

# World Journal of *Clinical Cases*

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## Diabetes and skin cancers: Risk factors, molecular mechanisms and impact on prognosis

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### Abstract

Diabetes and skin cancers have emerged as threats to public health worldwide. However, their association has been less intensively studied. In this narrative review, we explore the common risk factors, molecular mechanisms, and prognosis of the association between cutaneous malignancies and diabetes. Hyperglycemia, oxidative stress, low-grade chronic inflammation, genetic, lifestyle, and environmental factors partially explain the crosstalk between skin cancers and this metabolic disorder. In addition, diabetes and its related complications may interfere with the appropriate management of cutaneous malignancies. Antidiabetic medication seems to exert an antineoplastic effect, however, future large, observation studies with a prospective design are needed to clarify its impact on the risk of malignancy in diabetes. Screening for diabetes in skin cancers, as well as close follow-up for the development of cutaneous



malignancies in subjects suffering from diabetes, is warranted.

**Key Words:** Diabetes; Skin cancers; Squamous cell carcinoma; Melanoma; Basocellular carcinoma

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**Core Tip:** Diabetes and skin cancers have emerged as threats to public health worldwide. However, their association has been less intensively studied. In this narrative review, we explore the common risk factors, molecular mechanisms and prognosis of the association between cutaneous malignancies and diabetes.

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## INTRODUCTION

Skin cancers have become an important public health problem due to its increasing incidence, complex management and the need to closely follow-up patients in order to diagnose relapses or *de novo* cases[1].

Depending on the cell of origin, skin malignancies are classified into non melanocytic cancers, the most common of which are basocellular carcinoma (the most common cancer worldwide) and squamous cell carcinoma, and melanocytic cancers of which the most representative entity is melanoma. In each of these disorders, prognosis is variable and depends on the degree of local invasion and the potential for metastasis which increases in the case of squamous cell carcinoma and peculiarly in the case of malignant melanoma[2,3].

Diabetes is a chronic condition, characterized by an increase in blood glucose levels and which can be accompanied during its evolution by systemic complications that lead to significant morbidity and mortality[4]. Depending on the mechanisms responsible for the elevation in fasting plasma sugar, diabetes is classified into type 1 diabetes mellitus (T1DM) (characterized by the absence of insulin production by beta pancreatic cells), type 2 DM (T2DM) (characterized mainly by the resistance of tissues to the action of insulin), other specific types of diabetes, and gestational diabetes (idiopathic) of which T2DM is the most frequent[5,6].

Dietary patterns, lifestyle, obesity, stress and smoking are risk factors for both diabetes and malignancy which share multiple common mechanisms of development. Of these, low-grade chronic inflammation and oxidative stress can lead to the alteration of DNA structure, as well as to the activation of signaling pathways involved in cell growth, angiogenesis and metastasis, *e.g.*, mitogen activated protein kinase (MAPK) or Janus Kinase Signal Transduction and Activation of Transcription (JAK-STAT) pathways[7-9].

Thus, the aim of this narrative review is to evaluate the relationship between skin cancers and diabetes in terms of epidemiological trends, risk factors and shared molecular mechanisms, as well as to evaluate the impact of diabetes, its complications and of antidiabetic therapy on the management of skin cancers.

## EPIDEMIOLOGY OF DIABETES AND SKIN CANCERS

Diabetes has emerged as a threat to public health worldwide and has become not only a major cause of morbidity and mortality, but also a burden to the socio-economic system. The prevalence of diabetes continues to rise as a result of socio-economic development, adoption of an unhealthy lifestyle, and increased life expectancy. A sedentary lifestyle and unhealthy dietary patterns are known to increase the body mass index which is one of the most important risk factors associated with the development of T2DM[10].

