GSAR Journal of Applied Medical Sciences ISSN: 2584-2323 (Online)

GSAR Journal of Applied Medical Sciences
ISSN: 2584-2323 (Online)
Frequency: Monthly
Published By GSAR Publishers
Journal Homepage Link- https://gsarpublishers.com/gsarjams-home/

Endocrine Crosstalk: Diabetes as a Catalyst for Cancer Progression and Metastasis

BY

Muhammad Rasheed[1], Sonia Javed[1*], Muhammad Aftab Akram[1], Usama[1], Usama Azeem Khan[2], Tooba Ali[3], Maryam Fazal ur Rehman[4], Faraz Haider Faraz[1], Saad Abdullah[5].

[1]Department of Biochemistry, University of Agriculture, Faisalabad, Pakistan.
[2]Soil and Environmental Biotechnology Division, National Institute for Biotechnology and Genetic Engineering, Pakistan.
[3]Department of Biochemistry, Riphah International University, Faisalabad, Pakistan.
[4]Department of Zoology, University of Poonch Rawalakot, Pakistan.
[5]Department of Botany, Karakoram International University, Gilgit, Pakistan

Article History

Received: 05/06/2025
Accepted: 16/06/2025
Published: 18/06/2025

Vol – 2 Issue – 6

PP: -01-07

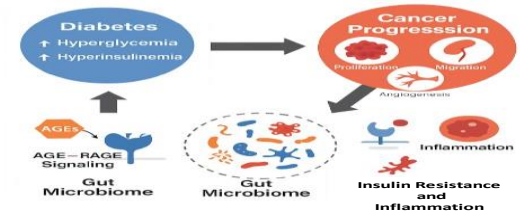
DOI:10.5281/zenodo.15696367

Abstract

Diabetes and cancer represent two of the most pervasive and challenging health crises worldwide, with a growing body of evidence revealing a profound and complex interplay between these diseases. Beyond being a mere comorbidity, diabetes acts as a potent catalyst in cancer progression and metastasis, driven primarily by the endocrine and metabolic disruptions characteristic of hyperglycemia and hyperinsulinemia. Chronic elevations in glucose and insulin levels foster a tumor-promoting microenvironment that accelerates cancer cell proliferation, survival, migration, and angiogenesis. This review synthesizes current understanding of the molecular and cellular mechanisms linking diabetes to cancer, emphasizing the pivotal roles of advanced glycation end products (AGEs), the AGE–RAGE signaling axis, insulin resistance, and inflammatory pathways. Moreover, we explore the emerging influence of the gut microbiome in modulating metabolic and oncogenic processes common to both diseases. Epidemiological data underscore the heightened cancer risk and mortality observed in diabetic patients, particularly for pancreatic, liver, colorectal, and breast cancers, while highlighting the need for integrated clinical strategies. By unraveling the endocrine crosstalk that connects diabetes and cancer, this review aims to illuminate potential therapeutic targets and inspire novel dual-action interventions that may curb the dual burden of these interlinked diseases.

Keywords: *Diabetes, Metastasis, Cancer progression, Hyperglycemia, Hyperinsulinemia.*

Graphical abstract



Introduction

Diabetes and cancer are two of the most prevalent and devastating diseases globally, each having a major impact on public health. Emerging evidence reveals a complex relationship between these conditions, with diabetes acting not only as a significant risk factor for cancer development but also as a catalyst for cancer progression and metastasis. The endocrine disruptions caused by diabetes, particularly the chronic elevation of insulin and glucose, create a tumor-friendly environment that promotes cellular proliferation, survival, and migration [1, 2].

Diabetes, a multifactorial disease, is divided into type 1 and type 2, which differ in both hormonal and metabolic traits [3]. Type 1 diabetes, characterized by a complete deficiency in

*Corresponding Author: **Sonia Javed.**

endogenous insulin secretion, accounts for approximately 5%–10% of all diabetic cases. This form of diabetes requires external insulin administration for effective management [4]. In contrast, type 2 diabetes, comprising 90%–95% of diabetes cases, is primarily associated with obesity, sedentary lifestyle, and aging [5]. It is characterized by chronic hyperglycemia accompanied by sustained hyperinsulinemia resulting from insulin resistance (IR) in peripheral tissues [6]. Insulin therapy is required only when pancreatic β-cells become dysfunctional and fail to produce adequate endogenous insulin [7].

