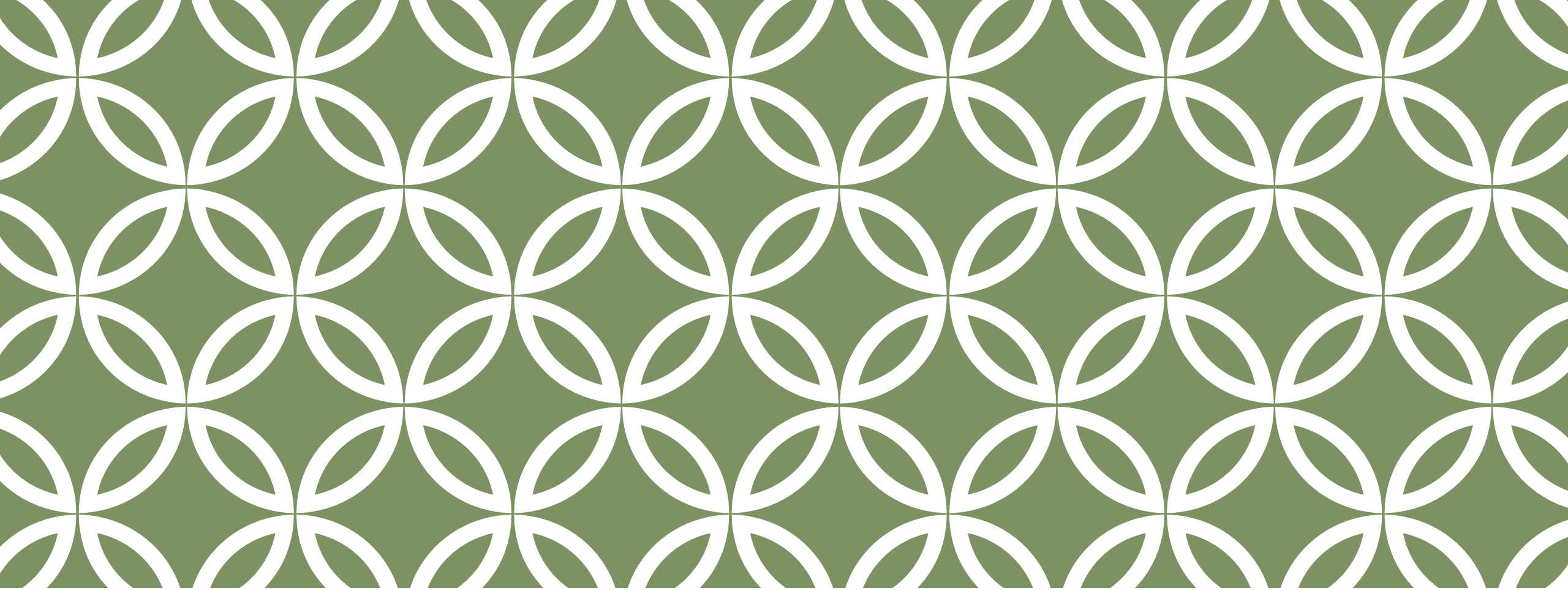

# IN THE NAME OF GOD

# DIABETES AND CANCER

Two of the most prevalent chronic pathologies—cancer and T2DM—appear to be interconnected and both have a serious effect on a patient's health. There is an ongoing debate regarding the details of this connection, which is currently being investigated analyzing common genetic and epigenetic risk factors. Several genes have been identified that increase the susceptibility both to T2DM and cancer development (e.g., TCF7L2, CDKN2A/B, AKT2, PPARG, PTEN and HNF1B) but the evidence for a common etiology of both conditions is scarce. An exception is the positive association between TCF7L2 alleles and higher risk of both T2DM and breast and colorectal cancer; and, also the association between type 2 diabetes predisposing alleles, and lower risk of prostate cancer.

There are several risk factors common to both conditions like hyperglycemia, which can lead to the production of advanced glycated end products (AGEs) and oxidative stress; hyperinsulinemia, which typically results from either impaired insulin function or insulin from extra sources; the inflammatory process; and obesity [5]. In T2DM insulin levels are high and may confer a higher cancer risk to these patients through its mitogenic effects, and, by the same token, anti-diabetic medications that lower insulin levels may be beneficial in cancer treatment [6]. Lack of physical activity and being overweight or obese are well-known risk factors for developing cardiovascular disease and diabetes [7], and at least thirteen types of cancers have been found to be related to obesity.

Diabetes is also closely associated with obesity and, obesity and tumorigenesis are related through a number of biological mechanisms some of them directly related to diabetes [9]. For example, increased levels of unbound IGF-1 protein are caused by obesity-related insulin resistance and hyperinsulinemia, which may also trigger the insulin and IGF-1 receptor signal transduction pathways, which may ultimately lead to tumor growth [10]. Although classically, insulin and IGF1 have been considered the major link between diabetes and cancer, as opposed to hyperglycemia [11], recently it has been demonstrated that high glucose levels increase the rate of cell mutation and decrease its capacity for repair [12].

As a result, the cell becomes more vulnerable to oxidative DNA damage and disruption of DNA integrity. Through a variety of mechanisms, including chemoresistance, drug deactivation, an impact on drug pharmacokinetics and dosages, and reduced immune responses, hyperglycemia may also diminish or even obstruct the effectiveness of cancer therapy. Moreover, compared to patients without hyperglycemia, cancer patients with high blood sugar have a greater proportion of metastatic disease and worse outcomes.

