Chapter-10

# Management and Treatment of Cancer and Diabetes: A Common Corridor

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## Abstract

The escalating global prevalence of cancer and diabetes underscores the need for proactive prevention and management strategies. With nearly 20 million new cancer cases reported in 2022, and India facing a significant public health challenge with 1.46 million new cases, urgent attention is required. Diabetes, affecting over 450 million globally, sees a 13% rise in mortality rates in lower-middle-income countries from 2000 to 2019. The coexistence of cancer and diabetes in 8- 18% of patients poses treatment challenges and elevates mortality risks. Shared risk factors, including obesity, genetics, inflammation, and unhealthy lifestyles, contribute to heightened risks, emphasizing the importance of lifestyle modifications. The complex link between cancer and diabetes involves mechanisms such as hyperglycemia, insulin resistance, and elevated insulin levels. Cancer treatments may impact blood sugar levels, necessitating close monitoring and potential adjustments to diabetes medications. While concerns arise about cancer risks associated with diabetes therapies like insulin and sulfonylureas, metformin shows potential protective effects. Managing cancer patients with diabetes requires a collaborative, multidisciplinary approach, incorporating regular blood glucose monitoring, individualized treatment plans, nutritional support, exercise, and cautious steroid use. Emphasizing prevention, early detection, and supportive care, along with patient education and empowerment, is crucial. Regular follow- ups and, in some cases, palliative care contributes to a comprehensive strategy to enhance the quality of life for those navigating both cancer and diabetes.

**Keywords:** Cancer, Diabetes, Obesity, Hyperglycemia, Insulin Resistance, Sulfonylureas, Metformin, Palliative Care.

## 1. INTRODUCTION

The global incidence and prevalence of cancer and diabetes are on the rise, emphasizing the increasing impact of these health issues worldwide (1). The growing number of affected individuals underscores the urgency for heightened awareness, comprehensive prevention strategies, and innovative approaches to tackle these pervasive problems. With the ongoing escalation of these diseases, it is crucial for healthcare systems and organizations to adapt and implement effective measures to alleviate the burden on individuals and societies globally.

As per the World Health Organization (WHO), cancer stands as a prominent contributor to global mortality, causing nearly 10 million deaths and accounting for almost one-sixth of worldwide fatalities in the year 2020 (2). The year 2022 witnessed an alarming report of approximately 20 million new cancer cases globally. The magnitude of the global cancer burden underscores the critical need for the development of safer, personalized, and more efficacious treatment modalities (3).

Specifically focusing on India, cancer presents a significant public health challenge, with an estimated 1.46 million new cases reported in 2022 alone. This statistic implies that one in nine individuals in India is at risk of developing cancer during their lifetime (4).

The prevalence of diabetes has seen a significant surge over the years, escalating from 108 million individuals in 1980 to a staggering 422 million in 2014 (5). By 2017, the estimate rose even higher, surpassing 450 million people globally living with diabetes (6, 7). Notably, between 2000 and 2019, there was a 3% increase in age- standardized mortality rates attributed to diabetes. Lower-middle-income countries experienced a particularly notable spike, with a 13% increase in the mortality rate associated with diabetes during this period. Adding to this global concern, the Indian Council of Medical Research - India Diabetes (ICMR INDIAB) study, published in 2023, revealed a significant prevalence of diabetes in India, reaching 100 million individuals (8).

## 2. EPIDEMIOLOGICAL COEXISTENCE OF CANCER AND DIABETES

The link between diabetes and cancer has been under investigation for over a century, revealing a frequent coexistence and a global increase in their incidence and prevalence (9). Approximately 8% to 18% of cancer patients also have diabetes, with both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) showing elevated cancer risks, particularly in T2DM cases

involving liver, pancreatic, and endometrial cancers (10, 11, 12). Extensive meta-analyses confirm a roughly 10% higher risk of cancer in individuals with T2DM, and an umbrella review of 27 meta- analyses supports a 10% relative risk of cancer associated with type 2 diabetes (13). Research establishes connections between T2DM and increased risks across various cancer types, including gastrointestinal, pancreas, kidney, liver, lung, breast, etc. (13, 14, 15, 16). A focused meta-analysis on women reveals a 1.27 relative risk for breast cancer in those with diabetes, while women with T1DM display a significantly lower risk (17). Notably, approximately 60% of cancer patients are aged 65 or older, and around 25% of individuals in the same age group develop diabetes mellitus (18).

