancer-protecting effect was also provided (see box-1). Particular attention was paid to the methodological flaws that were likely to affect the study findings.

2. Insulin and Insulin analogues

2.1 Rsk for any cancer

The hypothesis that insulin and insulin analogues may trigger or promote cancer in several organs and tissues stands on a reliable biological rationale (Box 1). A relationship between the use of insulin and insulin analogues (the most investigated in human has been insulin-glargine vs other insulin types) and all cancers was highlighted in the earliest observational studies.⁵⁻¹¹ However, important methodological shortcomings made the results of these studies questionable, and subsequent investigations were not able to replicate the initial findings.^{2 10 11}

The majority of most recent observational studies¹² and meta-analyses¹³⁻¹⁵ suggest a neutral effect of insulin glargine and other insulins for all cancer types. In the recently published Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial,¹⁶ a large (n=12537 patients) randomized clinical trial (RCT) designed to assess cardiovascular endpoints, cancers were included as a secondary endpoints. This study compared insulin glargine with a standard care based on investigator's best judgment and local guidelines. Results of this RCT did not confirm any risk of cancer in patients receiving insulin glargine.¹⁶ Unfortunately, even this study has important methodological limitations (e.g. not designed specifically to investigate cancer, short follow-up

period, uncertainties in the assessment of concurrent medications and cancer diagnosis), and therefore its results cannot be taken as a conclusive evidence.

2.2 The risk for site-specific cancers

Site-specific cancers were investigated in some studies. An analysis performed on a cohort of 114,841 patients reported a statistically significant risk of breast cancer for treatment with insulin glargine as compared with other insulins.⁸ However, a subsequent study on the same population with a longer follow up did not confirm the initially detected risk.¹⁷ Another study suggested a protective effect of insulin glargine vs any cancer compared with human insulin (hazard ratio, HR 0.75, 95% confidence interval [CI] 0.71-0.80), while in contrast the authors found statistically significant risk for breast cancer (HR 1.58, CI 1.22-2.05).¹⁸ Breast cancer was not associated with the use of any insulin (glargine, lispro, aspart, and human) in other observational studies.¹⁹⁻²¹ Likewise, the risk of breast cancer was not confirmed in a more recent meta-analysis of 13 observational studies (HR 1.04, CI 0.91-1.17).²² A meta-analysis of 19 observational studies suggested that the new use of any insulin carries a significant risk of developing pancreatic cancer (relative risk, RR 3.18, CI 3.27-3.71), while the new use of insulin glargine seems to be associated with a statistically significant risk of pancreatic (RR 1.63, CI 1.05-2.51) and prostate cancer (RR 2.68, CI 1.50-4.79), while exerting a protective effect on colon cancer (RR 0.78, CI 0.64-0.94).²³ Notably, the authors of both meta-analyses recommended caution in the interpretation of their own results, due to important limitations of the included studies.

2.3 Conclusion

Overall, based on the current evidence, the association of insulin-based treatments with the risk of any cancer appears to be unlikely, although further studies with adequate follow-up periods would be welcome.²⁴

3. Metformin

3.1 Risk for any cancer

In 2005, an observational study²⁵ showed an impressive protective effect of metformin against any cancer, thus triggering a “domino” effect that initially led to other observational studies and later to clinical trials to test the hypothesis that metformin could be used as an anticancer drug. In parallel, these observations fostered biological investigations to understand the mechanism underlying the effect of metformin on cell growth and proliferation. The possibility of re-inventing metformin, a cheap drug with a well-known safety profile, as an effective treatment for cancer chemoprevention suddenly appeared as extremely appealing. Moreover, evidence was provided that the biological plausibility of the reduction in the risk of cancer associated with metformin is supported by several mechanisms (Box 1).²⁶

3.2 Risk for site-specific cancers

Retrospective observational studies provided conflictual evidence about the chemopreventive effect of metformin against several kinds of cancer. Indeed, some studies showed remarkable protective effects²⁷⁻³⁰ while many others and often more recently published studies failed in demonstrating a statistically significant benefit.³¹⁻⁴² Nevertheless, the initial evidence was considered robust to such an extent to justify large investments in RCTs designed to

confirm the effectiveness of metformin in reducing cancer risk and mortality. A recent review pointed out that up to 2016 over 5,000 participants were expected to enroll in trials examining the effect of metformin on tumorigenesis in multiple organ systems,⁴³ including: 13 studies on breast cancer; 5 on colon cancer; 8 on endometrial hyperplasia or early stage endometrial cancer; 10 on prostate cancer, and 2 on the effect of metformin on progression of hepatitis C cirrhosis to liver cancer.⁴³ Chae and co-workers²⁶ described 55 ongoing clinical trials in various stages that were evaluating metformin as monotherapy (11 trials) or in combination with cytotoxic chemotherapy (38 trials), or radiotherapy (6 trials). These trials have been designed to evaluate the effect of metformin on biomarkers of cellular proliferation, disease response rate, progression free survival and recurrence free survival. At present, only 3 clinical trials on pancreatic cancer and 1 on breast cancer have been concluded. For pancreatic cancer, the first trial (n=20)⁴⁴ showed that, although the combination of metformin plus paclitaxel was not well tolerated with 42.1% patients experiencing grade 3-4 toxicity. This trial reported a median overall survival of 133 days and a median progression free survival of 43 days, but it did not meet the endpoint of disease control rate. The second trial (n=120)⁴⁵ showed that although the combination of metformin, gemcitabine and erlotinib was well tolerated, the 6-month survival rate was 55% in the metformin arm and 66% in the placebo arm. Furthermore, no significant difference was observed in the progression free survival and median overall survival when comparing metformin users with non-users. The third study (n=60) was ended for futility after an interim analysis. Indeed, the 6-month progression free survival was 52% in the control group and 42% in the metformin group (p=0.61).⁴⁶ With regard for breast cancer, the only available study (n=492) showed that at 6 months metformin, compared with placebo, may improve some surrogate markers of poor disease outcome (i.e. weight, insulin, glucose, leptin, and C-reactive protein).⁴⁷