Globally, the prevalence of diabetes was estimated at 6.1% in 2021, impacting around 529 million people. Alarming projections indicate that by 2050, this number could rise to 1.31 billion. Two important regions—North Africa and the Middle East (16.8%) and Latin America and the Caribbean (11.3%)—are expected to have prevalence rates above 10% [8]. Diabetes has severe long-term consequences that harm the heart, kidneys, eyes, nerves, and macrovasculature (big arteries) and microvasculature (small blood vessels). These complications highlight the need for more study to clarify the underlying mechanisms of diabetes and facilitate earlier detection and more efficient therapeutic approaches.

Diabetes is commonly reported in cancer patients, as both disorders have many risk factors such as aging, obesity, sedentary lifestyle and unhealthy diets [8]. Nevertheless, limited prospective research has investigated the effect of diabetes on cancer treatment and outcomes. Cells use glucose as the primary energy source throughout the body, including those in the muscles, brain and malignant tissues. High blood glucose levels offer a plentiful energy supply for cancer cells, thereby facilitating their growth and progression. The theory that "glucose fuels tumor growth" helps explain the association between hyperglycemia and an increased risk of cancer. Both epidemiological and experimental studies support this connection, indicating that factors like excess body weight, fat accumulation, and physical inactivity contribute to cancer development by elevating blood glucose and insulin levels [9, 10]. Vander Heiden and colleagues reported that cancer cells tend to rely on glycolysis, a less efficient pathway for ATP generation, rather than oxidative phosphorylation, to meet the energy demands of rapid proliferation [11]. Young and colleagues confirmed that this metabolic shift makes cancer cells more sensitive to nutrient deficiencies [12]. Additionally, Gatikrushna Panigrahi and colleagues found that hyperglycemia in diabetes promotes breast cancer progression by inducing mesenchymal and stem cell-like traits, enhancing cell mobility and metastasis. It also causes DNA repair deficiencies, oxidative stress, and metabolite accumulation, which may influence tumor biology. These changes make cancer cells more vulnerable to DNA repair inhibitors [13]. As a result, the previously provided explanation clarifies why diabetic people have higher cancer occurrences.

How Hyperglycemia Fuels Cancer: A Molecular Link Between Diabetes and Tumor Progression

Emerging research indicates that hyperglycemia, a defining feature of diabetes, plays a central role in initiating tissue damage and may also contribute to cancer progression. The damaging effects of high glucose levels arise through two main mechanisms: frequent disruptions in cellular glucose metabolism and the gradual accumulation of advanced glycation end products (AGEs) [14, 15]. In diabetes, AGEs are formed more rapidly and deposited in tissues, contributing to complications like uremia, macrovascular, and microvascular pathologies [15]. The non-enzymatic interaction of carbohydrates with the amino groups of proteins, lipids, or nucleic acids produces these AGEs, a varied class of compounds [14]. Commonly glycated proteins include albumin, lipoproteins, insulin, and hemoglobin. A key precursor in this process is methylglyoxal, a reactive aldehyde produced during glucose metabolism. One of the most harmful consequences of AGE formation is their interaction with a specific receptor called RAGE (Receptor for Advanced Glycation End-products). This binding triggers oxidative stress, proinflammatory signaling, and the activation of NF-κB, a transcription factor that promotes reactive oxygen species (ROS) production [16]. These events result in endothelial dysfunction, increased arterial stiffness, and various vascular complications [14]. Interestingly, this same AGE–RAGE pathway has been linked to the development of several types of cancer. For instance, elevated AGE/RAGE expression correlates with cancer cell proliferation, invasion, and metastasis in pancreatic, gastric, and melanoma cancers ([17-20]. Specifically, [17, 18] demonstrated that pancreatic cancer cells with high RAGE expression also exhibited increased NF-κB and MMP-9 activity, both of which are key to cancer metastasis. [21] further found that RAGE signaling promotes glioma growth through MAPK pathway activation and upregulation of MMP-2/9. [20] also reported that AGE2 (glyceraldehyde-derived) and AGE3 (glycolaldehyde-derived) promote melanoma cell proliferation, migration, and invasion in vitro. Hyperglycemia may also promote cancer by stimulating abnormal angiogenesis that supports tumor growth. [22] showed that hyperglycemia upregulates miRNA-467, which suppresses thrombospondin-1, a natural antiangiogenic protein. Other studies confirm that RhoA, a signaling molecule, plays a crucial role in hyperglycemia-driven angiogenesis [23-25]. [25] demonstrated that folic acid can inhibit RhoA-mediated angiogenesis by activating the FR/cSrc/p190RhoGAP pathway.