Cancer has been described as a wound that does not heal [16] and hyperglycemia is closely interfering with cellular repair mechanisms. Hyperglycemia impacts the organism at three levels related to oncogenesis: cellular, tissue, and systemic (Figure 1). Analyzing the cellular level, several studies have shown that hyperglycemia accelerates cell multiplication and slows cell repair mechanisms, by modifying the cell's sensibility to oxidative DNA damage and disruption of DNA integrity [17]. As a result, the major DNA repair pathways—base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ)—are activated, enabling cells to repair DNA damage [12].

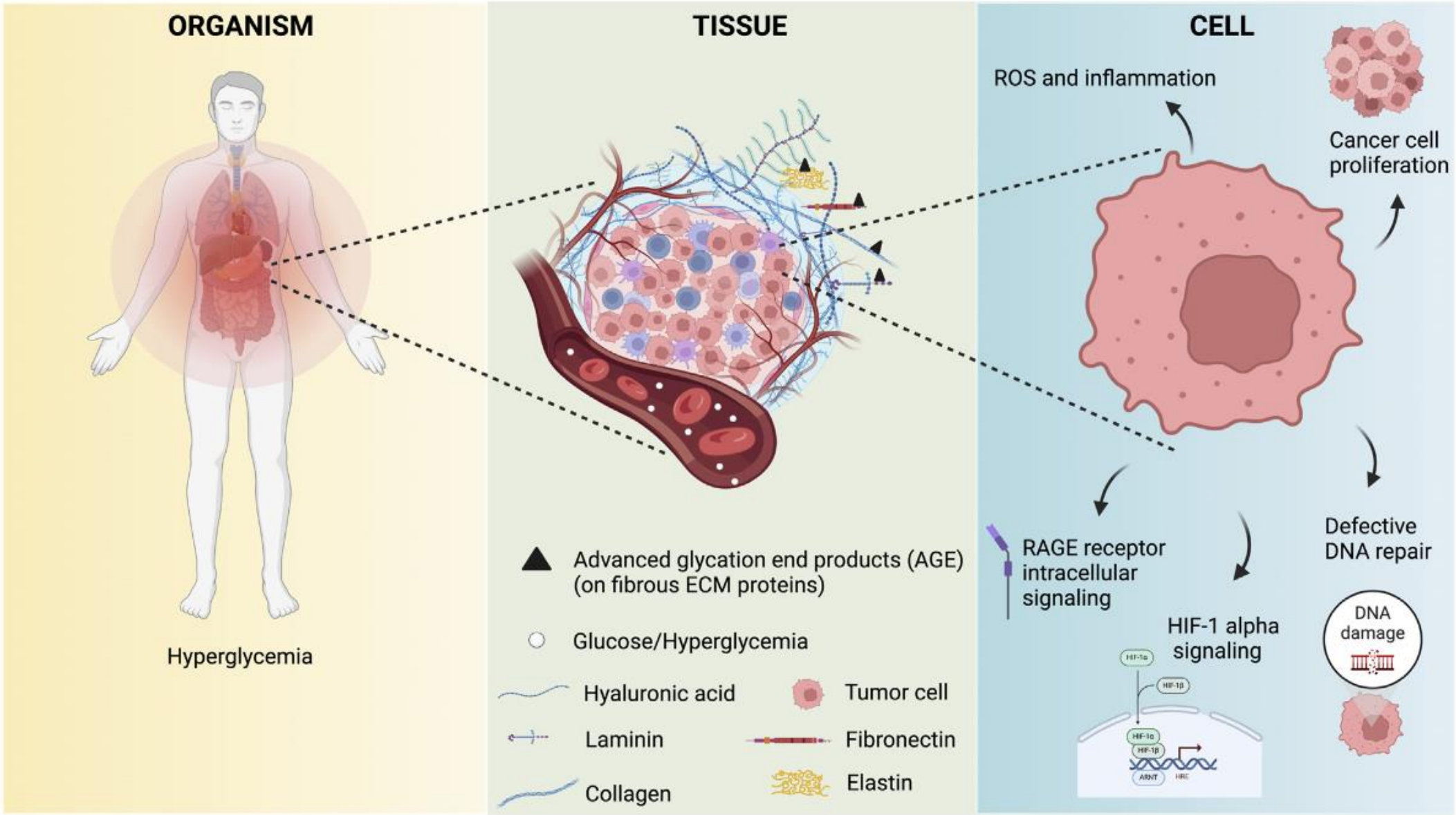


**FIGURE 1 |** Organism levels impinges by hyperglycemia related to oncogenesis.

Hypoxia-inducible factor 1-alpha is modified by hyperglycemia, which stimulates a number of DNA repair-related genes, including the NER genes, and, as a result, genomic instability is enhanced in patients with type 2 DM . Due to the interference of the error-prone NHEJ repair mechanism, these defects cause an accumulation of mutations, which is consistent with the detrimental effects of high glucose and the link between diabetes and cancer [12, 19]. Hyperglycemia also encourages the development of glycated moieties in different tissues, such as advanced glycation end products (AGE), which are the end result of a non-enzymatic reaction between reducing sugars and the amino groups of proteins, lipids, or nucleic acids.

By reacting with DNA bases and producing ROS, NFkB, the AGE receptor (RAGE), or inflammation, AGE, and its precursors, can build up and cause DNA damage, which can then contribute to carcinogenesis and initiate pancreatic cancer and hepatocellular carcinoma (HCC) [13, 20]. TP53 induced apoptosis and double- strand DNA breaks are induced by excessive glucose metabolism in cells, possibly through oxidative stress and ROS production. In normal colon cells, under folate-deficient conditions, high glucose increases the number of micronuclei, nucleoplasmic bridges, and nuclear buds, which contributes to genomic instability [22].