Research indicates that individuals facing both cancer and diabetes confront heightened cancer-related mortality, coupled with an increased susceptibility to diverse infections and associated morbidity and mortality in those with diabetes (19, 20). Generally, individuals with diabetes demonstrate an annual mortality rate twice that of the general population within a comparable age range (21, 22). Prior extensive meta-analyses estimate a 25%-41% elevated risk of mortality from any cancer in individuals with diabetes (23). Specifically, an analysis spanning 19 Asian cohorts over 21 years disclosed a 26% rise in the risk of cancer-related mortality linked to type 2 diabetes mellitus (24).

## 3. COMMON RISK FACTOR

Type 1 diabetes is a persistent autoimmune condition where the immune system erroneously targets and destroys insulin-producing beta cells in the pancreas. Insulin, vital for regulating blood sugar levels, becomes deficient, hindering the proper conversion of glucose from food into energy. Typically emerging before age 30 and often diagnosed in childhood or adolescence, the exact cause is not entirely known, but a blend of genetic and environmental factors is implicated, unrelated to lifestyle or diet. The mainstay treatment is insulin therapy, involving regular injections or insulin pump use to manage blood sugar. Managing Type 1 diabetes entails not only insulin but also adopting a health-conscious lifestyle, encompassing a balanced diet, regular exercise, and stress management.

Type 2 diabetes is a persistent metabolic disorder marked by insulin resistance, where the body's cells exhibit an inadequate response to insulin, coupled with a relative insulin deficiency. It typically manifests later in life, though onset can occur at any age, and is frequently linked to lifestyle factors like sedentary habits, an unhealthy diet, and obesity. The primary causes involve a combination of genetic predisposition, with certain ethnic groups

having a higher susceptibility, and lifestyle choices such as poor dietary habits and insufficient physical activity. In contrast to Type 1 diabetes, Type 2 diabetes still involves insulin production, but the body's cells develop resistance to its effects, leading to elevated blood sugar levels.

The majority of individuals diagnosed with diabetes have Type 2 diabetes, with only a small percentage, approximately 5-10%, having Type 1 diabetes. Additionally, diabetes can arise as a secondary condition due to certain medications or underlying illnesses (1). It's important to recognize that diabetes encompasses various forms and can result from different factors, including both primary and secondary causes.

Cancer comprises a diverse and intricate group of diseases characterized by the uncontrolled and abnormal growth of cells, leading to the potential invasion and destruction of surrounding tissues. This unregulated proliferation disrupts the normal cell replacement process, forming either benign or malignant tumors. The causes of cancer are multifaceted, involving genetic predisposition, environmental factors, and lifestyle choices. Genetic mutations, though sometimes inherited, usually interact with environmental influences. Carcinogen exposure, unhealthy habits like smoking and poor diet, advancing age, infections, hormonal imbalances, and weakened immune systems are among the contributing factors. Understanding these complexities is vital for prevention and effective cancer management through lifestyle adjustments, regular screenings, and minimizing exposure to known risk factors.

Cancer and diabetes are separate medical conditions with unique origins, yet they share common risk factors that can increase the likelihood of developing both diseases. It's crucial to emphasize that the presence of one condition does not necessarily cause the other, but overlapping risk factors contribute to the elevated risk of both cancer and diabetes. Some shared risk factors include obesity, genetic factors, inflammation, hormonal factors, insulin resistance, microbiome, aging, and unhealthy life style (unhealthy diet, physical inactivity, alcohol and smoking) (25).

Recognizing and addressing these factors through lifestyle modifications can play a key role in reducing the risk of both conditions. Regular screenings and medical check-ups are also important for early detection and effective management. Some common risk factors discussed below:

**Obesity**

The connection between obesity, Type 2 diabetes, and increased cancer risk is growing more apparent as these conditions become more prevalent. Both

obesity and Type 2 diabetes are linked to metabolic abnormalities like insulin resistance and dyslipidemia, contributing to their association with cancer (26). Obesity, a notable risk factor for Type 2 diabetes and various cancers (breast, colorectal, pancreatic etc.), involves adipose tissue producing hormones and growth factors that foster inflammation and cell proliferation (27, 28).