According to a study conducted by Sun *et al*[11] and published in 2022, the global prevalence of diabetes in adults aged 20-79 was estimated at 10.5% in 2021. In absolute terms, 536.6 million people suffered from this metabolic disorder. Diabetes is equally prevalent in men and women, but in terms of socio-economic status, industrialized countries have a greater prevalence than developing countries (11.1% compared to 5.5%). Similarly, urban regions have a higher prevalence than rural areas (12.1% compared to 8.3%). Currently, half a billion individuals suffer from diabetes, but this number expected

to rise and reach 783.2 million (12.2%) by 2045[11].

One in every two people with diabetes (50.1%) is unaware that they suffer from this metabolic disorder due to the chronic nature of the disease and its indolent evolution which is characterized by hyperglycemia-induced damage to internal organs[12,13].

Diabetes groups a complex of metabolic diseases that have in common the increase in fasting plasma glucose. According to the American Diabetes Association, diabetes is classified into 4 categories[14]. T1DM, previously called “insulin-dependent diabetes”, has as an etiological mechanism the autoimmune destruction of pancreatic beta-cells. This type of diabetes, known in the past as “juvenile-onset diabetes”, accounts for 5%-10% of all cases of the disease, affecting mostly children and adolescents, but can also occur in adults as latent autoimmune diabetes of adulthood[15]. T2DM, previously known as “noninsulin-dependent diabetes” or “adult-onset diabetes”, represents 90-95% of the cases of diabetes[16]. Another type of diabetes is that which occurs secondary to other causes: diseases of the exocrine pancreas, drug-induced or monogenic diabetes syndrome. Gestational diabetes mellitus affects pregnant women and has its onset in the second or third trimester of pregnancy and has an increasing prevalence in the United States, leading to fetal and maternal risks[17].

The incidence and prevalence of diabetes are on the rise, approaching epidemic proportions and significantly affecting the quality of life and leading to complications and comorbidities. Diabetes and cancer are two major diseases that are becoming more prevalent around the world. Due to hyperglycemia, elevated insulin and insulin-like growth factor-1 (IGF-1) levels, proinflammatory state, increased leptin levels, and decreased adiponectin levels, diabetes is linked to an increased risk of cancer. At the same time, the two disorders share common risk factors, *e.g.*, obesity, unhealthy diet, smoking, sedentary lifestyle, and increased life expectancy[18].

Skin cancers are the most common form of malignancy worldwide and their prevalence has constantly increased over the last three decades. According to the World Health Organization, about 2-3 million non-melanocytic skin cancers and about 130000 melanomas are diagnosed annually, which translated into an increase in disability-adjusted life years in the affected population[1,19]. Basocellular carcinoma is the most common form of cancer, with 4 million cases diagnosed worldwide in 2019 and an increasing incidence in the last few years[20]. The number of cases per 100000 inhabitants varies from 27 to 492 in different studies, with real incidences probably even higher due to the lack of cancer registries and inadequate reporting of cases[21].

Cutaneous squamous cell carcinoma is the second most frequent skin cancer, accounting for up to 20% of skin malignancies. Its incidence is increasing and has been reported to almost equal the one of basal cell carcinoma[22]. In 2017, squamous cell carcinoma was the 6<sup>th</sup> cancer by incidence, with over 1.7 million cases diagnosed worldwide, an increase of over 300% compared to the 1990-2017 timeframe[1]. Its increasing incidence, metastatic potential and aggressive local evolution add to the global burden of the disease. The age-standardized incidence varies with sex and geographical region from 5 to 96 cases per 100000 inhabitants, with numbers reaching almost 499 cases per 100000 inhabitants in Australia and neighboring regions[22].

Although a rare form of cancer (21<sup>st</sup> by incidence worldwide) melanoma is a relevant threat to public health globally due to its high incidence (an increase of 161% compared to the 1990-2017 timeframe) and poor prognosis due to late presentation and diagnosis[1]. According to the Center of Disease Control and Prevention, the incidence of melanoma in 2018 was 22 cases per 100000 inhabitants, with almost 84000 new cases diagnosed in that year and approximately 8200 deaths[23].