3.3 Conclusion

Current evidence seems to confirm the hypothesis that the benefit reported for metformin by some observational studies in diabetic patients, used as the backbone of the rationale for many clinical trials, was based on time-related biases.^{4 48} Once these biases are removed, the protective effect of metformin against cancer appear to be of lesser magnitude than previously claimed. Moreover, and most importantly, the putative benefit in non-diabetic individuals remains to be demonstrated.⁴³

4. Sulfonylureas

4.1 Risk for any cancer

Despite their widespread use in clinical practice since long time, there is still uncertainty about the potential effect of sulfonylureas (SUs) on cancer risk in patients with T2DM. This risk is particularly difficult to evaluate due the changes in prescription patterns occurred over years. Indeed, in the nineties, SU were the first line treatment for T2DM, but these were gradually replaced by metformin. Furthermore, their use is still declining, and the number of currently exposed patients is much smaller than in the past. Therefore, in observational studies including data that cover long follow-up periods (e.g. from 1990 to nowadays) differences in the populations of patients taking these drugs (i.e. severity of treated T2DM) should be carefully taken into account.⁴⁹ The majority of studies on SU evaluated the incidence of solid tumors as breast,⁴⁹⁻⁵² prostate,^{49 53 54} colorectal,^{49 55} lung,^{49 55} hepatocellular,^{1 56 57} esophageal,¹¹ thyroid,⁵⁶ and pancreatic cancer.⁵⁸ The overall evidence is supportive of protective, neutral or pro-oncogenic effects. Furthermore, the findings of some of these studies (including non-clinical experiments, Box 1) have suggested that these effects may not be equivalent with all SUs.

Studies investigating the occurrence of cancer in SUs users provided conflicting results. For instance, while RCTs did not point to a higher cancer risk in SUs treated patients compared with SU non-users, an increased risk was suggested in case-control studies.⁵⁹ ² A systematic review⁶⁰ evaluated 77 studies (33 RCTs, 27 cohort studies, and 17 case-control studies) and found some discrepancies between RCTs and both cohort and case-control studies. Pooling the results of RCTs did not suggest significant effects of SU on the risk of tumors (odds ratio [OR] 0.93, CI 0.77–1.12, n=33, I²=30%) and malignant tumors (OR 0.96, CI 0.78–1.18, n=32, I²=26%), compared with other hypoglycemic agents. Observational studies (cohort studies and case-control studies) suggested a statistically significant increase in the risk of cancer in SUs users versus metformin (HR 1.13, CI 1.06–1.19), but not versus thiazolidinediones (TZDs) and dipeptidyl-peptidase 4 (DPP-4) inhibitors users (HR 1.09, CI 0.96–1.24; and HR 1.28, CI 0.77–2.11, respectively). Interestingly, the trend of cohort studies was toward a non-significant protective effect for SUs users compared with non-SUs users for any cancer (HR 0.67, CI 0.41–1.11), whereas the trend of case-control studies pointed to a non-significant increase in cancer risk in SUs users vs non-users (OR 1.13, CI 0.93–1.37, I²=76%).

A meta-analysis (38 RCTs, 16 cohort studies and 18 case-control studies),⁶¹ assessing both the risk of cancer and mortality in patients with T2DM after therapy with different antidiabetic medications, found a statistically significant increased risk for cancer incidence in SU users (RR 1.20, CI 1.13-1.27), but not for cancer-related mortality (RR 1.08, CI 0.99-1.18). However, this result may be affected by inclusion of observational studies with important methodological issues.

4.2 Risk for site-specific cancers

Several studies have evaluated the risk of any cancer or tissue-specific cancer comparing cohort of patients on SUs therapy with those receiving metformin. For instance, a retrospective cohort study⁵⁵ showed a statistically significant risk of colorectal (HR 1.94, CI 1.15–3.27) and lung cancer (HR 1.76, CI 1.00–3.07) in patient on SUs monotherapy compared with metformin. By contrast, a retrospective observational study⁵⁹ did not found a significant risk of cancer in patients on SUs monotherapy versus those with metformin. It is reasonable to hypothesize that the difference in the risk of cancer in metformin versus SUs users might be attributed to a certain protective anticancer effect of metformin.⁵⁵ It is noteworthy that, unlike metformin, SUs are often used as second-line therapy in patient with longer duration of T2DM. Since cancer occurrence is related to T2DM progression, this would mean a possible selective prescription of SUs to patients with a higher cancer risk compared with those receiving metformin.⁶²

4.3 Cancer risks: any difference across SUs?

Finally, SUs display different pharmacological properties that might explain within class differences in cancer incidence and mortality.¹ Indeed, in some observational studies a higher risk of cancer was reported for glibenclamide (also known as glyburide) compared with other SUs.^{63 64} A recent population-based cohort study⁴⁹ compared the risk of cancer for glibenclamide versus other second-generation SUs in patients with T2DM. The results pointed toward a non-significant increase of any cancer risk with glibenclamide use (HR 1.09, CI 0.98-1.22], while a significant increased risk of any cancer was found after longer cumulative durations and doses (> 36 months: HR 1.21, CI 1.03-1.42; >1,096 DDDs: HR 1.27, CI 1.06-1.51). If a difference in cancer risk exists, we cannot exclude that this can be explained mainly by a lower protective effect of glibenclamide than by a specific risk associated with glibenclamide use.

4.4 Conclusion

The overall evidence supporting any effect of SUs on cancer incidence and mortality is limited and not conclusive. Further studies are warranted, including investigations aimed at assessing whether the effect on cancer incidence is differential within the class of SUs.