Additionally, [26] highlighted that overexpression of angiopoietin-2 (Ang2)—a key vascular regulator—may contribute to pancreatic vascular defects in hyperglycemic environments. Together, these findings reveal how chronic hyperglycemia contributes not only to the complications of diabetes but also creates a biological environment that may support tumor initiation, growth, and metastasis. Understanding these overlapping molecular mechanisms opens new possibilities for developing dual-targeted therapies

*Corresponding Author: **Sonia Javed.**

that address both diabetes and cancer. Hyperglycemia induces AGE–RAGE signaling, leading to oxidative stress, inflammation, and endothelial dysfunction, which together drive cancer progression, as shown in **Figure 1**.

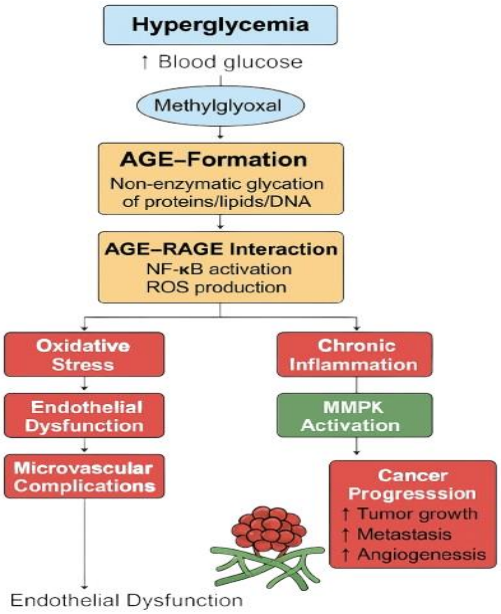


Figure 1 Mechanistic Pathway Linking Hyperglycemia to Cancer Progression via Endothelial Dysfunction.

Diabetes-Driven Oncogenesis: Unraveling the Metabolic and Inflammatory Links to Cancer Risk

Some biological processes linked to diabetes have been implicated in the increased risk of cancer observed in diabetic patients, including increased insulin and insulin-like growth factor-1 (IGF-1), hyperglycemia, pro-inflammatory cytokines, dyslipidemia, insulin resistance, elevated leptin levels, and decreased adiponectin [27]. Insulin, a key regulator of glucose metabolism, is also a member of growth factors that include IGF-I and IGF-II [28]. Beyond its metabolic functions, insulin exerts significant mitogenic effects, possibly contributing to tumor development [27, 28]. Hyperinsulinemia resulting from insulin resistance, together with chronic hyperglycemia, alterations in sex hormone regulation, oxidative stress, and persistent inflammation, are believed to play central roles in oncogenesis [28, 29].

Furthermore, elevated glucose levels have been demonstrated to promote the growth of various solid tumor cell lines [30, 31]. The pancreas and liver are particularly susceptible to high insulin levels, as insulin secreted by pancreatic β-cells is directly conveyed to the liver through the portal vein [32]. In addition, obesity, which frequently coexists with diabetes, exerts further cancer-promoting effects. These are mediated through increased peripheral conversion of androgens to estrogens, elevated levels of pro-mitogenic cytokines, and the release of growth factors from excess adipose tissue [27]. Chronic inflammation associated with obesity also contributes to carcinogenesis. Reactive oxygen species (ROS) production and the ongoing release of inflammatory cytokines can harm cells, which encourages the development, growth, and invasiveness of tumors [27, 31]. Diabetes-induced metabolic and inflammatory changes drive cancer development through insulin signaling and chronic inflammation as shown in **Figure 2**

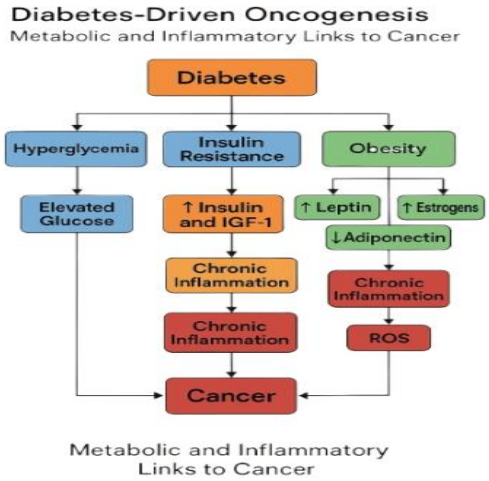


Figure 2 Diabetes-Driven Oncogenesis: Metabolic and Inflammatory Links to Cancer.