In addition to having a direct impact on genetic stability, hyperglycemia also results in epigenetic dysregulation, which sets off a series of downstream signaling cascades and raises the risk of neoplastic transformation [23]. Hyperglycemia also causes aberrant gene expression by altering the epigenome, leading to aggressive tumor progression that persists even after glycemic control is therapeutically achieved. High blood sugar levels cause also tissue-level changes that alter the extracellular matrix. These changes are incompletely understood, and links to stop tissue induced carcinogenesis are being sought [25]. Glycation, a non-enzymatic interaction between sugars and the amino groups of proteins, lipids, and nucleic acids, results in advanced glycation end products (AGEs) [26].

By altering enzymatic activity, disrupting conformation, and interfering with the ligand-receptor interaction, glycation can impair normal protein function [27, 28]. These changes at the protein level can affect cell signaling and possibly influence tumor growth. Hyperglycemia-induced glycation has been demonstrated to cross-link and stiffen collagen matrix in vitro in addition to altering cell signaling. Recent research has revealed a novel mechanism by which diabetes promotes the progression of breast tumors through glycation, and it suggests that one way to slow tumor growth in diabetics is by glycation targeting.

AGEs are known to be inhibited by metformin, a first- line treatment for type II diabetes [29]. Compared to patients with type 2DM taking non-metformin antidiabetic regimens, patients on metformin have a roughly one-third lower cancer incidence and mortality rate. Hyperglycemia has also a significant influence at the organism level. For example, several studies demonstrated the hyperglycemia impact on the immune system. Hyperglycemia is related to cytokine production suppression, phagocytosis decrease, immune cells dysfunctions, and failure to eradicate microorganisms [31].

Several studies have demonstrated that unbalanced type 2DM is the cause of inadequate cytokine production, such as IL-2, IL-6, and IL-10, which is crucial for both the body's defense against pathogens and its capacity to adjust its immune response . Additionally, it was discovered that obese leptin receptor-deficient mice and high-fat diet (HFD)- induced hyperglycemic mice produced less IL-22 than normal mice [33]. IL-22 is involved in innate host defense and tissue-protective and regenerative functions and, as a consequence, these mice are prone to infections. It has been also shown that diabetic hyperglycemia reduces the ability of macrophages and other leukocytes to destroy pathogens by significantly increasing endogenous production of tumor necrosis factor (TNF-α) and IL- 6 [34].

A large number of studies outlined how hyperglycemia may lead to neutrophil dysfunction, including defects in ROS production, impairment of neutrophil degranulation, inhibition of immunoglobulin-mediated opsonization, reduced phagocytosis, and defects in NET formation [31]. Hyperglycemia is also known for macrophage dysfunction [35], natural killer cell dysfunction [36], and inhibition of antibodies and complement effectors [37], which causes diabetic patients to become immune compromised, making them less able to handle all infection challenges.

# CANCER INFLUENCING DIABETES AND VICEVERSA

A century ago Warburg demonstrated for the first time that even in the presence of excess oxygen, several cancer cell types use glycolysis instead of oxidative phosphorylation [38]. In a different study, the researchers concluded that high consumption of calories made some cancers more aggressive, while diet made tumor aggression lower [11]. John Claras recently proposed in a provocative paper that tumor growth may be stimulated as an adaptive mechanism for consuming excessively circulating glucose, and once the metabolic event has been overcome, tumor growth is inhibited.

It is interesting to note that recent research indicates also that dietary restrictions, such as fasting and low-carb diets, do seem to slow tumor growth and reduce tumor size, suggesting that these lifestyle decisions can be used to lessen chronic inflammation and the related oncogenic signaling from the microenvironment to cancer [11]. If hyperglycemia contributes to tumor growth in some types of cancer [39], hypoglycemic-inducing methods like exercise may also reduce the risk of developing cancer [41]. The connection between diabetes and pancreatic cancer is well known for decades and is considered both a risk factor and an early sign of the disease [42].

Which one comes first? The two conditions are closely related and once one of them is present the risk of the other is increased. Another important aspect is the relationship between the metastatic process and T2DM. The vascular endothelium, whose function is disturbed in T2DM, plays an important role in the metastatic cascade [48]. In T2DM an increase in the permeability of the blood vessels may occur through an increase in advanced glycation end products and vascular inflammation [49]. Also, hyperglycemia leads to an increase in the Von Willebrand factor in the vascular endothelium promoting tumor cell adhesion and transendothelial tumor cell movement and the development of metastases [50].

A Japanese study suggested that diabetes mellitus may be associated with liver metastasis of colorectal cancer through the production of a biglycanrich cancer stroma [51], negatively affecting the prognosis, representing another intriguing theory about the relationship between CRC and diabetes. Recent research has shown that hyperglycemia may promote perineural invasion (PNI) in a number of malignancies, especially pancreatic carcinoma. Neuroinflammation is a well-known diabetic complication that causes nerve damage [56]. Neuronal glucose levels can increase by up to 4-fold in diabetic hyperglycemia. Intracellular glucose may damage neurons if spikes of hyperglycemia occur [57, 58].