The incidence of several solid cancers is higher in patients diagnosed with diabetes. However, the crosstalk between diabetes and skin malignancies has been less investigated. Tseng *et al*[24] evaluated, in a retrospective study conducted on 41898 patients with T2DM and 41898 healthy patients from Taiwan, the link between diabetes and skin cancers. They found that the incidence ratio for cutaneous malignancies in general (IRR = 1.44, 95%CI 1.07-1.94,  $P = 0.02$ , diabetes mellitus/non-diabetes mellitus:  $n = 99/76$ ) and peculiarly for non-melanocytic cancers (IRR = 1.57, 95%CI 1.15-2.15,  $P = 0.005$ , diabetes mellitus/non-diabetes mellitus:  $n = 94/66$ ) was notably higher in patients with diabetes over 60 years of age compared to the healthy population. However, no statistically significant association was highlighted between the risk of melanoma and the presence of T2DM in this investigation[24]. Another retrospective study conducted by Li *et al*[25] evaluated the prevalence of cancer in 25964 T2DM patients from the United States. They found an increased prevalence of non-melanoma skin cancers ( $P < 0.0001$ ) in patients with a history of T2DM longer than 15 years, whereas the prevalence of melanoma was similar between patients with/without T2DM ( $P = 0.08$ )[25].

## IS DIABETES A RISK FACTOR FOR SKIN CANCERS?

Growing evidence has over the course of time proposed a correlation between abnormalities in glucose homeostasis and the development as well as prognosis of certain neoplasms[26]. Diabetes, a disorder of the glucose metabolism, owing to its associated insulin resistance, has been particularly identified as an independent risk factor in several solid and hematological neoplasms ranging from hepatobiliary, pancreatic, gastric, colorectal, renal, breast and endometrial cancers. Furthermore, cancer mortality

ratings have been reported with hazard ratios ranging from 1.12 in prediabetic to 1.57 in known diabetic patients[27]. The observed relationship has sparked great interest in the research for novel cancer biomarkers to aid in establishing the risk, diagnosis and prognosis of cancers associated with diabetes [28].

Several hypotheses have been fronted in a bid to shed light on possible etiologies behind diabetes' relationship with cancers as a whole[28]. The general consensus has been that the progression of diabetes to cancer could possibly be due to the attendant hyper-insulinemic, hyperglycemic and inflammatory states. These have been reported to cause DNA structural damage and activate signaling pathways such as MAPK and JAK-STAT which are key in regulating cellular growth, angiogenesis as well as metastasis. Hyperinsulinemia, for instance, through IGF-1 pathways plays a role in initiating cancers and furthering their progression through enhancement of mitosis and inhibition of apoptosis [29].

Hyperglycemia independently increases cancer risk either directly or indirectly[30]. Its direct effect is seen on tumor cells where it favors their proliferation, induces mutations, augments invasion, migration as well as rewiring of cancer-related pathways such as the Wnt/ $\beta$ -catenin pathway. Indirectly, the effect is mediated through organs that will in the long run induce production of either growth factors such as insulin or IGF-1 or inflammatory cytokines[31]. Further, the state of oxidative stress in diabetes, with consequential DNA damage, is also considered responsible for the transformation of oncogenes and development of cancers[32]. Further, the commonality of risk factors (modern diet, sedentary lifestyle, obesity, stress, smoking, *etc.*) between diabetes and cancers accentuates the co-existence of these two chronic conditions.

Of the two broad categories of skin malignancies (melanoma and non-melanoma), few reports exist about the association between diabetes and the non-melanoma variant, with an overall varying association between T2DM and both malignant melanoma as well as the non-melanoma variant[24]. The variability in these reports, especially in epidemiological studies, has been attributed to dissimilar ethnic as well as environmental factors in the study populations. Despite the limited availability of reported literature, the association between diabetes and skin cancers remains critical owing to the growing burden of diabetes (estimated at 380 million individuals in the next 2 decades) and the possibility of under-reported cases[26].