Gut Microbiome Dynamics in the Onset and Progression of Cancer and Diabetes

A recent study emphasizes how the gut microbiota is increasingly implicated in the onset and progression of cancer and diabetes [33-35]. Human gastrointestinal tract is home to billions of microorganisms, including bacteria, viruses, fungus, protozoa, and yeasts. These microbial communities interact intricately with each other and with the host, contributing to physiological homeostasis and, under certain conditions, the pathogenesis of various diseases. Cancer cells are known to rely heavily on glucose metabolism and glycolysis as primary energy sources. However, the precise mechanisms linking the gut microbiome, glucose metabolism, insulin resistance, and carcinogenesis remain incompletely understood. Current evidence indicates that external factors like diet, environmental exposures, and sugar consumption can disturb the diversity and function of the gut microbiota, leading to a condition known as dysbiosis. This imbalance may elevate the risk of insulin resistance, type 2 diabetes, and various cancers, especially those affecting the gastrointestinal and hepatobiliary systems. Dysbiosis, in particular, has been linked to a higher risk of colorectal, pancreatic, liver, esophageal, and head and neck cancers [33, 34, 36-38]

Epidemiological Association Between Diabetes and Cancer

Type 1 and type 2 diabetes were not distinguished in the majority of studies investigating the relationship between diabetes and cancer. The majority of studies has been on those with type 2 diabetes since it is far more prevalent. However, well-designed type 1 diabetes studies have also shown that individuals with type 1 or type 2 diabetes have a higher chance of developing certain forms of cancer as well as

*Corresponding Author: **Sonia Javed.**

a higher risk of dying from cancer [39, 40]. Data from six European groups, comprising around 274,000 men and 275,000 women, were analyzed in a comprehensive research conducted by [41]. The results showed that the risk of cancer rose by 11% in women and 5% in men for every 1 mmol/L increase in blood glucose. Pancreatic, liver, colorectal, breast, bladder, and endometrial cancers are among the many cancers for which diabetes and hyperglycemia have been linked to an increased risk, whereas prostate cancer has been linked to a decreased risk [42-45]. A meta-analysis of 151 cohort studies involving over 32 million individuals, 1.1 million cancer cases, and 150,000 cancer-related deaths found that type 2 diabetes is strongly linked to an increased risk of liver, pancreatic, and endometrial cancers, as well as a higher death rate from pancreatic cancer [42]. Furthermore, utilizing SEER data, a population-based case-control study revealed that diabetes was an independent risk factor for hepatocellular carcinoma, with an odds ratio of 3.08 (95% CI: 2.74–3.46) [46].

Diabetes was linked to an almost twofold higher relative risk of pancreatic cancer (RR: 1.94; 95% CI: 1.66–2.27), according to another meta-analysis of 35 cohort studies [48]. However, there is a complicated association between diabetes and pancreatic cancer since newly diagnosed diabetes may be a sign of pancreatic cancer early on and may result from insulin resistance brought on by tumors [49]. Lastly, a comprehensive study that included the results of 27 meta-analyses found that type 2 diabetes is linked to a 10% higher overall relative risk of cancer (RR: 1.10; 95% CI: 1.04–1.17) [47]. Although the exact mechanisms through which dysbiosis contributes to cancer development are not yet fully elucidated, several pathways have been proposed. These include chronic low-grade inflammation, impaired immune surveillance, the production of carcinogenic microbial metabolites, and interference with normal apoptotic processes [35, 50]. Furthermore, emerging evidence indicates that specific infections, such as candidiasis, which is more prevalent in individuals with diabetes, may also contribute to tumorigenesis.

Organ-Specific Pathways Connecting Hyperglycemia to Cancer Development

Pancreatic Cancer

Pancreatic cancer occurrence is reported to be two to threefold higher among individuals with diabetes. This strong association is further supported by the observation that approximately 80% of patients diagnosed with pancreatic cancer exhibit glucose intolerance or overt diabetes. Numerous studies have reported an association between diabetes and peripheral insulin resistance (IR) with pancreatic cancer [51, 52]. In addition to the role of hyperinsulinemia, Fisher and colleagues (1995) suggested that elevated levels of glucose and free fatty acids in blood, both commonly observed in diabetes, may contribute to the proliferation and progression of pancreatic cancer [53]. Despite these associations, the precise biological mechanisms underlying the link between hyperglycemia and pancreatic tumorigenesis remain to be fully elucidated.

