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Exploring the Link between Diabetes Mellitus and Cancer Risk: A Systematic Review of the Evidence

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ABSTRACT

Diabetes mellitus (DM) is a common endocrine disorder that affects people worldwide. A significant body of clinical research has investigated the association between diabetes and cancer and has investigated potential causative factors. This review examined recent literature on the cancer risk in people with DM. Databases such as PubMed, Science Direct, Web of Science, EBSCO, and the Cochrane Library were searched. Articles were screened based on titles and abstracts using Rayyan QCRI, followed by a full-text evaluation. A total of 15 studies involving 1,080,106 diabetic patients with various types of cancer were included. Most studies found that DM is associated with an increased risk of cancer; however, some reported a lower risk for prostate cancer. This review highlights the potential association between diabetes and cancer, but many findings remain unclear and contradictory, emphasizing the need for further research to clarify the relationship between the two conditions.

Keywords: Cancer, Malignancy, Diabetes mellitus, Systematic review

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Introduction

Diabetes is the sixth leading cause of death globally and ranks as one of the most widespread chronic conditions, trailing only cardiovascular diseases (WHO). Diabetes mellitus (DM) is a complex disorder marked by insulin resistance and impaired regulation of blood glucose. Its causes are multifactorial, and it is categorized into two primary types: type 1 and type 2. Type 1 diabetes, also referred to as insulin-dependent or juvenile diabetes, results from the destruction of pancreatic beta cells, leading to a lack of insulin production. This form of diabetes typically manifests in children, adolescents, and young adults. On the other hand, type 2 diabetes (T2DM), often referred to as adult-onset diabetes, occurs when the body's cells or tissues become resistant to insulin [1].

Epidemiological studies have highlighted a connection between diabetes and an increased risk of various cancers in different parts of the body. However, only a few studies have provided robust evidence supporting this association [2]. A thorough meta-analysis of observational studies examining the link between diabetes and cancer at different anatomical sites found clear evidence only for cancers of the breast, endometrium, and colon [3].

The mechanisms linking diabetes to cancer are still being explored, but experimental studies suggest that factors such as high blood sugar, excessive insulin production, insulin resistance, and chronic inflammation play important roles [4]. Several studies have suggested that increased insulin levels might correlate with an elevated risk of certain cancers. Additionally, research on fasting blood glucose and glycated hemoglobin (HbA1c) has indicated that high glucose levels could contribute to cancer risk [5, 6]. HbA1c is particularly useful as it reflects average glucose levels over a two- to three-month period, is not influenced by daily glucose fluctuations, and can be measured without fasting [7].

The molecular mechanisms behind the diabetes-cancer relationship involve factors like sex hormones, hyperglycemia, inflammatory cytokines, and insulin resistance, all of which can contribute to cancer development [8]. Insulin is a growth-promoting factor that can directly encourage tumor formation by activating insulin receptors in tissues. It may also promote cancer indirectly by increasing levels of insulin-like growth factor I (IGF-I), a protein that stimulates the growth of preneoplastic and neoplastic cells. Furthermore, elevated insulin and IGF-I levels in diabetes lead to decreased production of sex hormone-binding globulin (SHBG), resulting in increased levels of free estradiol and testosterone, especially in women [9, 10].

The rising prevalence of diabetes mellitus (DM) and its correlation with the growing global cancer burden have led to increased interest in understanding the epidemiological and molecular connections between these two conditions. Despite a growing body of research, many of the findings remain inconclusive and contradictory, indicating the need for further studies to clarify the true relationship between diabetes and cancer. This systematic review aims to examine the most recent studies on the risk of cancer development in individuals with diabetes.

Materials and Methods

This review was conducted following the established guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Study design

This review is classified as a systematic review.

Study duration

The review focuses on studies published between November and December 2022.

Study condition

The scope of this review is limited to examining studies published recently that discuss the risk of cancer in patients with diabetes mellitus.

Search strategy

A comprehensive search strategy was employed, covering five major databases: PubMed, Web of Science, Science Direct, EBSCO, and the Cochrane Library. The search was confined to articles in English, and specific modifications were made for each database. Relevant studies were identified using a combination of keywords, including “Diabetes mellitus,” “DM,” “Type 1 diabetes mellitus,” “T1DM,” “Type 2 diabetes mellitus,” “T2DM,” “Insulin-dependent diabetes mellitus,” “IDDM,” “Non-insulin-dependent diabetes mellitus,” “NIDDM,” “Cancer,” “Carcinoma,” “Tumor,” “Malignancy,” “Hazard,” and “Risk,” combined with logical operators such as “AND” and “OR.” Only studies that were full-text, available for free, and involved human trials were included.