5. *Glinides*

5.1 Risk for any cancer

Glinides are expected to exert proliferative effects through their hyper-insulinemic potential, although pre-clinical evidence has shown also protective activities (Box 1). Several observational studies have investigated the risk of any cancer associated with glinides. In many of these studies, glinides were evaluated as a part of large composite groups of antidiabetic treatments, and sometimes these studies lacked an adequate statistical power to evaluate appropriately the sub-groups of patients receiving glinides, particularly when site-specific cancers were examined.^{1 55 65} A nationwide nested case-control study, performed on 108,920 Taiwanese patients with newly diagnosed T2DM, showed a significant increase in the risk of overall cancer for glinides (OR 1.16, CI 1.06-1.28) with specific risks for liver, colorectal, lung, stomach, and pancreas.⁶⁶ Notably, case and controls were matched for T2DM duration and not for duration of treated T2DM, thus exposing the results to possible time-related bias. However, these results were not confirmed in other observational studies.^{67 68} For instance, a nested case-control study on 275,164 T2DM patients did not find a significant increase in the risk of cancer for each evaluated antidiabetic drug (OR for repaglinide: 0.96, CI 0.66-1.40).⁶⁷ Similarly to the above mentioned study,⁶⁶ inappropriate matching using T2DM duration instead of duration of treated

T2DM may have biased the results. A retrospective analysis⁶⁸ of the electronic health record-based Cleveland Clinic Diabetes Registry (n=25,613) was cross-indexed with the histology-based tumour registry (48,051 cancer occurrences), over an 8-year period (1998-2006), to analyse the association between cancer incidence and oral T2DM therapy (biguanides, SUs, TZDs and glinides). The comparison of glinides with SUs did not demonstrate an increased cancer risk.⁶⁸ The association of risk for any cancer and glinides has been also recently evaluated in a systematic review and meta-analysis of eight studies (3 cohort studies, 3 case-control studies and 2 clinical trials). The results did not show a significant association between glinides and risk of cancer (OR 1.06, CI 0.83-1.37).⁶¹

5.2 Risk for site-specific cancers

Some authors have evaluated the risk of site-specific cancer associated with glinides. Three studies have been specifically designed to assess the risk of endometrial cancer,⁶⁹ urinary bladder cancer⁷⁰ and gastric cancer⁷¹ in diabetic patients, but none highlighted a significant risk for glinides. In a population-based study in Taiwan, including 36,270 T2DM patients and 145,080 subjects without T2DM from 2005 to 2010, glinides did not show significant effects on the baseline risk of cancers in the digestive system (including liver, pancreas, and colorectal cancer).⁷² However, the results of this study were likely affected by immortal time bias, since the exposure to drugs was calculated from the T2DM diagnosis and not since the first drug prescription. These findings are in line with a previous nationwide, population-based study in Taiwan (2000-2007), exploring the relationship between T2DM and cancer of the digestive tract (esophagus, stomach, small intestine, colon, rectum, liver, gallbladder and pancreas), which showed a lack of association between the use of glinides and digestive cancers.⁷³ Another study evaluated the risk of a set of malignancies (liver, colorectal, lung, and urinary bladder cancer) in diabetic patients (n=606,583) who received TZDs, with sub-analysis of other medications.⁷⁴ In this study, glinides were significantly associated with an increased risk for liver (adjusted OR 1.29, CI 1.15-1.44), colorectal

(adjusted OR 1.46, CI 1.30-1.65), bladder (adjusted OR 1.71, CI 1.30-2.24) and lung cancer (adjusted OR 1.75, CI 1.38-2.20).⁷⁴ Relevant shortcomings of this study, namely the inclusion of prevalent diabetic patients and the lack of control (or matching) for duration of treated T2DM, may have importantly biased the results. Another study analysed the role of various antidiabetic drugs on hepatocellular carcinoma using the healthcare utilization databases of the Lombardy Region in Italy.⁷⁵ This study included 190 diabetic subjects with a hospital discharge reporting a diagnosis of malignant hepatocellular carcinoma and 3,772 diabetic control subjects. Repaglinide showed a statistically significant increased risk of hepatocellular carcinoma (OR 2.12, CI 1.38-3.26), with similar findings for insulin and other drugs acting on insulin secretion. Based on this observation, the authors hypothesized that the potential tumorigenic effect of repaglinide on liver, if any, is likely insulin-mediated.⁷⁵

5.3 Conclusion

In summary, owing to methodological limitations of the available studies and to the lack of comprehensive evaluations, there is a lack of conclusive evidence supporting an association of glinides with cancer occurrence.¹²

6. Alpha-glucosidase inhibitors

6.1 Risk for any cancer

The risk of any cancer and tissue specific cancer for alpha-glucosidase inhibitors has been investigated in several studies. The majority of observational studies were performed using the data of the National Health Insurance of Taiwan.^{55 71 72 76-81} In many cases, relevant protective

effects of alpha-glucosidase inhibitors or acarbose, likely due to time-related bias, were found.⁷¹⁻⁷³

76 79

A systematic review and meta-analysis of 13 studies (2 cohort studies, 6 case-control studies, 5 clinical trials) suggested that alpha-glucosidase inhibitors are associated with a 10% significant increase in the risk of cancer incidence (RR 1.10, CI 1.05-1.15), but not with a significant increase in cancer mortality (RR 1.40, CI 0.09-21.94).⁶¹ Other studies did not show a statistically significant association between alpha-glucosidase inhibitors and cancer. A nested case-control study conducted on 275,164 T2DM patients, including 1,040 cases with any cancer and 3,120 controls, did not find a significant increase in the risk of cancer for alpha glucosidase inhibitors (OR 0.76, CI 0.48-1.21).⁶⁷ Smaller studies confirmed the lack of a significant effect on the incidence of any cancer.^{55 64}

6.2 Risk for site-specific cancers

Early pre-clinical evidence of kidney tumour associated with acarbose has not been confirmed in later studies (Box 1). In line with this evidence, a small study of 24 women with T2DM, treated with acarbose in dosages up to 1500 mg daily for 12 months, showed no evidence of kidney tumours.⁸² Conversely, a population-based case-control study using data from the National Health Insurance programme in Taiwan, which included 116 patients with kidney cancer and 464 controls, showed a significant association of alpha-glucosidase inhibitors with the risk of kidney cancer (adjusted OR use vs no use: 4.31, CI 1.07-17.3). These results have never been replicated and should be taken with caution given the smaller number of cases analysed.⁷⁷