Liver Cancer

Clinical studies have consistently shown that individuals with diabetes face a two to threefold higher risk of developing hepatocellular carcinoma (HCC). Non-alcoholic fatty liver disease (NAFLD), a known risk factor for non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis, and, finally, hepatocellular carcinoma (HCC), has been found in up to 80% of persons with type 2 diabetes. These findings highlight the strong epidemiological link between diabetes and liver cancer. One proposed mechanism for this increased risk is chronic liver exposure to elevated insulin levels caused by insulin resistance. Since insulin is delivered directly to the liver via the portal vein, prolonged hyperinsulinemia may promote hepatic tumor development [54]. Supporting this hypothesis, [54] suggested that hyperinsulinemia may increase hepatocellular carcinoma risk by elevating circulating levels of IGF-1. IGF-1, which is primarily synthesized in the liver, promotes cellular proliferation and growth while simultaneously inhibiting apoptosis, mechanisms that may facilitate cancer development.

Colorectal Cancer

Diabetes, particularly type 2 diabetes, has been reported to increase the chance of getting colorectal cancer by 20% to 30%. This association has not been observed in cases of type 1 diabetes or gestational diabetes [54-56]. Hyperinsulinemia has been recognized as a key factor linking diabetes to colorectal cancer. Increased amounts of insulin in the circulation can stimulate tumor growth through many mechanisms: (1) by directly activating the insulin receptor or the insulin-like growth factor 1 (IGF-1) receptor, and (2) by reducing insulin-like growth factor-binding proteins (IGFBP-1 and IGFBP-2), which improves IGF-1 bioavailability [57]. In addition to insulin, C-peptide, an indicator of endogenous insulin synthesis, has been linked to colorectal cancer risk. A study by [58] reported that higher circulating levels of C-peptide were associated with an elevated risk of colorectal cancer, suggesting that this peptide may serve as an additional mediator in the pathophysiological link between type 2 diabetes and colorectal malignancy.

Prostate Cancer

The risk of prostate cancer appears to be reduced in individuals with diabetes, in contrast to most other malignancies. Epidemiological studies have reported a relative risk (RR) ranging from 0.81 to 0.89 among diabetic patients, indicating a protective association [27]. One potential explanation involves hormonal regulation, particularly testosterone. Men with diabetes frequently have decreased circulating testosterone levels, and high testosterone levels have been linked to an increased risk of prostate cancer [59]. Therefore, the reduced androgen levels observed in diabetic individuals may contribute to the decreased incidence of prostate cancer in this population. Another proposed mechanism relates to genetic factors, specifically variants in the HNF1B gene. Genome-wide association studies (GWAS) have identified HNF1B as a significant genetic risk locus for prostate cancer. Variants in this gene have been shown to increase susceptibility to

*Corresponding Author: **Sonia Javed.**

diabetes, while paradoxically conferring a protective effect against prostate cancer among individuals carrying specific haplotypes [60]. This dual role highlights the complex interplay between metabolic and oncogenic pathways.

Dual Benefit Therapies: Targeting Cancer via Antidiabetic Pathways and Future Perspective

Hyperglycemia and cancer are linked through both general and site-specific mechanisms. Among antidiabetic medicines, metformin is notably significant; it stimulates the AMPK pathway, increasing glucose absorption in muscle tissue, decreasing insulin resistance, and lowering blood glucose levels [61]. Beyond its glucose-lowering effects, metformin shows promising anticancer properties, inhibiting tumor growth in colon, lung, and breast cancers through a p53-dependent mechanism [62-64]. At least two clinical trials are now evaluating metformin in cancer patients in combination with other treatments. Additionally, improperly controlled blood glucose accelerates the growth of tumors by compromising immunological responses [65].

Several key questions remain unresolved about how prediabetes and diabetes contribute to increased cancer risk. Additional factors needing further study include diabetes type, metabolic control levels, treatments used, dietary influences, and disease stage. Because diabetes and cancer are inherently heterogeneous, research at their crossing is made much more difficult. The general and site-specific processes that connect diabetes and cancer require more research to find new therapeutic targets for the prevention, diagnosis, and treatment of cancer in diabetic patients. Metformin's dual role in lowering blood glucose and inhibiting cancer progression through AMPK and p53 pathways is illustrated in **Figure 3**.