The relationship between diabetes and skin cancers has been attributed to a couple of factors. Lifestyle-associated risk factors, for instance, such as obesity and sedentary lifestyle have particularly been correlated with an amplified risk of melanoma and diabetes and in a similar manner, leptin and serum adiponectin have also been implicated[33,34]. Further, the chronic periods of insulin resistance associated, in particular, with T2DM, has been identified as an independent risk factor for melanoma [35]. The chronicity of both insulin resistance and the attendant hyperinsulinemia are known to stimulate growth of tumors by decreasing the levels of IGF binding protein-1 and hence increasing the production of IGF-I[36]. Of note, abnormalities in IGF pathways seem to form the center point in the path to carcinogenesis through favoring tumor proliferation and metastases. Since IGF regulates proliferation of epidermal cells, elevated serum levels of insulin or IGFs in diabetes patients subsequently enhance its proliferation and further activates oncogenic epidermal growth factor receptors[37]. The result of this cascade is an alteration of the mitotic and apoptotic properties of these cells, mediated by expression of BCL2, BCL-X(L) and survivin proteins, with consequential malignant transformation[38]. Evidence of the aforementioned has been documented in several studies. For instance, keratinocyte response (senescence and apoptosis) to ultraviolet B irradiation was observed to be reliant on activation of the IGF receptor. This dependency draws key focus, especially since there have been observed abnormalities in insulin receptor binding and phosphorylation in insulin-resistant melanoma cell lines [24,39]. Recently, studies have also implicated vitamin D deficiency, as well as vitamin D receptor gene (FokI, BsmI, TaqI) polymorphism to increase the risk of both diabetes and melanoma[34]. Another theory also held responsible for skin cancers in diabetic patients is the immunosuppressive state brought about secondary to the insulin deficiency and hyperglycemic state[40]. Immunosuppression has been observed as a potential risk factor for developing skin cancers[41]. Overall, there are a handful of studies attempting to describe the relationship between diabetes and cancers in general, however, those with particular focus on skin cancer and diabetes are relatively few. As a result most theories held for the former association are extrapolated to form the pathophysiology behind skin cancers and diabetes.

Conclusively, studies show evidence of an association between diabetes and skin cancers as a whole with particular preference for melanoma, and while there are few reported cases, the growing burden of diabetes globally makes it a looming concern. This association is due to shared risk factors, and the role of molecules such as IGF, vitamin D receptors, leptin and adiponectin. Prevention and management of diabetes therefore brings us a step closer to lowering the prevalence of skin cancers. In fact, some treatment modalities used in diabetes such as the use of insulin and rosiglitazone have been reported to possibly reduce the incidence of non-melanoma skin cancer in diabetes patients[34]. Hence an emphasis on aggressive surveillance and treatment of diabetes remains strategic in combating skin cancers.

## MOLECULAR MECHANISMS LINKING DIABETES AND SKIN CANCERS

Hyperglycemia and high amounts of insulin or IGF in human serum, have been considered to be responsible mechanisms for oncogenesis in diabetes patients. Cell growth, superoxide overproduction, decreased expression of antioxidants, DNA damage, and ROS generation are results of continuous hyperglycemia[24,42,43]. IGF ameliorates the proliferation of skin epidermal cell layer. Increased insulin and IGFs in diabetes patients can lead to an upregulation in cell proliferation and carcinogenic epidermal growth factor receptors. This activation can result in increasing mitogenic activity and inducing apoptosis and malignant transformation[44].