Evidence of protective effects of alpha glucosidase inhibitors in biomarker studies (Box 1), fostered the conduction of observational studies specifically designed to test whether alpha-

glucosidase inhibitors or acarbose can be associated with reductions of colorectal cancer incidence in patients with T2DM. In particular, two studies performed in Taiwan confirmed a reduction of 36% in the risk of colorectal cancer in patients taking alpha-glucosidase inhibitors⁷² and a 27% protective effect against colorectal cancer for acarbose.⁷⁶ Notably, the results of these studies are likely affected by important time-related bias and must be taken with caution. A third Taiwanese study did not show a significant association of acarbose use with colon cancer (RR 1.255, CI 0.827-1.906).⁷⁸

Gastric cancer has been also investigated for its putative association with alpha-glucosidase inhibitors.⁸³ An observational study showed a 62% reduction in the risk of gastric cancer associated with alpha-glucosidase inhibitors.⁷¹ However, this impressive protective effect could be likely explained by an immortal time bias. Similar pictures can be described for protective effects obtained in studies assessing the risk of liver,^{72,73} breast⁷² and lung cancer⁷⁹ with alpha-glucosidase inhibitors. No risk was observed for bladder⁸⁰ and thyroid cancer.⁸¹

6.3 Conclusion

Based on available data, the association of alpha-glucosidase inhibitors with cancer remains unclear. Further well-designed studies are necessary to clarify a possible effect on cancer incidence and mortality for these drugs.

7. Thiazolidinediones

7.1 Risk for any cancer and site-specific cancers

The thiazolidinediones (TZDs), pioglitazone and rosiglitazone, are likely the most problematic and controversial class of antidiabetic drugs, due to their involvement in drug safety emergencies, including the potential for cancer-inducing effects, over the last decade.⁸⁴

Several studies, including systematic reviews and meta-analyses, have tested the association of TZDs use and any cancer, and the majority of them have suggested a neutral effect.¹ Among the most recently published, a meta-analysis of 22 clinical trials (13,197 patients receiving TZDs vs 12,359 receiving placebo or active comparators) showed a significant reduction in the incidence of any cancer (OR 0.85, CI 0.73-0.98) without any difference between rosiglitazone and pioglitazone.⁸⁵ In particular, subgroup analyses suggested a significant reduction for rosiglitazone (OR 0.82, CI 0.69-0.98), but not for pioglitazone (OR 0.66, CI 0.34-1.28). Another systematic review and meta-analysis of 17 observational studies, testing the association of TZDs use with the risk of overall cancer, found neutral effects (RR 0.96, CI 0.91-1.0).⁸⁶ The same study pointed out a significantly lower risk of liver cancer in patients using either rosiglitazone or pioglitazone.⁸⁶ This result was not confirmed in another systematic review and meta-analysis including 334,307 patients with T2DM, where TZDs did not significantly affect the risk of hepatocellular cancer (OR 0.54, CI 0.28-1.02).⁸⁷ A 6-year population-based cohort study showed an important dose-dependent decrease in cancer risk in diabetic patients using TZDs, for several site-specific cancers, including colorectal cancer, breast, brain, uterus, stomach, prostate, ear-nose-throat, kidney, lung and lymphatic malignancies.⁸⁸ However, the benefit observed in this study likely resulted from methodological shortcomings in the definition of the exposure (immortal time bias).⁸⁹ The risk of colorectal cancer for TZDs did not differ from controls in a systematic review and meta-analysis performed on 840,787 diabetic patients.⁵⁶ Few reports have addressed the risk of breast cancer. In the above mentioned meta-analysis of 22 RCTs, a significant reduction of breast cancer risk for pioglitazone, but not rosiglitazone, was observed.⁸⁵ Further evidence of a neutral effect comes

from another meta-analysis, including data from 3 case-control and 14 cohort studies, that did not report an association of TZDs with breast cancer.⁸⁶

7.2 Pioglitazone and bladder cancer

The only exception to this general quite reassuring scenario is represented by the evidence of a risk of bladder cancer associated with pioglitazone. In 2005, the PROactive randomized controlled trial⁹⁰ unexpectedly showed an increase of cases of bladder cancer with pioglitazone compared with placebo. A similar finding was never observed in clinical trials with rosiglitazone, thus suggesting that this was a pioglitazone specific effect.^{91 92}

The above observation fostered a large debate, lasted for years, about the hypothetical biological mechanisms underlying the inducing and/or promoting effect of pioglitazone on bladder cancer (Box 1). In addition, it raised the attention of scientific community and prompted the regulatory agencies to implement appropriate confirmatory studies.⁹³⁻¹⁰¹ In the five year interim analysis of a large observational study, requested by the United States Food and Drug Administration (FDA), using the Kaiser Permanente Northern California database,¹⁰² the use of pioglitazone for 24 months or more was significantly associated with an increased risk of bladder cancer (HR 1.4, CI 1.03-2.0). However, in the final analysis of the same study, which used the same cohort with follow-up extended to 10 years, the use of pioglitazone was no longer significantly associated with an increased risk of bladder cancer in a duration-response fashion.¹⁰³ The retrospective cohort study by Korhonen et al.¹⁰⁴, prompted by the European Medicine Agency (EMA), showed no evidence of association between ever use of pioglitazone and the risk of bladder cancer compared with never use. These null findings are consistent with those of another large multicohort study.¹⁰¹ Amongst the other studies, some supported the findings of the

PROactive trial, showing a significant increase of the risk⁹³⁻⁹⁵ while others rejected this association.^{96-101 105} From a methodological standpoint, the conflicting results of the aforementioned studies might reflect the inclusion of prevalent users of pioglitazone in the analyses,^{95-97 100-103} the presence of immortal-time bias,^{95 96 100} selection bias,^{97 101} important residual confounding,⁹³ and time-lag bias.^{97 102} In the attempt of overcoming all the relevant shortcomings of the available studies, a cohort study,¹⁰⁶ involving 145,806 patients with T2DM under treatment with non-insulin antidiabetic drugs, highlighted a significant increase in the risk of bladder cancer with pioglitazone rather than other antidiabetic agents (HR 1.63, IC 1.22–2.19), but not for rosiglitazone (HR 1.10, CI 0.83–1.47). These findings confirmed that the association reported for pioglitazone is likely a drug-specific and not a class effect. Furthermore, this specific cancer risk of pioglitazone varies in a duration-dependent and dose-dependent fashion.¹⁰⁶