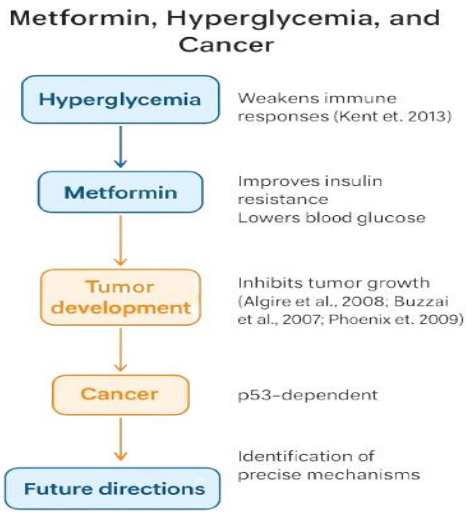


Figure 3 Metformin, Hyperglycemia, and Cancer: Mechanisms and Future Perspectives

References

1. Vulichi, S.R., et al., *Type-2 diabetes mellitus-associated cancer risk: In pursuit of understanding the possible link.* Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2022. **16**(9): p. 102591.
2. Zhang, F., et al., *Cellular senescence and metabolic reprogramming: Unraveling the intricate crosstalk in the immunosuppressive tumor microenvironment.* Cancer Communications, 2024. **44**(9): p. 929-966.
3. Marchetti, P., et al., *Diabetes Mellitus: Classification and Diagnosis*, in *Transplantation of the Pancreas*. 2023, Springer. p. 3-12.
4. Morran, M.P., et al., *Immunogenetics of type 1 diabetes mellitus.* Molecular aspects of medicine, 2015. **42**: p. 42-60.
5. Buzzetti, R., et al., *Adult-onset autoimmune diabetes.* Nature reviews Disease primers, 2022. **8**(1): p. 63.
6. Janssen, J.A., *Hyperinsulinemia and its pivotal role in aging, obesity, type 2 diabetes, cardiovascular disease and cancer.* International journal of molecular sciences, 2021. **22**(15): p. 7797.
7. Lima, J.E., N.C. Moreira, and E.T. Sakamoto-Hojo, *Mechanisms underlying the pathophysiology of type 2 diabetes: From risk factors to oxidative stress, metabolic dysfunction, and hyperglycemia.* Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 2022. **874**: p. 503437.
8. Ng, M., et al., *Global, regional, and national prevalence of adult overweight and obesity, 1990–2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021.* The Lancet, 2025. **405**(10481): p. 813-838.
9. Bosso, M., et al., *Targeting the metabolic paradigms in cancer and diabetes.* Biomedicines, 2024. **12**(1): p. 211.
10. Supabphol, S., et al., *High glucose: an emerging association between diabetes mellitus and cancer progression.* Journal of Molecular Medicine, 2021. **99**(9): p. 1175-1193.
11. Vander Heiden, M.G., L.C. Cantley, and C.B. Thompson, *Understanding the Warburg effect: the metabolic requirements of cell proliferation.* science, 2009. **324**(5930): p. 1029-1033.
12. Young, C.D. and S.M. Anderson, *Sugar and fat–that's where it's at: metabolic changes in tumors.* Breast Cancer Research, 2008. **10**: p. 1-9.
13. Panigrahi, G., et al., *Diabetes-associated breast cancer is molecularly distinct and shows a DNA damage repair deficiency.* JCI insight, 2023. **8**(23): p. e170105.
14. Negre-Salvayre, A., et al., *Hyperglycemia and glycation in diabetic complications.* Antioxidants & redox signaling, 2009. **11**(12): p. 3071-3109.
15. Friedman, E.A., *Advanced glycosylated end products and hyperglycemia in the pathogenesis of diabetic complications.* Diabetes care, 1999. **22**: p. B65.