In a hyperglycemic setting, levels of oxidative stress and proinflammatory substances may lead to nerve injury and an inflammatory reaction, simultaneously promoting cancer cell proliferation, migration, and metastasis. A similar pathophysiologic process has been described in diabetic women with ovarian cancer. Pancreatic, colorectal, breast, endometrial, ovarian, hepatocarcinoma, and prostate cancer are only a few of the cancers that have been linked to diabetes and are significantly tied with obesity and insulin resistance [14, 61, 62]. On the other hand, several epidemiological studies have shown that certain cancers and T2DM are closely related and diabetes raises a person's risk of developing cancer of pancreatic, liver, colon, breast, and endometrial cancer [14, 61].

The third most often diagnosed malignancy, colorectal cancer (CRC), accounts for more than 6% of all cancer cases worldwide. There are several theories regarding the association between colorectal cancer and diabetes. In a large cohort study conducted in Canada between 2007 and 2015 on 44,178 participants with CRC, diabetes had a greater impact on non-cancer than cancer mortality risk for patients with CRC [64]. A large study published in 2016 in the British Journal of Cancer reported that diabetes mellitus is significantly associated with larger pancreatic tumors and also may elevate the overall risk of death of pancreatic cancer patients (HR of 1.19) [42].

Another epidemiological study found that sugar consumption is strongly correlated with an increase in both incidence and mortality of breast and colon cancer, independent of obesity [65]. Preclinical studies suggest that high-sucrose or high-fructose diets activate several pathways, including inflammation, glucose, and lipid metabolic pathways. Interestingly, some cancers, such as those of the brain, buccal cavity, esophagus, lung, breast, urinary bladder, and larynx, demonstrated a null or decreased occurrence risk in diabetic patients in some studies [67]. It is noteworthy that several American and European studies have shown that individuals with type 2 diabetes have a lower risk of developing prostate cancer [68, 69].

Furthermore, patients with more than 10 years of T2DM duration showed a stronger protective effect [70]. Men with diabetes had lower testosterone levels [70] than men without the disease, and research has shown that testosterone is linked to a higher risk of prostate cancer [71]. Also, large studies found no correlation between T2DM and the risk of dying from cancers of the lung, bladder, stomach, cervix, esophagus, or leukemia. Cancer incidence of liver, pancreas, kidney, esophagus, stomach, lung, thyroid, squamous cell carcinoma, and leukaemia significantly increased for both sexes with T1DM [75]. Incidence of non-Hodgkin's lymphoma and colon cancer significantly increased for men [74];

while incidence of the ovary, esophagus, endometrium, vulva and vagina, and thyroid cancer significantly increased for women [76]. Likewise, when compared to the general population, men with T1DM had significantly lower incidences of testis and prostate cancer [74]. Melanoma, Hodgkin's lymphoma, and breast cancer were notably less common in women with type 1 diabetes [74, 77]. Additionally, compared to the general population, patients with T1DM had an overall higher standardized mortality ratio for cancers, according to prior cohort studies . The MR studies demonstrate that the relationship between hyperglycemia,  diabetes, hyperinsulinemia, inflammation, obesity and cancer is not straightforward.

> The authors of a large Japanese study using MR concluded that there is no strong evidence supporting a direct association between diabetes and the risks of total cancer, colon cancer, pancreatic cancer or liver cancer [93].

There seems to be a strong and very strong relationship between hyper insulimia or obesity and cancer and a much weaker relationship between diabetes or hyperglycemia and cancer .

# TREATMENT AND PREVENTION

Recent data indicate that metformin [94], besides its benefit for diabetic patients may have also a benefit in cancer patients. Metformin promotes the liver kinase B1 (LKB1)/AMPKsignaling pathways and inhibits the mTOR pathway, it decreases insulin levels, protein translation, and circulating levels of insulin and IGF-1 in peripheral blood and may ameliorate dyslipidemia. Currently, the use of metformin in cancer prevention is still under scrutiny [95]. Large epidemiologic data suggest that metformin decreases the incidence of prostate, pancreas, liver, colon, thyroid, endometrial and esophageal cancers [97].

It may also improve the progression free survival of patients with ovarian cancer [39], the prognostic of patients with breast cancer [97] and the overall survival of patients with metastatic non-small cell lung cancer [98] and nasopharyngeal cancer. Metformin's potential to upregulate AMP kinase (AMPK), which inhibits mTOR and impairs angiogenesis as well as cell growth and proliferation—both essential for the progression of cancer—may explain how cancer growth is restricted but more mechanisms may be present, and sometimes it's effect is counter-intuitive.

Accumulating evidence suggests the association of type 2 diabetes with an increased risk of cancer incidence and poor prognosis in certain types of cancers1–3. Common metabolic abnormalities of type 2 diabetes, such as hyperglycemia, hyper-insulinemia, insulin resistance and chronic inflammation, are known to contribute to cancer development. In addition, long-term use of diabetes medications potentially affects cancer cell biology and the tumor microenvironment.

# INSULIN AND INSULIN ANALOGS ON CANCER

Hyperinsulinemia is most relevant to tumor progression in type 2 diabetes. Mechanistically, insulin has been reported to promote cell proliferation, survival and invasiveness in both normal cells and cancer cells. In contrast, a recent preclinical study showed that insulin might act on the gut insulin receptor and modulate intestinal barrier function to attenuate the pro- gression of nonalcoholic steatohepatitis-associated hepatocellular carcinoma4. However, there are no clear answers as to whether the exogenous administration of insulin influences cancer devel-opment similar to endogenous insulin signals.

risk of cancer incidence has been debated for years. A retro- spective cohort study5 showed that the incidence of colorectal cancer was higher in insulin users compared with that in non-insulin users among patients with type 2 diabetes. Another meta-analysis of observational studies6 also supported this result. In addition, another concern is that long-acting insulin analogs might increase some types of cancer incidence com- pared with neutral protamine Hagedorn insulin. Indeed, insulin analogs were reported to exert cell proliferative and anti-apoptotic effects through their higher binding affinity to insulin-like growth factor-1 receptor than that of human insulin in many types of cancer cell lines.