Selection criteria

Inclusion criteria

Studies were selected based on their relevance to the research focus, which included diabetic patients diagnosed with any type of cancer. Only articles published within the last five years were considered.

Exclusion criteria

Research articles that were duplicate publications, reviews, or studies that did not align with the main focus were excluded from the review.

Data extraction

Rayyan (QCRI) [11] was used to identify and remove duplicate records from the search results. The research team then reviewed the titles and abstracts to determine their relevance according to the inclusion and exclusion criteria. Full texts of studies meeting the inclusion requirements were further assessed. Discrepancies were resolved through discussion. A standardized data extraction form was created to collect key details such as study title, authors, publication year, design, sample size, participant demographics (including gender), type of diabetes, type of cancer, and primary findings.

Risk of bias assessment

The risk of bias in the included studies was evaluated using the ROBINS-I tool, specifically designed for non-randomized studies [12]. Any identified issues with the quality assessment were addressed by the review team.

Data synthesis strategy

Summary tables were compiled to present a qualitative overview of the results from the selected studies. After completing data extraction, decisions were made about how best to interpret and synthesize the data. Studies that met the inclusion criteria but lacked relevant data on the link between DM and cancer development were excluded from further analysis.

Results and Discussion

Search results

The initial search resulted in 844 studies. After eliminating 97 duplicates, 747 studies were screened based on their titles and abstracts. This led to the exclusion of 480 studies. A total of 267 articles were then requested for full-text retrieval, although 10 articles were not available. Out of the remaining 257 articles, 135 were excluded due to irrelevant study outcomes, 80 were excluded for lacking information on the impact of MRI on pancreatic cancer, and 27 were removed for including the wrong population group. Ultimately, 15 studies met the inclusion criteria and were selected for the systematic review. The study selection process is summarized in **Figure 1**.

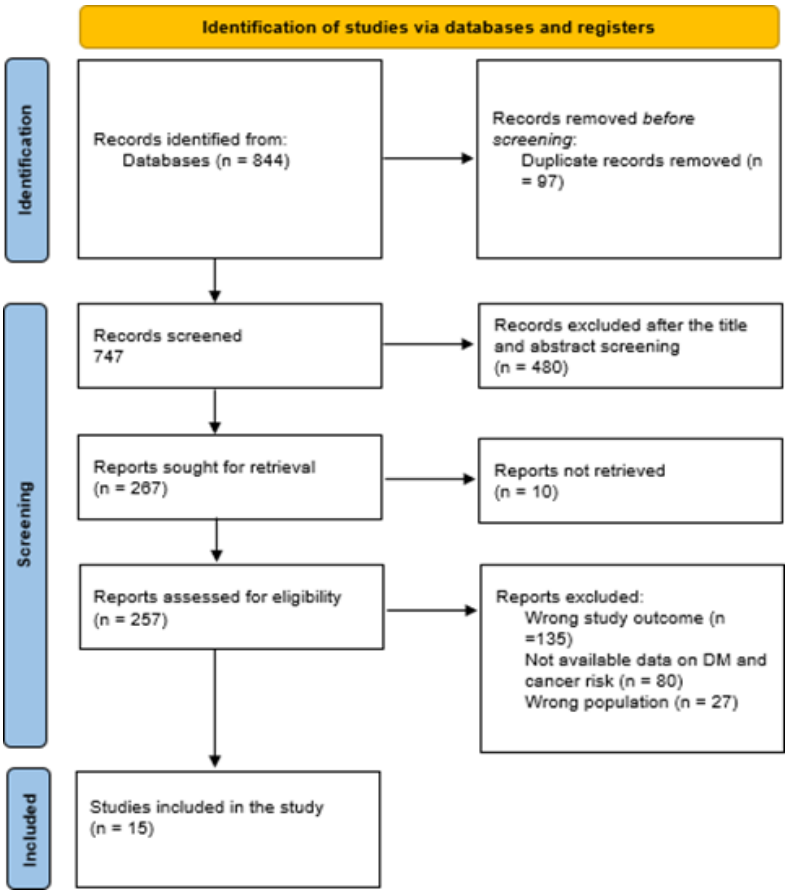

Figure 1. The PRISMA flowchart summarizes the study selection process

Characteristics of the included studies

A total of 15 studies were included in this review, encompassing 1,080,106 diabetic patients who developed various types of cancer. The studies were conducted across multiple countries: 7 in the USA [13-19], 2 in China [20, 21], and 1 each in Canada [22], Australia [23], Lithuania [24], Poland [25], Finland [26], and the UK [27].