Complex mechanisms underlie the link between obesity, diabetes, and cancer. These mechanisms include modifications to adipokine and cytokine profiles, insulin/IGF-1 signaling, lipid and glucose metabolism, and adipose tissue located in close proximity to cancer sites. By overlapping processes such as hormone imbalance, cellular proliferation and inflammation, obesity may impact the relationship between Type 2 diabetes and cancer (12, 29).

**Unhealthy Life Style**

Engaging in an unhealthy lifestyle marked by factors such as an imbalanced diet, physical inactivity, alcohol consumption, and smoking serves as a shared risk for both diabetes and cancer.

Unfavorable dietary choices, insufficient exercise, excessive alcohol use, and smoking contribute to the onset of conditions like Type 2 diabetes and various cancer types. These lifestyle elements can lead to obesity, insulin resistance, inflammation, and hormonal imbalances, fostering an environment conducive to both diseases.

Studies indicate that diets high in foods with a high glycemic index or load are linked to an increased risk of Type 2 diabetes and certain cancers (30, 31). Conversely, diets rich in vegetables, fruits, and whole grains are associated with a lower risk of cancer (32, 33). Plant-based dietary patterns are gaining recognition for their potential in reducing the risk of several chronic diseases, including Type 2 diabetes and cancer (34). A diet rich in fruits, vegetables, whole grains, and lean proteins is generally recommended for reducing the risk of both diseases.

Regular **physical activity** plays a vital role in maintaining a healthy weight, improving insulin sensitivity, and reducing inflammation, thereby lowering the risk of diabetes and certain cancers (35, 36).

**Smoking** is a major contributor to lung cancer, while **alcohol** consumption is associated with liver cirrhosis, certain cancers, and cardiovascular diseases (37, 38). The International Agency for Research on Cancer (IARC) has designated alcohol as a carcinogen specifically for the liver (39). Engaging in alcohol consumption is linked to an increased risk of

developing significant noncommunicable diseases, including liver cirrhosis, specific types of cancers, and cardiovascular diseases (40). For diabetics, alcohol intake can exacerbate blood sugar control issues (41).

In essence, adopting a health-conscious lifestyle, encompassing balanced nutrition, regular exercise, and avoidance of harmful habits, is essential for mitigating the risk of diabetes and cancer, emphasizing the interconnected nature of lifestyle choices in promoting overall well-being. It's crucial for individuals to be aware of these shared risk factors and adopt a healthy lifestyle, including regular physical activity, a balanced diet, and weight management, to reduce the risk of both cancer and diabetes. Regular medical check-ups and screenings can also aid in the early detection and management of these conditions.

### Genetic Factors

Genetic factors play a central role in the development of cancer and diabetes, influencing susceptibility to these conditions. Individuals with a history of cancer are notably more likely to develop diabetes, highlighting a complex connection between the two diseases (42). The interplay of shared genetic factors, along with diverse lifestyle and clinical elements, poses challenges in definitively determining whether the association is causal or influenced by confounding factors. Distinct genetic mutations, such as BRCA1 and BRCA2 in breast and ovarian cancers, or TP53 mutations in various cancers like lung and colorectal, contribute to an elevated risk of cancer. Similarly, diabetes shows a genetic component, with specific gene variants impacting insulin resistance, beta-cell function, and glucose metabolism, particularly in Type 2 diabetes. Instances occur where genetic factors simultaneously contribute to the risk of both cancer and diabetes within individuals or families, with certain variations influencing insulin regulation and cell growth. The involvement of the transforming growth factor-beta (TGFB) signaling pathway, specifically the regulatory function of the TGFB1 gene in the SMAD pathway, further underscores the intricate association between diabetes and cancer (43).