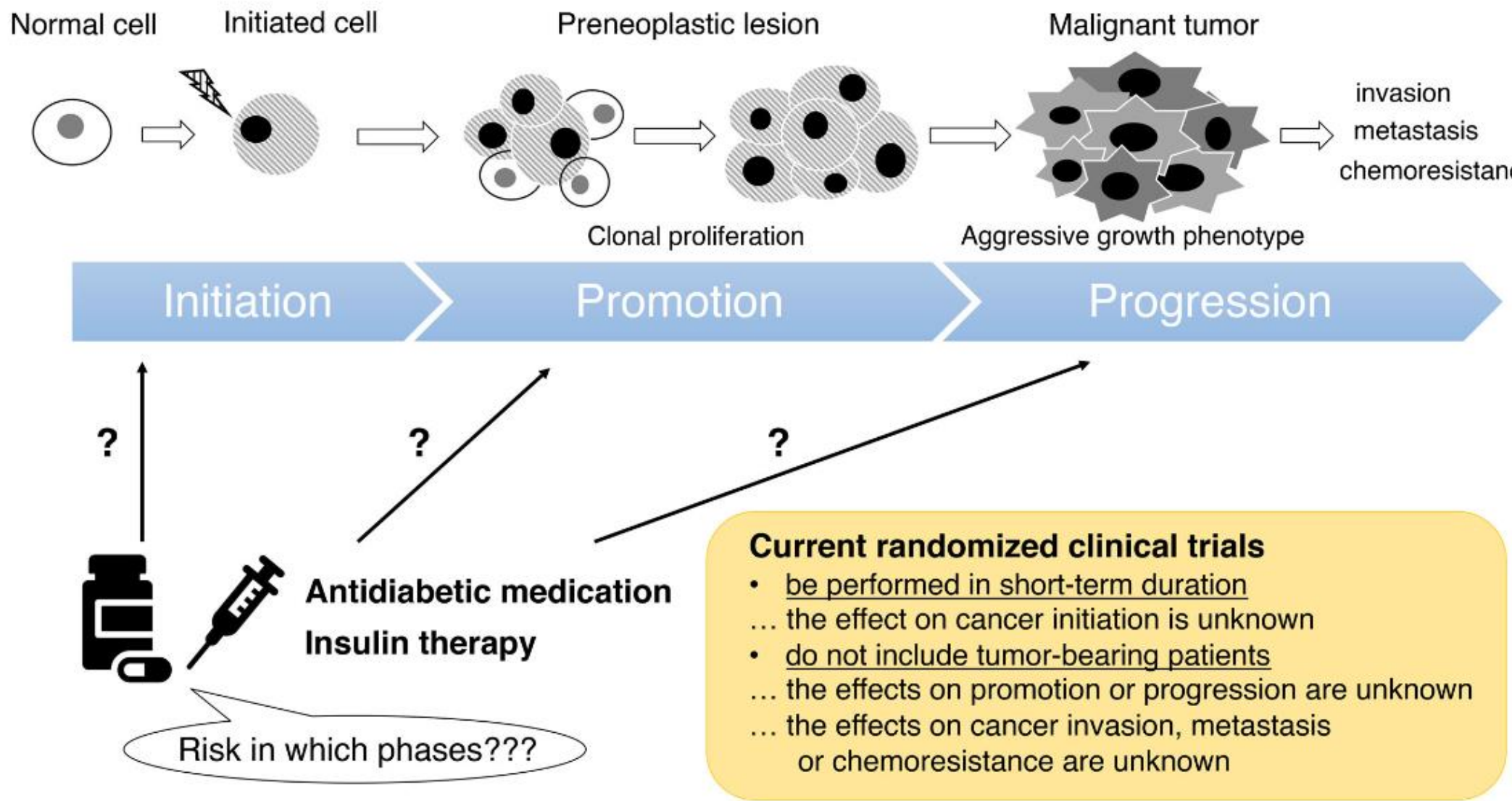


**Figure 1** | Cancer risk assessment against each carcinogenesis phase in the current randomized trials of antidiabetic drugs. Cancer is developed through multiple steps including cancer initiation, promotion and progression. In the cancer 'initiation' phase, certain genetic damage irreversibly occurs in a normal cell. This initiated cell clonally proliferates, and this cell population forms a preneoplastic lesion in the next cancer 'promotion' phase. In the final step, known as the cancer 'progression' phase, cell populations with further critical mutations acquire an aggressive growth phenotype, and cancer cells spread throughout the body by invasion and metastasis. Current prospective studies of antidiabetic agents did not evaluate the cancer risk in each carcinogenesis phase.

# SULFONYLUREAS, GLINIDE AND CANCER

Increased levels in circulating insulin as a result of the use of sulfonylureas and glinides, insulin secretagogues, have potential effects on cancer biology. Cohort studies showed that the use of sulfonylureas increases the risk of cancer incidence and cancer-related mortality in patients with type 2 diabetes8,25. However, this cancer risk associated with sulfonylureas use was found when compared with metformin treatment. In 2012, a study using a Taiwan database also suggested that sulfonylureas and glinides significantly increased the overall cancer incidence in patients newly diagnosed with type 2 diabetes26. In contrast, Zhao et al.27 recently showed no relationship between sulfonyl- ureas use and any cancer risk.