7.3 Conclusion

Based on the overall available evidence, both the FDA and the EMA issued restrictions on the use of pioglitazone and required a close monitoring of patients. Nevertheless, the risk-benefit profile of pioglitazone remained favorable as a second or third line treatment for T2DM.^{107 108}

8. Incretin mimetics

8.1 Risk for pancreatic cancer

The possibility that incretin mimetics, including both glucagon like peptide 1 (GLP-1) receptor agonists and DPP-4 inhibitors, are associated with cancer has been debated after pharmacovigilance studies identified a potential signal of pancreatic cancer. The FDA post-

marketing surveillance activity recorded some spontaneous reports of pancreatitis and pancreatic cancer associated with incretin mimetics since their marketing authorization.^{109 110} The signal of pancreatic cancer was recently confirmed in a case/non-case study performed on the FDA database particularly for linagliptin, saxagliptin and sitagliptin.¹¹¹ Of note, pre-clinical studies have provided controversial results, and different mechanisms can be hypothesized to account for both tumour-protective and tumour-inducing effects (Box 1).

After a review of available evidence, the causal relationship between incretin mimetics and pancreatic cancer was considered unlikely.^{109 110} Indeed, data from observational studies, as discussed below, have provided quite reassuring findings. Most of these studies appear to be reliable, even though in some cases there are relevant limitations possibly related to residual confoundings,⁶⁷ short follow up^{67 112-117} or potential protopathic bias.^{113 117 118}

A recent retrospective nested case-control analysis on a cohort of 275,164 T2DM patients in 16 Primary Health Care Centres of Barcelona did not find evidence of risk of any cancer associated with DPP-4 inhibitors (OR 1.01, CI 0.59-1.74).⁶⁷ A nested case-control analysis, conducted on an international multicentre cohort of 972,384 newly non-insulin antidiabetic users, from 1 January 2007 to 30 June 2013, did not observe a significant risk of pancreatic cancer for incretin therapies compared with SUs (pooled adjusted HR 1.02, CI 0.84 - 1.23).¹¹⁸ In a retrospective population-based cohort study on Taiwanese patients no differences were reported in the occurrence of pancreatic cancer for incretin users (including saxagliptin, vildagliptin, sitagliptin, exenatide, linagliptin) compared with the matched (1:1) non-incretin group (0.05% vs 0.08%, $p = 0.3172$).¹¹² A retrospective population-based cohort study from the United Kingdom Clinical Practice Research Datalink, including 182,428 adult patients, did not show a significant association between the use of incretin mimetics (fully adjusted HR 1.36, CI 0.94-1.96) or the use of specific incretin subclasses (DPP-4 inhibitors: fully adjusted HR 1.43, CI 0.96–2.13; GLP-1

receptor agonists: fully adjusted HR 1.18, CI 0.52–2.69) with pancreatic cancer, compared with other non-insulin antidiabetic drugs. Notably, a statistically significant increase in risk among incretin users receiving 4-7 prescriptions was observed (fully adjusted HR 1.86, CI 1.01–3.42), while the risk dropped down in patients receiving more prescriptions (fully adjusted HR 0.95, CI 0.53–1.72).¹¹³ A meta-analysis of 36 double-blind controlled trials on DPP-4 inhibitors versus placebo, with at least 1 year of follow-up and which have enrolled at least 500 patients, investigating mortality for all causes and cardiovascular death as primary endpoints, did not reported a significant risk for pancreatic cancer (only two trials included in this sub-analysis: SAVOR-TIMI 53^{119 120} on sitagliptin and TECOS¹²¹ on saxagliptin; total events 14 vs 26; RR 0.54, CI 0.28–1.04).¹¹⁵ A meta-analysis of 134 trials on DPP-4 inhibitors compared with placebo or active drugs, found no significant risk of pancreatic cancer (OR 0.72, CI 0.32–1.61).¹¹⁶ In a population-based study on Medicare claims data, new users of DPP-4 inhibitors showed a significant reduction in the risk of pancreatic cancer compared with SUs users (HR 0.62, CI 0.41-0.94), and no risk compared with TZDs users (HR 0.97, CI 0.65-1.43).¹¹⁷ Of note, the loss of statistical significance after introduction of a 6-month lag period in the sensitivity analysis suggested that the protective effect of DPP-4 inhibitors against SUs likely depended on reverse causality effect or the inclusion of early cancers, for which the causative role of the drug was unlikely (HR 0.73, CI 0.40, 1.32).¹¹⁷

8.2 Risk for medullary thyroid cancer

A signal of risk of medullary thyroid cancer for exenatide has been pointed out by an analysis of the FDA spontaneous reporting database,¹⁰⁹ and some evidence suggests a plausible biological rationale for this risk (Box 1). In a pooled analysis of 8 randomized Phase III trials, conducted on patients receiving exenatide once weekly, exenatide twice daily, liraglutide once

daily and non GLP-1 receptor agonist treatments, the incidence of thyroid benign neoplasms did not differ across groups (0.2, 0.4, 0.5 per 100 patient-years, respectively).¹¹⁴ The lack of association between GLP-1 analogues and thyroid cancer was also showed in a meta-analysis of 25 trials conducted on exenatide and liraglutide.¹²²

8.3 Risk for colorectal cancer

Overall, since GLP-1 receptor is expressed in organs and tissues other than pancreas and thyroid, and since DPP-4 is a multifunctional enzyme cleaving more peptides than just GLP-1,¹²³ the potential effects of incretins on proliferation could involve many other anatomical districts (Box 1). The risk of colorectal cancer was investigated in a cohort study of elderly Medicare US patients new-users of DPP-4 inhibitors, in comparison with users of TZDs and SUs, and new users of GLP-1 receptor agonists compared with long acting insulin (LAI).¹²⁴ No significantly increased risk for colorectal cancer was detected for any comparison (DPP-4 inhibitors vs TZDs HR 1.17, CI 0.88-1.71; DPP-4 inhibitors vs SUs HR 0.98, CI 0.74-1.30; GLP-1 receptor agonists vs LAI HR 0.82, CI 0.42-1.58).¹²⁴ Of note, residual confoundings and short follow-up may represent important limitations of this study.