Immunosuppression is a probable risk factor for skin cancers, *e.g.*, non-melanoma skin cancer and melanoma[45]. Uncontrolled, persistent diabetes weakens the immune system. In fact, an inflammatory activity occurs in response to the high blood glucose, as well as an upregulation in inflammatory mediators generated by adipocytes and macrophages in fat tissue. This immunologic response and chronic inflammation pathologically change the pancreatic beta cells and causes insufficient insulin production, which results in persistent hyperglycemia. Hyperglycemia in diabetes is thought to cause dysfunction of the immune response[46].

Studies have demonstrated that keratinocytes facing with ultraviolet B light radiation develop a premature stress-induced senescence or apoptosis, which is dependent on the activation of the IGFs[47]. The IGF biological pathway has a vital role in growth regulation and IGF level deregulation might lead to carcinogenesis and cell differentiation[48-50]. The relationship between the IGF system and melanoma cell proliferation have been demonstrated in the previous literature. Insulin binding insufficiency and receptor phosphorylation were investigated in an insulin-resistant melanoma cell line[51]. Melanoma cells are shown to be differentiated by IGF1 through an upregulation in antiapoptosis proteins [BCL2, BCL-X (L), and surviving][32]. Hyperinsulinemia is another responsible mechanism for cancer. Hyperinsulinemia may help tumor growth by upregulating IGF-1, known to promote tumor cell proliferation and metastases[52].

Different diabetes treatment regimens can increase the risk for cancer development[29]. This finding has also been confirmed in the case of skin malignancies. Different formulations of insulin or rosiglitazone have been demonstrated to be possibly correlated with the incidence of non-melanoma skin cancer in diabetes[53,54].

Vitamin D deficiency is also associated with diabetes and vitamin D receptor polymorphisms are responsible for an increased susceptibility to diabetes[55,56]. FokI, BsmI, and TaqI have been reported to affect melanoma cell growth and differentiation[57-59].

## EVOLUTION AND MANAGEMENT OF SKIN CANCERS IN PATIENTS WITH DIABETES

The escalation of skin cancer rates globally has resulted in multiple treatment options available for patients[60]. Choice of treatment is dependent on tumor factors including type, location, margins, and metastatic spread[61]. Patient comorbidities, like diabetes, are equally taken into consideration for skin cancer treatment[18]. Definitive curative therapy for skin cancer includes surgical excision of the cancer site[61]. Types of surgical excision techniques available include Mohs micrographic surgery, complete circumferential peripheral and deep margin assessment (CCPDMA) or standard surgical excision with wide margins of > 10 mm[62]. In cases with spread to lymph nodes and distant metastatic sites further surgical management through a metastasectomy may be required[62].

Surgical curative treatment techniques available are identical for both diabetic and nondiabetic skin cancer patients. Surgical outcomes for diabetic skin cancer patients are not well studied. Of importance, diabetic cutaneous, general and vascular surgical patients have an increased risk of developing postoperative complications leading to poorer surgical outcomes, when compared to nondiabetic patients[63,64]. Of greatest concern in skin cancer diabetes patients is postoperative wound healing delay and impairment[65]. The pathophysiological mechanism responsible for altered wound healing is caused by the effects of hyperglycemia on complex biochemical pathways which result in the oversaturation of reactive oxygen species and oxidative stress stimulating the formation of advanced glycosylation end products (AGEs)[66]. AGEs play a pivotal role in vascular injury through the activation of chemokine receptors causing a chronic low-grade pro inflammatory response through epigenetic macrophage deregulation and impairment of pro-healing cytokines, local ischemia through microvascular constriction, and local pro-coagulative effects[65,67-70]. Simultaneously, AGEs form cross-linkages with extracellular matrix proteins causing direct cellular injury with diminished proliferative repair[65,66]. Combination of multiple complex mechanisms stimulated through hyperglycemia results impaired and ultimately failed wound healing which leaves patients with functional limitations, poor cosmetic outcomes and increased risk of developing wound site infections such as cellulitis and abscesses and more seriously gangrene, osteomyelitis and septicemia[65]. Infection is a particular issue for diabetic patients due to their chronic state of immunosuppression lending an increased risk of opportunistic infections[71]. Importantly, skin cancer, unlike other cancers, directly impairs the functional dermatological tissue important to the immune, endocrine and neurological systems. This



direct impairment occurs with direct replacement of skin parenchyma with malignant transformative tissue[44]. The impacts of skin cancers and diabetes on functional skin integrity results in more difficult and higher risk management on diabetic skin cancer patients.