# THIAZOLIDINEDIONES, PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR-C AND CANCER

Thiazolidinediones (TZDs) act as an insulin sensitizer and a selective agonist of peroxisome proliferator-activated receptor- gamma (PPARc), which is expressed in many types of cancer cell lines28–30. TZDs could modulate cellular differentiation, proliferation and apoptosis both in normal cells and cancer cells31–36. In addition, the systemic influence of TZDs treatment, such as improvement of insulin resistance and adipocyte differentiation, potentially plays a protective role in carcinogenesis.

Indeed, clinical studies have shown the association of TZDs use with the decreased risk for liver, colorectal, lung, lymphatic, prostate, stomach, kidney, breast and brain cancer37–44 in patients with diabetes. A large cohort study47 showed that pioglitazone use of >2 years is associated with an increased risk of bladder cancer occurrence in patients with diabetes. Tuccori et al.48 also reported the elevation in bladder cancer occurrence by 63% among patients with diabetes prescribed pioglitazone in a large population-based cohort study, whereas rosiglitazone did not exert an increased trend of bladder cancer cases.

Obser- vational studies also supported these findings49–54 , whereas others reported no statistically significant increased risk of bladder cancer after treatment with pioglitazone38,55–63. Although the concern about bladder cancer incidence in pioglitazone users is still discussed, little is known about the molecular mechanism of how pioglitazone activates bladder cancer initiation or promotion. Regarding the other types of cancers, several meta-analyses have shown the neutral effect of TZDs on any cancer incidence40,43,64,65. In contrast, Lewis et al.55 reported the increased risk of prostate and pancreatic cancer associated with ever use of pioglitazone in cohort and nested case control ana- lyses among patients with diabetes.

Recently, the result of a Mendelian randomization analysis exploring the pharmacological perturbation of diabetic medications on cancer risk was published66. The authors used PPARG as the genetic instrument of the PPARc agonist target and analyzed a link between PPARG variants and the risk of breast, colorectal and prostate cancer. It was found that genetically proxied PPARG perturbation is associated with a higher risk of prostate cancer and lower risk of estrogen receptor-positive breast cancer.

# METFORMIN AND CANCER

Metformin has been well established as an anticancer agent. Mechanically, previous basic investigations reported the tumor suppressive effect of metformin through various molecular mechanisms including repression of insulin and insulin-like growth factor-1, the mammalian target of rapamycin (mTOR) pathway inhibition with or without the activation of adenosine monophosphate-activated protein kinase, the accumulation of nicotinamide adenosine dinucleotide and modulation of the immune response or gut microbiota.

# EFFECTS OF GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS ON CANCER: FOCUSING ON CLINICAL EVIDENCE

chronic activation of the GLP-1 receptor by 12 weeks of exendin-4 injection to KrasG12D mice was reported to induce chronic pancreatitis with increased dysplastic lesions, known to be a precursor for pancreatic cancer134. It was also published that DPP-4i treatment increases the risk of acute pancreatitis occurrence by 75%131. Pancreatitis is an important risk factor of pancreatic cancer initiation and promotion. Hence, the impact of long-term use of incretin therapy on pancreatic can-cer development also remains a topic of interest.

This population-based cohort study showed a 77%increased risk of cholangiocarcinoma incidence among DPP-4is users compared with other antidiabetic drugs. Although retrospective studies often include a methodological shortness, such as a prescription bias, cholangiocarcinoma is a progressive cancer type, like pancreatic cancer, thus the possible risk of incretin therapy for these rare types of cancer cannot be ignored. Despite these findings suggesting the cancer incidence risk associated with incretin drugs use, there is strong evidence showing the clinical benefit of GLP-1RAs treatment against renal–cardiovascular diseases in patients with diabetes123–129; however, all RCTs with DPP-4is never showed such an organ protective influence119–122.

Therefore, when prescribing these incretin-based drugs, clinicians should consider their benefits versus risk, such as the influence on cancer biology.

Several basic studies have addressed the influence of DPP-4is on cancer progression. Suppression of DPP-4 was reported to induce cancer cell adhesion, migration and invasion146,147. Wang et al.148 showed that DPP-4is, saxagliptin and sitagliptin increase tumor metastasis of multiple cancers through activation of the nuclear factor E2-related factor 2-mediated anti-oxidant response.

For another possible mechanism, we have previously elucidated that DPP-4 inhibition accelerates breast cancer progression through its substrate C-X-C motif chemokine 12-mediated pathway. C-X-C motif chemokine 12 binds to C-X-C chemokine receptor 4 (CXCR4) and plays significant role in several physiological processes149. CXCR4 is expressed in many cancers and its overexpression in human tumor tissues was reported to be associated with poor prognosis in various types of cancer.