*Corresponding Author: **Sonia Javed.**

16. Abe, R. and S.-i. Yamagishi, *AGE-RAGE system and carcinogenesis.* Current pharmaceutical design, 2008. **14**(10): p. 940-945.
17. Takada, M., et al., *Differential expression of RAGE in human pancreatic carcinoma cells.* Hepato-gastroenterology, 2001. **48**(42): p. 1577-1578.
18. Takada, M., et al., *Expression of receptor for advanced glycation end products (RAGE) and MMP-9 in human pancreatic cancer cells.* Hepato-gastroenterology, 2004. **51**(58): p. 928-930.
19. Kuniyasu, H., et al., *Expression of receptors for advanced glycation end-products (RAGE) is closely associated with the invasive and metastatic activity of gastric cancer.* The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland, 2002. **196**(2): p. 163-170.
20. Abe, R., et al., *Regulation of human melanoma growth and metastasis by AGE–AGE receptor interactions.* Journal of Investigative Dermatology, 2004. **122**(2): p. 461-467.
21. Taguchi, A., et al., *Blockade of RAGE–amphoterin signalling suppresses tumour growth and metastases.* Nature, 2000. **405**(6784): p. 354-360.
22. Bhattacharyya, S., et al., *Novel tissue-specific mechanism of regulation of angiogenesis and cancer growth in response to hyperglycemia.* Journal of the American Heart Association, 2012. **1**(6): p. e005967.
23. Cascone, I., et al., *Temporal and spatial modulation of Rho GTPases during in vitro formation of capillary vascular network: adherens junctions and myosin light chain as targets of Rac1 and RhoA.* Journal of Biological Chemistry, 2003. **278**(50): p. 50702-50713.
24. Oviedo, P.J., et al., *Estradiol induces endothelial cell migration and proliferation through estrogen receptor-enhanced RhoA/ROCK pathway.* Molecular and cellular endocrinology, 2011. **335**(2): p. 96-103.
25. Hou, T.-C., et al., *Folic acid inhibits endothelial cell migration through inhibiting the RhoA activity mediated by activating the folic acid receptor/cSrc/p190RhoGAP-signaling pathway.* Biochemical pharmacology, 2013. **85**(3): p. 376-384.
26. Calderari, S., et al., *Angiopoietin 2 alters pancreatic vascularization in diabetic conditions.* PloS one, 2012. **7**(1): p. e29438.
27. Sciacca, L., et al., *Clinical and molecular mechanisms favoring cancer initiation and progression in diabetic patients.* Nutrition, Metabolism and Cardiovascular Diseases, 2013. **23**(9): p. 808-815.
28. Hirsch, I.B., et al., *The evolution of insulin and how it informs therapy and treatment choices.* Endocrine reviews, 2020. **41**(5): p. 733-755.
29. Wang, M., Y. Yang, and Z. Liao, *Diabetes and cancer: Epidemiological and biological links.* World journal of diabetes, 2020. **11**(6): p. 227.
30. Duan, W., et al., *Hyperglycemia, a neglected factor during cancer progression.* BioMed research international, 2014. **2014**(1): p. 461917.
31. Masur, K., et al., *Diabetogenic glucose and insulin concentrations modulate transcriptom and protein levels involved in tumour cell migration, adhesion and proliferation.* British journal of cancer, 2011. **104**(2): p. 345-352.
32. Giovannucci, E., et al., *Diabetes and cancer: a consensus report.* CA: a cancer journal for clinicians, 2010. **60**(4): p. 207-221.
33. Lee, K., et al., *The gut microbiome: what the oncologist ought to know.* British journal of cancer, 2021. **125**(9): p. 1197-1209.
34. Gurung, M., et al., *Role of gut microbiota in type 2 diabetes pathophysiology.* EBioMedicine, 2020. **51**.
35. Vivarelli, S., et al., *Gut microbiota and cancer: from pathogenesis to therapy.* Cancers, 2019. **11**(1): p. 38.
36. Vallianou, N., et al., *Mycobiome and cancer: what is the evidence?* Cancers, 2021. **13**(13): p. 3149.
37. Le Chatelier, E., et al., *Richness of human gut microbiome correlates with metabolic markers.* Nature, 2013. **500**(7464): p. 541-546.
38. Nicholson, J.K., et al., *Host-gut microbiota metabolic interactions.* Science, 2012. **336**(6086): p. 1262-1267.
39. Carstensen, B., et al., *Cancer incidence in persons with type 1 diabetes: a five-country study of 9,000 cancers in type 1 diabetic individuals.* Diabetologia, 2016. **59**: p. 980-988.
40. Harding, J.L., et al., *Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation.* Diabetes care, 2015. **38**(2): p. 264-270.
41. Stocks, T., et al., *Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts.* PLoS medicine, 2009. **6**(12): p. e1000201.
42. Ling, S., et al., *Association of type 2 diabetes with cancer: a meta-analysis with bias analysis for unmeasured confounding in 151 cohorts comprising 32 million people.* Diabetes care, 2020. **43**(9): p. 2313-2322.
43. Bjornsdottir, H.H., et al., *A national observation study of cancer incidence and mortality risks in type 2 diabetes compared to the background population over time.* Scientific Reports, 2020. **10**(1): p. 17376.
44. Cannata, D., et al., *Type 2 diabetes and cancer: what is the connection?* Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine: A Journal of Translational and Personalized Medicine, 2010. **77**(2): p. 197-213.