Medical treatment techniques in skin cancer are utilized as an adjuvant treatment method and in patients unsuitable for surgery. These techniques can be categorized into radiotherapy, chemotherapy, immunotherapy and targeted drug therapy[72]. The pharmacodynamics of each of these medical treatments has unique impacts on diabetic skin cancer patients. Radiotherapy is used in nonmelanoma skin cancer for patients unsuitable for surgery[18]. There are no direct studies exploring toxicity following radiotherapy treatment in diabetic skin cancer patients. Alternative studies on radiotherapy in lung, breast and prostate cancer patients have indicated diabetic patients are subjected to worsened radiation damage including radiation pneumonitis[73-76]. Skin cancer patients with a background of diabetes undergoing radiotherapy should be treated with caution. Similarly, diabetic patients receiving chemotherapy regimens are at an increased risk of developing chemotherapy toxicities compared to nondiabetic patients. Chemotherapy induced gastrointestinal adverse effects influences blood glycaemic levels in diabetic patients increasing the risk of developing hypo- or hyper- glycaemic episodes. To date, there have been no skin cancer studies on diabetic patients receiving chemotherapy. Similar studies on diabetic chemotherapy breast cancer patients does highlight the increased risk of hospitalization for neutropenia, infection and anemia[77]. On the other hand, chemotherapy treatment for colon cancer in diabetic patients does not increase the risk of hospitalization[78]. It is believed that chemotherapy toxicity in diabetics is related to the treatment dose since, colon cancer chemotherapy dose is substantially lower compared to breast cancer doses. Further studies are required to determine the value and safety of chemotherapy in diabetic skin cancer patients. Immunotherapy agents such as pembrolizumab and nivolumab that target PD-1 proteins are used in skin cancer management. The mechanism of action of these drugs is that they block the PD-1 protein on the T-cell which triggers an immune mediated response towards malignant cells. In some cases, this immune response can damage normal host cells including pancreatic islet cells, therefore reducing insulin production. These drugs can cause increased blood glycemic levels, which is exacerbated in diabetic patients and in rare circumstances diagnosis of autoimmune diabetes have been reported[79]. Epidermal growth factor receptor inhibitors such as cetuximab are also drug therapies used in the treatment of skin cancer. The mechanism of action of this drug type does not have an effect on glucose metabolic pathways and therefore are well tolerated in diabetic patients with skin cancer[18].

Targeted drug immunotherapies are available for specific melanoma skin cancer patients. Most widely used are the BRAF-inhibitor agents such as dabrafenib and vemurafenib. These therapies work by selectively targeting the BRAF protein on malignant cells which interfere with the RAS/MAPK pathway, thus regulating the proliferation and survival of melanoma cells. Unfortunately, these therapies can only be utilized short term due to patients developing resistance to these therapies[80]. Evidence suggests that BRAF therapies are nephrotoxic causing tubulointerstitial renal disease and significant electrolyte derangements with hypokalemia, hyponatremia and hypophosphatemia being reported[81,82]. Evidence does suggest that dabrafenib has lower rates of kidney dysfunction than vemurafenib[81]. This is an important consideration in diabetic skin cancer patients who may already have poor renal function secondary to diabetic nephropathy. Recent studies in animal models have suggested topical BRAF inhibitors have shown evidence of accelerated wound healing[83]. Further studies should look to investigate the outcomes of topical BRAF inhibitors on diabetic wounds secondary to skin cancer excisions.