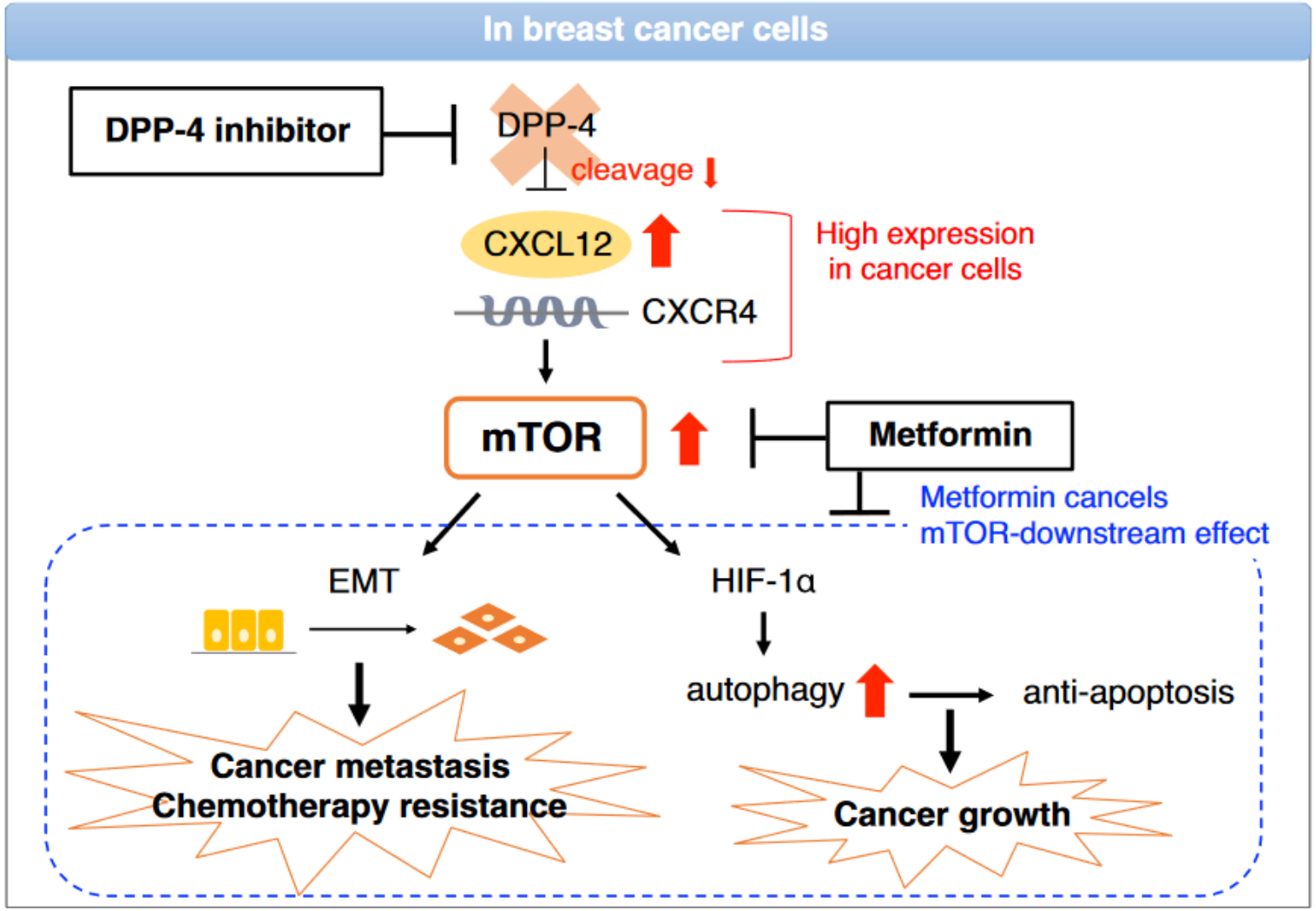


**Figure 2** | Dipeptidyl peptidase (DPP)-4 inhibitor accelerates C-X-C motif chemokine 12 (CXCL12)/mammalian target of rapamycin (mTOR)-mediated breast cancer progression; metformin mitigates DPP-4 inhibitor-induced undesirable effects through mTOR suppression. C-X-C chemokine receptor 4 (CXCR4) is known to highly express in multiple cancers, including breast cancer. DPP-4 inhibitor suppresses the cleavage of CXCL12 by DPP-4, which induces a downstream CXCL12/CXCR4/mTOR pathway. DPP-4 suppression-mediated mTOR activation results in breast cancer metastasis and chemotherapy resistance by induction of the epithelial–mesenchymal transition (EMT) process. Also, mTOR induces an autophagic response to promote breast cancer cell survival in a hypoxia-inducible factor-1α (HIF-1α)-dependent manner. Metformin could abolish these mTOR-downstream effects induced by DPP-4 inhibitor.

Also, cancer progression risk is hypothesized for drugs with pleiotropic effects on cancer biology, such as DPP-4is. However, there are no prospective studies evaluating the influence of antidiabetic drugs on tumor progression, hence, we cannot draw any conclusions about the possible risk of diabetes treatment in cancer-bearing patients. As an exception, the clinical efficacy of metformin as cancer treatment has been well investigated for recent years; however, most results have been disappointing to date. Further investigations are required to elucidate the possible effect of each diabetic agent for cancer initiation, promotion and progression. A certain treatment algorithm for patients with diabetes and cancer is also needed in the future.

# SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS AND CANCER

Indeed, a pooled analysis171 and meta-analyses172 of RCTs showed no significant association of SGLT2is use with an increased risk of overall cancer incidence Contrary to the possible risk of SGLT2is for cancer incidence, many preclinical studies have shown the protective effects of SGLT2 inhibition in cancer progression. Several basic and clinical investigations have elucidated that SGLT2is could mitigate the development of nonalcoholic steatohepatitis108, which is one of the important risk factors of liver cancer initiation or promotion.