*Corresponding Author: **Sonia Javed.**

45. Hu, Y., et al., *Incident type 2 diabetes duration and cancer risk: a prospective study in two US cohorts.* JNCI: Journal of the National Cancer Institute, 2021. **113**(4): p. 381-389.
46. Davila, J., et al., *Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study.* Gut, 2005. **54**(4): p. 533-539.
47. Tsilidis, K.K., et al., *Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies.* Bmj, 2015. **350**.
48. Ben, Q., et al., *Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies.* European journal of cancer, 2011. **47**(13): p. 1928-1937.
49. Wang, F., S. Gupta, and E.A. Holly, *Diabetes mellitus and pancreatic cancer in a population-based case-control study in the San Francisco Bay Area, California.* Cancer Epidemiology Biomarkers & Prevention, 2006. **15**(8): p. 1458-1463.
50. 50. Karpiński, T.M., *Role of oral microbiota in cancer development.* Microorganisms, 2019. **7**(1): p. 20.
51. Permert, J., et al., *Pancreatic cancer is associated with impaired glucose metabolism.* The European journal of surgery= Acta chirurgica, 1993. **159**(2): p. 101-107.
52. Schwartz, S., et al., *Use of a glucose controlled insulin infusion system (artificial beta cell) to control diabetes during surgery.* Diabetologia, 1979. **16**: p. 157-164.
53. Fisher, W.E., L.G. Boros, and W.J. Schirmer, *Reversal of enhanced pancreatic cancer growth in diabetes by insulin.* Surgery, 1995. **118**(2): p. 453-458.
54. Wang, G.-L., et al., *Elimination of C/EBPα through the ubiquitin-proteasome system promotes the development of liver cancer in mice.* The Journal of clinical investigation, 2010. **120**(7): p. 2549-2562.
55. Hu, F.B., et al., *Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women.* Journal of the National Cancer Institute, 1999. **91**(6): p. 542-547.
56. Will, J.C., et al., *Colorectal cancer: another complication of diabetes mellitus?* American journal of epidemiology, 1998. **147**(9): p. 816-825.
57. Renehan, A.G. and S.M. Shalet, *Diabetes, insulin therapy, and colorectal cancer*. 2005, British Medical Journal Publishing Group. p. 551-552.
58. Ma, J., et al., *A prospective study of plasma C-peptide and colorectal cancer risk in men.* Journal of the National Cancer Institute, 2004. **96**(7): p. 546-553.
59. Vigneri, P., et al., *Diabetes and cancer.* Endocrine-related cancer, 2009. **16**(4): p. 1103-1123.
60. Frayling, T., H. Colhoun, and J. Florez, *A genetic link between type 2 diabetes and prostate cancer.* Diabetologia, 2008. **51**: p. 1757-1760.
61. Luo, Z., et al., *AMPK, the metabolic syndrome and cancer.* Trends in pharmacological sciences, 2005. **26**(2): p. 69-76.
62. Algire, C., et al., *Metformin attenuates the stimulatory effect of a high-energy diet on in vivo LLC1 carcinoma growth.* Endocrine-related cancer, 2008. **15**(3): p. 833-839.
63. Buzzai, M., et al., *Systemic treatment with the antidiabetic drug metformin selectively impairs p53-deficient tumor cell growth.* Cancer research, 2007. **67**(14): p. 6745-6752.
64. Phoenix, K.N., F. Vumbaca, and K.P. Claffey, *Therapeutic metformin/AMPK activation promotes the angiogenic phenotype in the ERα negative MDA-MB-435 breast cancer model.* Breast cancer research and treatment, 2009. **113**: p. 101-111.
65. Kent, D., et al., *Reducing the risks of diabetes complications through diabetes self-management education and support.* Population health management, 2013. **16**(2): p. 74-81.

*Corresponding Author: **Sonia Javed.**