## 4. LINK BETWEEN CANCER AND DIABETES: UNDERLINE MECHANISM

Having diabetes increases the risk of specific solid cancers, including those affecting the pancreas, liver, colon, and breast (11). The elevated risk is associated with various factors such as high blood sugar (hyperglycemia), insulin resistance, heightened insulin and insulin-like growth factor-1 (IGF-1) levels, inflammatory cytokines, dyslipidemia, increased leptin, and reduced adiponectin. These metabolic and hormonal changes in individuals with

diabetes are linked to the heightened susceptibility to certain types of cancer (44).

The link between cancer and diabetes involves intricate mechanisms that connect these two conditions. While the relationship is multifaceted and not fully understood, several key mechanisms contribute to the association:

**Hyperglycemia**

High blood sugar levels, a characteristic of diabetes, can create an environment that favors cancer cell growth. Hyperglycemia may influence the development and progression of certain cancers.

Various reports indicate a heightened risk of colorectal, liver, gastric, lung, and pancreatic cancers associated with elevated blood sugar levels, known as hyperglycemia (45, 46). This condition triggers the production of advanced glycation end products (AGEs), which, upon interaction with their receptor (RAGE), activate NF-κB and induce the generation of reactive oxygen species (ROS) within cells. This process intensifies oxidative stress, leading to an increase in proinflammatory signaling (47, 48). The activation of the AGEs pathway has been observed to facilitate the transformation of epithelial cells, promoting tumor development (59, 50, 51). Additionally, hyperglycemia contributes to DNA damage, marking the initial stage in the process of tumorigenesis (52).

**Insulin Resistance and Hyperinsulinemia**

Insulin resistance, a common feature of Type 2 diabetes, leads to elevated insulin levels in the bloodstream. Increased insulin levels may promote cell growth and proliferation, potentially contributing to cancer development.

Increased insulin levels (hyperinsulinemia) resulting from insulin resistance, elevated blood sugar, oxidative stress, and inflammatory cytokines play a crucial role in the origin of various cancers, including those affecting the ovaries, breasts, colon, pancreas, kidneys etc. (53, 54, 55). Elevated glucose levels further contribute to the growth of solid tumor cell lines (56, 57). In individuals with type 2 diabetes, chronic hyperinsulinemia triggers the insulin/insulin-like growth factor-1 (IGF-1) signaling, activating the PI3K/Akt/mTOR pathway. This pathway governs numerous metabolic and mitogenic effects of insulin, influencing cancer cell survival, proliferation, invasion, migration, and metastasis (58, 59).

The interconnection between diabetes and cancer highlights the potential for combining immunotherapy with metabolic interventions to enhance the effectiveness of anticancer therapy (60).

## 5. CANCER THERAPY AND DIABETES

Certain cancer treatments, specifically some forms of chemotherapy and targeted therapies, carry side effects that can influence blood sugar levels, potentially resulting in the development of diabetes or worsening pre-existing diabetes. The utilization of new cancer therapies or simultaneous steroid administration may unveil latent diabetes or induce secondary diabetes (61).

Some specific **Chemotherapy Drugs** can induce insulin resistance, leading to elevated blood sugar levels. Many chemotherapeutic agents target rapidly dividing cells, causing damage to the cell cycle or cellular DNA and triggering apoptosis. **Steroid Therapy**, commonly integrated into cancer treatment regimens, may induce or worsen diabetes, with prolonged use potentially contributing to diabetes onset (62).

**Glucocorticoids**, often used in blood system cancer treatments, induce insulin resistance through mechanisms such as increasing serum fatty acid levels and directly affecting components of the insulin signaling cascade (63, 64). Furthermore, glucocorticoids reduce insulin sensitivity by directly affecting components of the insulin signaling cascade, including glycogen synthase kinase-3, glycogen synthase, and GLUT4 translocation (65, 66).

**Corticosteroids**, a key component in some cancer treatments, elevate blood sugar levels and induce insulin resistance, resulting in hyperglycemia. Patients treated with glucocorticoids generally have an odds ratio of 1.5 to 2.5 for new-onset diabetes mellitus (67).

**Androgen-Deprivation Therapy** (ADT) for prostate cancer, utilizing luteinizing hormone releasing hormone agonists, is associated with an elevated risk of type 2 diabetes, possibly due to insulin sensitivity loss and hormonal effects (62).