In this line, animal studies showed that a SGLT2i canagliflozin attenuates the development of hepatocellular carcinoma through the suppression of hepatic steatosis, inflammation, fibrosis and pro-angiogenic activity. Great advances in diabetes medication have significantly improved the prognosis of type 2 diabetes patients. Although current evidence suggests the association between type 2 diabetes and the increased risk of certain cancer incidence and poor prognosis, the possibility that long-term use of antidiabetic agents influences carcinogenesis has not been fully discussed yet. For cancer initiation risk, uncertainty remains with some drugs, such as insulin glargine and pioglitazone.

# DIABETES AND FURTHER RISK OF CANCER

We observed a 20% higher risk of total cancer incidence [hazard ratios (HR), 1.20; $p < 0.001$] in the diabetes cohort compared to the non-diabetes cohort. The highest HR was observed for liver and pancreas cancers. Moderately increased risks were observed for oral, colon, gallbladder, reproductive (female), kidney, and brain cancer. Furthermore, there was a borderline significantly increased risk of stomach, skin, soft tissue, female breast, and uri- nary tract (except kidney) cancers and lymphatic and hematopoietic malignancies

The stratified analysis revealed that the total cancer incidence was significantly higher in the DR cohort compared to the non-DR cohort (HR, 1.31;$p < 0.001$), and there was a borderline increased risk in the PDR cohort compared to the NPDR cohort (HR, 1.13;$p = 0.001$). The increasing global prevalence of diabetes and cancer has significant global health implications. Epidemiological evidence suggests that people with diabetes are at a significantly higher risk of various cancers, including hepatic, pancreatic, endometrial, colorectal, bladder, and breast cancers, whereas male patients with diabetes have a lower prevalence of prostate cancer than those without diabetes [1].

Clinical evidence has indicated a positive association between cancer and concomitant abnormalities in glucose metabolism. Diabetic retinopathy (DR) is the most common micro- vascular complication in patients with diabetes and the leading global cause of vision loss in working middle- aged adults [2]. The pathological processes of DR include hyperglycemia and the polyol pathway, advanced glycation end-product formation, protein kinase C activation, hexosamine pathway flux, and poly (ADP-ribose) polymerase activation, which share similar pathogenic features with cancer initiation and progression [3–7].

Furthermore, oxidative stress, inflammation, vascular abnormalities, and angiogenesis are closely associated with pathological changes in the progression of DR, which are also involved in pathophysiological conditions for cancer development [8–10]. These findings suggest that DR and cancer may share similar pathogenic features and that improving diabetes control may further reduce the risk of cancer development. Diabesity is a condition where an individual has both diabetes and obesity, which can lead to severe complications including cardiovascular disease, a leading cause of mortality.

Recently, cancer has become a leading cause of excess hospitalizations, and both diabetes and obesity are associated with a higher risk of developing several types of cancer. type 2 diabetes is associated with a higher risk of developing several types of cancer, including those affecting the liver, pancreas, endometrium, colon and rectum, and breast. This connection may be due to shared risk factors, such as aging, Obesity, dietary habits, and physical inactivity. Cancer incidence is increasing in both type 1 and type 2 diabetes patients, regardless of the underlying causes [8]. A comprehensive meta-analysis has shown that the presence of type 2 diabetes is associated with a more than 20% increase in the risk of developing cancer [9].

A pooled analysis of 19 prospective Asian population-based cohorts showed that Diabetes was associated with a 26% increased risk of death from any cancer in Asians, emphasizing the need for better control of the growing epidemic of Diabetes as well as Obesity to reduce cancer mortality [10] patients with type 1 diabetes have a significantly higher incidence of cancer, particularly in the liver, pancreas, kidney, endometrium, and ovarian cancers [11].

Prediabetes is also linked to an increased risk of cancer, specifically in the liver, endometrium, stomach, and colorectal regions.

Various systemic anticancer therapies, such as cytotoxic chemotherapy, hormone therapy, targeted therapy, and immunotherapy, can affect glycemic control [14]. Several anticancer agents increase the risk of hyperglycemia, even in individuals without a prior diabetes diagnosis. A study has indicated that 11% of individuals undergoing routine chemotherapy received a new diabetes diagnosis, with most receiving short-course steroids alongside chemotherapy and 40% undergoing curative/adjuvant treatment . The EPIC and UK Biobank report underscores the strong correlation between Obesity and 13 different cancers, including breast, colorectal, endometrial, esophageal, pancreatic, renal, liver, stomach, gallbladder, ovarian, thyroid, multiple myeloma, and meningioma [17].

Moderate evidence suggests an association with cancers of the mouth, pharynx, larynx, prostate, male breast, and diffuse large B-cell lymphoma. Moreover, high risks are observed for challenging-to-treat cancers such as pancreatic, esophageal, and gallbladder, as well as prevalent malignancies like breast and colorectal cancer. An umbrella review consisting of 204 systematic reviews and meta-analyses has highlighted an array of elevated cancer risks associated with excess body fat [18]. The risks range from 9% for rectal cancer in men to 56% for biliary tract system cancer. Every 5 kg/m 2 increase in BMI leads to an increase in cancer risk [19].

It is important to note that for women who do not receive hormone replacement therapy, weight gain of 5 kg in adulthood increases the risk of post-menopausal breast cancer by 11%. On the other hand, the risk of endometrial cancer increases by 21% for every 0.1 increase in waist-hip ratio.

A Mendelian randomization study has indicated that there is a robust causal link between an increase in body mass index (BMI) and a higher risk of pancreatic cancer [20]. The study suggests that there is a 34% increase in pancreatic cancer risk for every standard deviation increase in BMI.