Choice of management in diabetic patients is individualized and often will largely depend on the end organ diabetic complications of the patient. Important considerations include diabetic nephropathy with reduced renal function causing a change in the drug dosage or type of drug, cardiovascular disease with most chemotherapy agents having cardiac adverse effects and chronic infections suffered[18].

Of significance, skin cancer treatments mostly occur within hospital settings. Diabetic patients have an increased risk of morbidity and mortality following a hospital admission and longer hospitalization rates.

There is also evidence of patients with breast, ovarian and colon cancer that diabetic patients receive less aggressive treatment[84]. This approach to these patients increases their likelihood of relapse. To date, there is no research published investigating the aggressiveness of treatment for skin cancer diabetic patients. Persistent hyperglycemia may contribute to malignant cellular growth, and the overproduction of superoxide and reactive oxygen species[66]. Recent studies have highlighted that in colon cancer there is an increased risk of cancer relapse and mortality in diabetic patients compared to nondiabetic patients[85].

## ANTI-DIABETIC MEDICATION AND RISK OF SKIN CANCERS

Anti-diabetic drugs can affect cancer risk both directly and indirectly by affecting cancer cell metabolism and risk factors. Metformin has beneficial effects in many site-specific cancers, lowering the incidence of liver, gastric, colorectal, endometrial and breast cancers, with reducing the mortality and improving the

**Table 1 Effect of antidiabetic drugs on skin cancers**

Antidiabetic drug[86-102]	Effect on skin cancers
Metformin	Protein synthesis inhibition in the skin cancer cells by blocking the mTOR pathway <i>via</i> DNA DDIT 4
Thioglitazones ( <i>e.g.</i> , pioglitazone)	Upregulation of p27kip1 and apoptotic induction <i>via</i> gene upregulation like PTEN, p53, and BAX, and downregulation of antiapoptotic molecules and survival in the skin cancer cells
SGLT-2 inhibitors ( <i>e.g.</i> , canagliflozin)	Reducing skin cancer growth by inhibition of cellular respiration
Insulin-like analogues	Promote tumour proliferation by functioning as growth factors
DPP-4 inhibitors ( <i>e.g.</i> , sitagliptin)	Reducing the risk of skin cancer by inhibiting the cutaneous autoimmunity
Glucagon-like peptide-1 receptor agonists ( <i>e.g.</i> , albiglutide)	Inhibiting the epidermal growth factor and growth of cancerous cells

BAX: BCL2-associated X; DDIT 4: Damage inducible transcript 4; DPP-4: Dipeptidyl peptidase-4; mTOR: Mechanistic target of rapamycin; SGLT-2: Sodium-glucose cotransporter-2.