8.4 Conclusion

The signal of risk of pancreatic cancer associated with both GLP-1 receptor agonists and DPP-4 inhibitors has substantially not been confirmed in observational studies. However, since the debate remains open,^{110 111} further studies, with adequate follow-up periods, would be welcome. Other kinds of cancer (i.e. colonic cancer, thyroid cancer) warrants further investigations.

9. Sodium glucose cotransporter 2 (SGLT2) inhibitors

9.1 Dapagliflozin and risk for breast and bladder cancer

Despite pre-clinical experiments have suggested the lack of tumorigenic effects or even anticancer potential (Box 1), initial concerns about the risk of cancer associated with sodium glucose cotransporter 2 (SGLT2) inhibitors were raised during the recent approval of dapagliflozin, the first marketed SGLT2 inhibitor. Indeed, excess numbers of male bladder cancer and female breast cancer were noted in phase 2b and phase 3 trials.^{1 125-127} On the basis of the Surveillance, Epidemiology, and End Results Program and the review of literature about incidence rates of cancer in T2DM, it was concluded that the number of observed bladder and breast cancer in the dapagliflozin-treated patients was higher than the expected number of cases in the general population with T2DM.¹²⁸ Despite the limited number of cases and the lack of statistically significant differences versus comparators, these initial observations led the FDA to suspend dapagliflozin approval. Manufacturers were required to provide more data from ongoing studies and to perform new clinical trials to define the risk-benefit profile of the drug, with particular regard for bladder and breast cancer incidence in the exposed patients.^{129 130} The cancer risk was subsequently re-evaluated and the drug approved by FDA in 2014.¹³¹ However, updated data from the dapagliflozin clinical development program, based on 21 clinical trials, presented to the FDA in 2013, showed that there had been a total of 10 cases (0.15%) of bladder cancer in patients taking dapagliflozin (n=6,045), compared to 1 case (0.03%) of bladder cancer in the control group (n=3,512), with an incidence rate ratio (IRR) of 5.17 (CI 0.68-233.55). For breast cancer, 12 cases (0.45%) were reported in patients taking dapagliflozin (n=2,693) compared to 3 (0.21%) cases in the comparator group (n=1,439), with an IRR of 2.47 (CI 0.64-14.10). Based on these observations,

the FDA decided to continue the surveillance on the risk of bladder cancer associated with dapagliflozin through the DECLARE TIMI 58 trial.^{12 125 132 133} In the meantime, the use of dapagliflozin was contraindicated in patients with active bladder cancer and use with caution was advised in patients with history of bladder cancer. Furthermore, as an additional precautionary measure, in Europe dapagliflozin was not recommended in patients concomitantly treated with pioglitazone, considering the increase in the risk of bladder cancer observed in diabetic patients taking this drug.^{132 134-136}

9.2 Risk for any cancer

When the risk of cancer was assessed for the other SGLT2 inhibitors, canagliflozin and empagliflozin were not associated with the risk of any cancer in humans.^{125 129 130 137 138} This finding may suggest that, if a risk of bladder cancer exists for dapagliflozin, this is likely not a class effect of SGLT2 inhibitors.^{125 134} Notably, canagliflozin and empagliflozin have been found to induce tumors in rats and mice, but the proposed underlying mechanisms have not been considered relevant for humans.¹³⁹⁻¹⁴² Recently, a post-marketing surveillance study (n=8,505) was performed to investigate the real-world safety of ipragliflozin administered for up to 1 year in elderly Japanese patients with T2DM. Adverse drug reactions (ADRs) associated with malignant tumors included gastric cancer and pancreatic carcinoma (3 cases each, 0.04%), colonic cancer and lung neoplasm malignant (2 cases each, 0.02%), and breast cancer (1 case, 0.01%). All ADRs related to malignant tumors occurred 45 days after the start of treatment, except for one event with an unknown time of onset.¹⁴³

9.3 Conclusion

In recent years, some pooled analyses on dapagliflozin studies have confirmed that the overall incidence of malignancies does not significantly differ in groups of patients exposed or not exposed to dapagliflozin.^{135 138 142 144} New clinical data suggest that the imbalance of bladder and breast cancer observed with dapagliflozin in early studies might be due to an early diagnosis of preexisting cancer, rather than a real increase in cancer incidence, and to detection biases.¹³⁸ Indeed, it has been suggested that, due to the glycosuria and/or increased symptoms of urinary tract infection, patients taking dapagliflozin likely underwent more urinalyses compared to controls, leading to an easier identification of early stage bladder cancer. Likewise, breast masses were likely better identified in patients on dapagliflozin because of the higher frequency of drug-related weight loss compared to controls.¹²⁸ Overall, the causal association between bladder cancer and dapagliflozin therapy is yet to be conclusively demonstrated, and the results of the ongoing DECLARE TIMI 58 trial will hopefully provide more definitive evidence.^{125 134}

10. Expert Opinion

Since T2DM prevalence is expected to further increase in the near future, this disease represents one of the most appealing target for investments by pharmaceutical industries. Therefore, novel antidiabetic drugs will enter the market over the next years. As a consequence, a continuous re-appraisal of older versus newer antidiabetic medications will be required. In particular, the availability of at least equally effective, but safer, new therapeutic options will represent one of the major conditions to decide whether to restrict the prescription of an older drug to specific populations of patients with peculiar clinical features, or even to withdraw that drug from the market. TZDs currently represent a paradigmatic example of the latter situation.