**Cancer Immunotherapies**, encompassing immune checkpoint inhibitors, adoptive cell therapy, oncolytic viruses, and cancer vaccines, manipulate the immune system to target and combat cancer cells. Specific immunotherapies, like PD/PD-L and CTLA-4 inhibitors, may reduce insulin production akin to type 1 diabetes, while targeted treatments such as PI3K/mTOR inhibitors can induce insulin resistance resembling type 2 diabetes (68).

**Targeted Cancer Therapies** focus on modifying cellular pathways driving uncontrolled growth by influencing abnormal signaling pathways or proteins in malignant cells (69). The frequently activated PI3K/Akt/mTOR pathway in solid cancers is affected by PI3K/mTOR pathway inhibition, resulting in insulin resistance (70).

**Radiation therapy** to the abdomen or pancreas poses a risk to insulin-producing cells, potentially disrupting the body's ability to regulate blood sugar.

It's important for individuals undergoing cancer treatment to be monitored closely for changes in blood sugar levels, and healthcare providers will often assess and manage any diabetes- related complications. Patients with pre-existing diabetes may need adjustments to their diabetes medications during cancer treatment.

Patients should communicate any concerns or symptoms to their healthcare team promptly, and regular check-ups and screenings may be recommended to monitor for diabetes or related complications. Lifestyle modifications, such as a healthy diet and regular exercise, may also be beneficial in managing blood sugar levels during and after cancer treatment.

## 6. DIABETES TREATMENT AND CANCER

There is no conclusive evidence suggesting that standard diabetes therapies or drugs directly cause cancer. However, the relationship between diabetes medications and cancer risk is a complex and evolving area of research.

Certain investigations have prompted worries regarding the potential correlation between the utilization of **insulin or insulin analogs** and specific cancers, especially in individuals diagnosed with type 2 diabetes. Numerous observational studies indicate a potential link between insulin therapy and an elevated risk of cancer development. Notably, insulin analogs like insulin glargine have been implicated, potentially attributed to their heightened binding affinity for the IGF-1 receptor. However, the evidence supporting insulin-induced mitogenicity remains highly controversial (66).

**Sulfonylureas** represent a category of oral medications prescribed for diabetes management. Earlier research findings have pointed to a heightened occurrence of cancer and an elevated risk of cancer-related mortality, particularly in pancreatic and breast cancer patients undergoing sulfonylurea therapy (71). Several investigations have hinted at a potential association between prolonged sulfonylurea use and an augmented risk of specific cancer types.

**Metformin,** extensively prescribed for type 2 diabetes, is often a frontline or combined treatment (72). Research suggests metformin's potential protective role against specific cancers, impacting cell growth and inflammation, as evidenced in laboratory studies with cancer cell lines (73). While the precise mechanism in diabetes remains incompletely understood, metformin typically reduces circulating glucose and insulin levels in individuals with insulin resistance. This effect is primarily attributed to decreased hepatic glucose output (74). The anticancer mechanism involves metformin-induced activation of AMP kinase in epithelial cells, stimulating growth inhibitory and protein synthesis pathways. AMPK activation significantly lowers cancer risk and inhibits cell proliferation, potentially through regulating the cell cycle and protein synthesis (75).

The relationship between the use of **Thiazolidinediones** (TZDs) and the risk of cancer is complex and not fully elucidated. Thiazolidinediones (TZDs) act as insulin sensitizers through peroxisome proliferator-activated receptor-gamma (PPARg), enhancing lipid and glucose metabolism (76). They show strong insulin-sensitizing effects by activating PPARs. In vitro research implies potential anti-cancer characteristics of TZDs, including the inhibition of cell growth, induction of apoptosis, and promotion of cell differentiation (77). Nonetheless, specific animal data raises the possibility that PPAR agonists, including TZDs, could potentially contribute to the enhancement of tumorigenesis (78).

## 7. MANAGEMENT OF CANCER PATIENT WITH DIABETES

The management of cancer patients with diabetes involves a multidisciplinary approach to address the complexities of both conditions. Here are key aspects of their management:

1. **Collaborative Care:** A collaborative approach between oncologists and endocrinologists is essential. Regular communication and coordination between healthcare providers are crucial to optimize cancer treatment and diabetes management.