survival from lung, colorectal, prostate, endometrial, pancreatic and breast cancers[86]. Metformin reduces the risk of neoplastic and pre-neoplastic cell proliferation by decreasing production of hepatic glucose and increasing glucose uptake peripherally, primarily by the muscle cells. This results in decreased release of insulin from pancreatic cells and lower levels of insulin in the plasma, thereby reducing the risk of cancer growth[87]. In addition, metformin inhibits the synthesis of protein in the cancer cells by blocking the mechanistic target of rapamycin (mTOR) pathway *via* DNA damage inducible transcript 4 (DDIT 4). Furthermore, when metformin is taken with other chemotherapy medications, it has an additive or synergistic impact, enhancing its anticancer activity[88,89]. Dicembrini *et al*[90] conducted a meta-analysis of randomized controlled trials and found that dipeptidyl peptidase-4 (DPP-4) inhibitors had no effect on total cancer risk, regardless of the investigated molecule or the cancer site, with an exception where the DPP-4 inhibitor use was related to a considerably lower risk of colorectal cancer[90]. Thioglitazones in time dependent doses can exert anticancer effects by inhibiting the Mitogen-activated protein kinase (MEK)/extracellular-signal-regulated kinase (ERK)-MEK/ERK signaling pathway, which leads to upregulation of p27kip1 and apoptotic induction *via* gene upregulation like PTEN, p53, and BCL2-associated X (BAX), and downregulation of antiapoptotic molecules and survivin[91]. A meta-analysis by Cao *et al*[92] found that usage of glucagon-like peptide-1 receptor agonists was not linked to an elevated cancer risk. Furthermore, albiglutide use was linked to a lower overall cancer risk, which needs to be investigated further[92]. Lowering blood glucose levels and decreasing endogenous insulin secretion and improving insulin sensitivity peripherally are among the metabolic related to sodium-glucose cotransporter-2 inhibitor use. This implies that they have an indirect positive impact on factors linked to cancer risk[93]. A study by Jojima *et al*[94] found that use of *in vitro* canagliflozin had attenuated HepG2 (a human liver cancer cell line) cell proliferation through the activation of caspase-3, reducing the risk of hepatic cancers. Canagliflozin has also been found to be effective in the inhibition of *in vitro* cancer cell growth in the prostate and lungs through inhibition of cellular respiration aided by mitochondrial complex-I[95]. A Taiwanese study by Liu *et al*[96] observed that except the pioglitazone that belong to thiazolidinediones group of drugs and injectable insulin analogues like the long acting or intermediate combinations with rapid acting drug group, all other antidiabetic drugs are not associated with an increased cancer risk. The usage of insulin-based regimens was linked to a 40% greater risk of all malignancies, according to a Currie *et al*[97] study from the United Kingdom. Metformin use was also linked to a lower incidence of colon and pancreatic cancer in this study, but had no influence on breast and prostate cancer. In cohort research from Germany, Emkens *et al*[98] found that the synthetic insulin glargine has a dose-response connection with cancer risk when compared to human insulin. Metformin has been shown to be an effective antitumor drug in the treatment of a variety of cancers, including melanoma. Metformin has been shown in some cohort studies to inhibit the invasion and migration of various types of cancers[99] (Table 1). Metformin inhibits melanoma cell invasion and metastasis by activating adenosine monophosphate-activated kinase activator, which reduces cancer cell mTOR signaling and protein synthesis. Metformin treatment prevents melanoma cell migration and epithelial-mesenchymal transition. Notably, metformin suppressed miR-5100 expression while increasing SPINK5 expression, which inhibits STAT3 expression and Tyr705 phosphorylation[100]. Metformin significantly slows the progression of ocular melanoma through autophagy inhibition by histone deacetylation of optineurin[101]. Metformin increases the cytolytic activity of NK-92 cells over time and metformin-induced cytotoxicity was observed in NK cells from healthy peripheral blood and ascites of cancer patients. Metformin has been observed to improve cancer surveillance of NK cells in mouse models of lymphoma and metastatic melanoma *in vivo*. The combination of metformin and anti-PD-1 antibodies improved therapy response rates in B16F10 melanoma and, furthermore, metformin treatment increased tumor NK and T cell infiltration[102]. However, we must emphasize that there is no data derived from randomized controlled trials (RCTs) to

support that antidiabetic drugs impact on cancer incidence *per se*.

## CONCLUSION

Diabetes and skin cancers share many pathogenic links; however, there is an unmet need to carefully assess their association in randomized controlled trials, cohort studies or at least large observational prospective cancer and diabetes registries. Diabetes can complicate the management of cutaneous malignancies, particularly if left uncontrolled or if it is poorly managed in terms of glucose control. The antineoplastic effect of antidiabetic medication remains to be assessed with caution in future studies, however, as subjects suffering from diabetes often require changes in their drug prescription, it will be difficult to clarify this research question. Irrespective, screening for diabetes in skin cancer patients, as well as close follow-up for the development of cutaneous malignancies in subjects diagnosed with this metabolic disorder, are warranted.

## FOOTNOTES

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