The present narrative survey highlights the presence of the following pitfalls in the assessment of the safety of antidiabetic medications, with particular regards for cancer-inducing or cancer-protecting effects: a) evidence of increased cancer risk stems mainly from observational studies; b) evaluating the risk of cancer in diabetic patients is challenging due to the complexity of the clinical setting; c) several studies are affected by methodological shortcomings that might lead to inconsistent conclusions. These items represent an important lesson that should encourage a cautionary approach in decision making, while raising three main recommendations.

The first recommendation is for investigators. The performance of observational studies to assess the relationship of antidiabetic drugs use with cancer requires a thorough experience in epidemiology to ensure the necessary methodological quality. Having access to good data does not automatically confers the expertise for performing an analysis. Involving skilled pharmacoepidemiologists is a good starting point for such analyses. Moreover, several studies reviewed in this article evaluated the risk of any cancer associated with the use of an overall drug class. This strategy is likely originated by the will of investigators of constraining the analysis of a rare outcome in a population of patients which is often smaller than that indicated by the sample power estimation. Cancer includes a plethora of both biologically and clinically heterogeneous diseases. This means that investigating the risk of any cancer is a very preliminary and often not informative strategy. Whenever the risk of any cancer is found, subsequent studies should be performed in an attempt of identifying which specific cancers lead the risk. Likewise, tumorigenic effects are not automatically class effects. In this respect, the example of bladder cancer associated with pioglitazone, but not with rosiglitazone, is paradigmatic.

The second recommendation is for journal editors. Editors have the great responsibility of protecting readers from biased results that lead to unreliable conclusions. Biased studies can trigger consequences like that occurred for the putative chemopreventive effect of metformin (i.e.

stimulating unfruitful investments in clinical trials where patients can be exposed to unnecessary risk to demonstrate a “mirage” benefit). A false risk identified in a biased study can be dangerous as well, since it may jeopardize patient’s adherence to therapy. The editor decision about publication should be based on the advice made by qualified experts: it is the qualified reviewer who makes reliable a journal, and not the impact factor!

The third recommendation is for regulatory authorities. Any decision should be taken the evidence originated by good quality studies. Quality assessment of the available evidence should be performed every time a decision regarding the use of a drug is debated. Given the complexity of the clinical setting, this requirement is particularly true for antidiabetic drugs and the risk of cancer, as shown in the present review.

11. Conclusion

Evidence supporting the effect of antidiabetic medications on cancer incidence stems mainly from observational studies. Unfortunately, these studies pose methodological challenges and their results are frequently influenced by the effect of limitations that are often intrinsic to the study design and, as such, unavoidable. Accordingly, the available results are often not conclusive, and early evidence of a protection or a risk have not been replicated in subsequent confirmatory studies. Exceptions might be the protective effect of metformin against some kind of malignancies in diabetic patients (although not that protective as shown in some observational study) and the risk of bladder cancer associated with pioglitazone. Although current evidence is reassuring for the majority of antidiabetic medications, research in this field must remain well awaken and active.

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Box 1: Summary of the biological rationales propose to account for the cancer promoting or inhibiting actions of antidiabetic drugs

Drug Class	Biological rationale supporting cancer promoting effects	Biological rationale supporting cancer-inhibiting effects
Insulin analogues	Hyperinsulinemia ¹⁴⁵ and overexpression of IGF-1R ^{146 147} are involved in cancer. The stimulation of IR and IGF-1R by insulin and insulin analogues may promote cell proliferation. ¹⁴⁸⁻¹⁵² Mitogenic effects mediated by IGF-1R have been also observed. ¹⁵³ However, there is no firm evidence that insulin can promote malignant transformation of target cells (cancer initiation or mutagenesis). ¹⁵³	Not reported
Metformin	Not reported	Metformin may inhibit mTOR complex 1 in cancer cells, leading to inhibition of mRNA translation, ribosomal biogenesis and cell proliferation. This effect is mediated by the inhibition of pathways downstream to IGF-1 and insulin hormone receptor binding, particularly through the activation of AMPK, which inactivates mTOR both indirectly (TSC2 activation) and directly (mTOR receptor binding). Furthermore, metformin enhances the immune response to cancer cells through a reduction of the immune exhaustion of CD8+ tumor infiltrating lymphocytes. ²⁶
SUs	SUs exerts indirect cancer promoting actions mediated by stimulation of insulin release. Insulin binding to IR A, overexpressed in tumor cells, resulting in tumor growth. Insulin also promotes the liver synthesis of IGF-1, which in turn activates IGF-1R on tumor cells with consequent proliferative responses. ⁶⁰	Glipizide exerts antiangiogenic effects on cancer growth and metastasis through its direct action on endothelial cells. ^{58 154} Gliclazide exerts antioxidant and antiapoptotic activities. ¹⁵⁵ This drug is endowed with a variety of pharmacological actions: ROS scavenging, the reversible binding to SUR-1, and up-regulation of antioxidant enzymes along with reduced mitochondrial alterations ^{63 155 156} , which have been ascribed to the azabicyclooctyl ring that is unique in gliclazide structure. ^{63 156} In addition, gliclazide has been associated with nucleotide excision repair and non-homologous end joining double-strand-break repair. ¹⁵⁷ Glibenclamide promotes cancer cell death through its interaction with ROS, ^{158 159} induces cytostatic effects through cell-cycle arrest in the G ₀ /G ₁ phase, ¹⁶⁰ and contributes to tumor cell damage and apoptosis through K ⁺ -ATP channel inhibition. ^{60 161 162} Glibenclamide has been shown to exert inhibitory effects on several cancer cells, including colon and bladder cancer cells. ¹⁶²
Glinides	Glinides can cause hyperinsulinemia, which increase cancer risk through stimulation of IGF-1, an inducer of cell proliferation and metabolism in several tissues. ⁷⁵	Repaglinide can exert antiproliferative effects in hepatocellular carcinoma and cervical cancer cells, but further studies are needed. ¹⁶³
Alpha-glucosidase inhibitors	Not reported	An initial long-term study in rats showed an excess of renal tumours at very high doses of acarbose (up to 300 mg/kg daily). Subsequent studies in rats, hamsters, and dogs suggested that these events were related to carbohydrate malabsorption. In gavage studies, with adequate glucose intake, tumour incidence did not differ in placebo- and acarbose-treated groups. ⁸² Glucosidase inhibitors may affect the biosynthesis and structure of oligosaccharides on the cell surface, thus modifying the proliferation of tumour cells, and may suppress the metastatic potential of malignant cells by interference with the synthesis of correct carbohydrate patterns. ¹⁶⁴ Alpha-glucosidase inhibitors are known also to block starch digestion, thus suggesting a decrease in risk for gastric cancer. ⁸³ Acarbose may increase faecal concentrations of butyrate, a short-chain fatty acid endowed with anticancer effects on colonocytes. ^{165 166} and has been shown to modulate colonic cancer occurrence through a regressive effect on the sizes of adenomas. ^{1 167}