2. **Blood Glucose Monitoring:** Regular monitoring of blood glucose levels is fundamental. Cancer treatments and medications may influence blood sugar, requiring adjustments to diabetes medications.

3. **Individualized Treatment Plans:** Tailoring cancer treatment plans to accommodate the patient's diabetes is important. Some cancer therapies, such as steroids or certain chemotherapies, can affect blood sugar levels.

4. **Nutritional Support:** Nutrition plays a vital role in managing both cancer and diabetes. Individualized dietary plans considering the nutritional needs of the patient and glycemic control are essential.

5. **Exercise and Physical Activity:** Incorporating physical activity into the patient's routine, based on their health status, is beneficial for both cancer and diabetes management. Exercise can help improve insulin sensitivity and overall well-being.

6. **Medication Adjustments:** Some diabetes medications may need adjustments during cancer treatment. For example, insulin dosages may need modification based on the impact of cancer therapies on blood sugar levels.

7. **Cautious Use of Steroids:** Steroids, commonly used in cancer treatment, can lead to elevated blood sugar levels. Careful monitoring and management of diabetes medications may be necessary during steroid therapy.

8. **Prevention and Early Detection:** Cancer patients with diabetes should be vigilant about preventive measures, such as cancer screenings and vaccinations, to minimize the risk of infections.

9. **Supportive Care:** Providing psychological and emotional support is crucial for cancer patients with diabetes. The stress of managing both conditions simultaneously can impact the patient's overall well-being.

10. **Education and Empowerment:** Patient education is vital. Empowering the patient with knowledge about their conditions, medications, and self-management strategies fosters active participation in their care.

11. **Regular Follow-ups:** Regular follow-up appointments with healthcare providers are essential to monitor both cancer and diabetes, assess treatment responses, and make necessary adjustments to the care plan.

12. **Palliative Care:** In cases where curative treatment may not be possible, palliative care focuses on improving the patient's quality of life. This includes effective pain management and addressing symptoms related to both cancer and diabetes.

Each patient's situation is unique, and the management approach should be individualized based on the specific characteristics of their cancer, the type of diabetes, and other relevant factors. Therefore, close collaboration between healthcare providers and open communication with the patient are key components of effective management.

## 8. CONCLUSION

The increasing global prevalence of cancer and diabetes necessitates urgent attention to develop proactive prevention and management strategies. With nearly 20 million new cancer cases reported in 2022, and India facing a significant public health challenge with 1.46 million new cases, coupled with diabetes affecting over 450 million globally, the coexistence of both conditions in 8-18% of patients emphasizes the need for comprehensive approaches. Shared risk factors, including obesity, genetics, inflammation, and unhealthy lifestyles, underscore the importance of lifestyle modifications. The intricate link between cancer and diabetes involves mechanisms such as hyperglycemia, insulin resistance, and elevated insulin levels. Collaborative, multidisciplinary approaches are crucial for managing cancer patients with diabetes, encompassing regular blood glucose monitoring, individualized treatment plans, nutritional support, exercise, and cautious steroid use. Emphasizing prevention, early detection, and supportive care, along with patient education and empowerment, contributes to a comprehensive strategy to enhance the quality of life for individuals navigating both cancer and diabetes.

## 9. FUTURE PROSPECTIVE

The complex interplay between cancer and diabetes warrants continuous research to unravel underlying mechanisms and improve management strategies. Future studies should delve deeper into the genetic factors influencing susceptibility to both diseases, allowing for targeted interventions. Advances in personalized medicine and the development of safer and more effective cancer treatments should be prioritized. Additionally, investigations into the impact of emerging cancer therapies on blood sugar levels and diabetes risk are essential for refining treatment protocols. Further exploration of the potential protective effects of diabetes medications, such as metformin, against certain cancers, and addressing concerns about cancer risks associated with insulin and sulfonylureas, will contribute to optimizing diabetes management in cancer patients. A holistic approach, integrating mental health support and palliative care, should be emphasized to enhance the overall well-being of individuals navigating the complex intersection of cancer and diabetes.

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