Box 1: Summary of the biological rationales propose to account for the cancer promoting or inhibiting actions of antidiabetic drugs

Drug Class	Biological rationale supporting cancer promoting effects	Biological rationale supporting cancer-inhibiting effects
TZDs	<p>Pioglitazone was found to induce bladder cancer in male rats only, and not in mice of either sex.¹⁶⁸ The proposed mechanism, according to which pioglitazone and other PPAR-targeting drugs, namely glitazars,¹⁶⁹⁻¹⁷¹ would indirectly stimulate urothelial proliferation through the induction of crystalluria in bladder cannot be excluded^{169 172-174} but is unlikely to fully explain the phenomenon. The involvement of PPARγ is also debated. Indeed, the little differences observed in the bladder expression of PPARγ among genders and species are not consistent with the evidence of a tumor-inducing effect of pioglitazone only in male rats.¹⁷⁵ Furthermore, rosiglitazone alone did not demonstrate similar effects in rats.¹⁷⁶ Some authors reported that in the rat urothelium in vivo, PPARα activation would be responsible for cancer initiation while PPARγ activation supports cancer promotion.¹⁷⁷ The simultaneous activation of PPARα and PPARγ using a combination of fenofibrate (PPARα selective agonist) and rosiglitazone (PPARγ selective agonist) was shown to increase the expression of Egr-1 transcription factor,¹⁷⁸ a potential carcinogenic biomarker.¹⁷⁷ In this experiment, the use of rosiglitazone or fenofibrate alone did not increase the Egr-1 expression.¹⁷⁹ These two receptors display apparently, a unique co-expression pattern in the urothelium of male compared with female rats, and a similar pattern has been reported in humans.^{179 180} In comparison with rosiglitazone, Pioglitazone is less selective for PPARγ, and it has a residual activity toward PPARα.^{181 182} This pattern would explain the different tumorigenic potential of pioglitazone and rosiglitazone as well as the cancerogenic similarity of pioglitazone with glitazars.</p>	<p>TZDs can exert PPARγ-dependent^{183 184 185 186} and PPARγ-independent antitumor effects,¹⁸⁷ which seem to be dose-dependent, as well as cell-, species-, and compound-specific.¹⁸³</p>
Incretin mimetics	<p>GLP-1R agonists stimulate calcitonin secretion and promotes C-cell hyperplasia and medullary thyroid cancer in rodents. This species-specific observation is dose-dependent and associated with GLP-1R agonists only.¹⁸⁸⁻¹⁹¹ GLP-1R stimulation may induce cell proliferation and neoplastic transformation activating the PI3K signaling pathway.^{192 193} Changes in the expression and activity of DPP-4 have been described for malignancies such as colon cancer,¹⁹⁴ ovarian carcinoma,¹⁹⁵ cervical cancer,^{196 197} endometrial adenocarcinoma,^{198 199} and prostate cancer.^{200 201} Loss of DPP-4 activity results in more aggressive tumour features and higher metastatic grade.^{195 198 200 202}</p>	<p>Liraglutide, through GLP-1R activation, can exert inhibitory effects on human pancreatic cancer cells via PI3K/Akt pathway.²⁰³ Some studies have shown a potential anticancer activity for sitagliptin and vildagliptin in colorectal cancer cells,²⁰⁴ as well as for sitagliptin in breast and cervical cancer cell lines.^{197 205} In rodent pre-clinical studies, an anti-tumour effect has been described for vildagliptin in colorectal lung metastases,²⁰⁶ and for sitagliptin in colon cancer.²⁰⁷ Exendin-4 (exenatide analogue) reduces cell migration in neuroblastoma cell lines²⁰⁸ and attenuates neoplastic cell growth through ERK-MAPK inhibition in prostate cancer,²⁰⁹ with an enhancing effect when the treatment is combined with metformin.²¹⁰</p>
SGLT2 inhibitors	<p>Canagliflozin and empagliflozin have been found to induce tumors in rats and mice, but the proposed underlying mechanisms have not been considered relevant to humans.¹³⁹⁻¹⁴²</p>	<p>SGLT2 inhibitors suppress glucose uptake, thus reducing tumor growth and survival, through a limitation of glucose availability.²¹¹ Canagliflozin, but not dapagliflozin, inhibits cellular proliferation and clonogenic survival of prostate and lung cancer cells, alone or in combination with ionizing radiation or chemotherapy with docetaxel.²¹² In mice bearing tumor xenographs, both dapagliflozin and canagliflozin increased tumour necrosis and delayed tumor growth, either alone or in combination with cytostatic therapy.²¹³</p>

IR: insulin receptor; IGF-1: insulin-like growth factor; IGF-1R: IGF-1 receptor; SUs: sulfonylureas; GLP-1: glucagon like peptide 1; GLP-1R: glucagon like peptide 1 receptor; ROS: reactive oxygen species; TZDs: thiazolidinediones; PPAR: peroxisome activated proliferating receptor; DPP-4: dipeptidyl-peptidase 4; PI3K: Phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin; AMPK: AMP-activated protein kinase; TSC2: Tuberous Sclerosis Complex 2; SGLT2:

Box 1: Summary of the biological rationales propose to account for the cancer promoting or inhibiting actions of antidiabetic drugs

Drug Class **Biological rationale supporting cancer promoting effects**

Biological rationale supporting cancer-inhibiting effects

sodium glucose co-transporter 2

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