Regarding study designs, 8 were retrospective [13, 16, 19, 20, 22, 24-26], 4 were prospective [14, 17, 23, 27], and 2 were case-control studies [15, 21]. 7 studies focused on patients with type 2 diabetes mellitus (T2DM) [16-19, 23-25], 2 included patients with type 1 diabetes mellitus (T1DM) [26, 27], and 6 included both T1DM and T2DM patients [13-15, 20-22].

The cancers studied varied across the included studies: lung cancer [13, 19], prostate cancer [16, 22], thyroid cancer [21, 26], colorectal cancer [18, 25], multiple cancer types [14, 27], biliary tract cancer (BTC) [20], breast cancer [15], pancreatic cancer [23], endometrial cancer [24], and bladder cancer [17].

Most studies indicated that DM is associated with an increased risk of developing cancer **(Table 1)**. However, two studies found that DM was linked to a lower risk of prostate cancer [14, 22]. Additionally, some studies reported no association between diabetes and the incidence of lung cancer [13], thyroid cancer [21], and bladder cancer [17].

Table 1. Overview of the characteristics of included studies

Study	Study design	Country	Total participants	Male (%)	Mean age (years)	Type of DM	Cancer type	Key findings	ROBINS-I
Leiter *et al.* [13]	Retrospective cohort	USA	10,819	56	59-68 (range)	T1DM and T2DM	Lung cancer	No correlation was found between diabetes and lung cancer incidence, nor with lung cancer histology.	Moderate

Park *et al.* [20]	Retrospective cohort	China	829,032	61.4	57.2 ± 12.0	T1DM and T2DM	Biliary tract cancer (BTC)	A strong association between diabetes and an elevated risk of BTC, with longer diabetes duration increasing the risk.	High
Peila *et al.* [14]	Prospective cohort	USA	25,544	61.2	59.4 ± 7.3	T1DM and T2DM	Multiple cancers (esophageal, stomach, colon, liver, pancreatic, bladder, kidney, endometrial, lung, prostate)	Diabetes is linked to an increased risk of most cancers, except for a decreased risk of prostate cancer.	Moderate
Chen *et al.* [22]	Retrospective cohort	Canada	80,001	100	64.7 ± 9.4	T1DM and T2DM	Prostate cancer	Diabetes is associated with a reduced risk of prostate cancer.	High
Wang *et al.* [21]	Case-control	China	2,937	23	49.27 ± 1.19	T1DM and T2DM	Thyroid cancer	No overall association between diabetes and thyroid cancer, but factors like age, sex, BMI, and family history modify the risk.	High
Parada *et al.* [15]	Case-control	USA	1,508	0	59	T1DM and T2DM	Breast cancer	Genetic variations that increase diabetes risk also increase the risk of breast cancer (BC) development and mortality.	High
Davis *et al.* [23]	Prospective cohort	Australia	1,291	48.7	64.0 ± 11.2	T2DM	Pancreatic cancer	T2DM is associated with double the risk of developing pancreatic cancer.	High
Zhu *et al.* [16]	Retrospective cohort	USA	1,303	100	60 ± 6.9	T2DM	Prostate cancer	Obesity and diabetes are independently associated with high-risk prostate cancer.	High
Zabuliene *et al.* [24]	Retrospective cohort	Lithuania	77,708	0	40-70 (range)	T2DM	Endometrial cancer	Diabetic women are at a significantly higher risk of developing endometrial cancer compared to the general population.	Moderate
Miłek *et al.* [25]	Retrospective cohort	Poland	967	47.5	65	T2DM	Colorectal cancer	The prevalence of colorectal adenomas is significantly associated with T2DM.	Moderate
Li *et al.* [17]	Prospective cohort	USA	8,381	0	50-79 (range)	T2DM	Bladder cancer	No correlation was found between diabetes, diabetes duration, or treatment with bladder cancer risk among postmenopausal women.	High

Ma *et al.* [18]	Prospective cohort	USA	3,000	40.3	67.7 ± 9.4	T2DM	Colorectal cancer	Men with T2DM have a slightly higher risk of developing colorectal cancer, with a weaker association in women.	Moderate
Kim *et al.* [19]	Retrospective cohort	USA	14,133	*	55 ± 7.7	T2DM	Lung cancer	Those without diabetes had a lower risk of lung cancer, particularly among male smokers and female nonsmokers.	Moderate
Mäkimattila *et al.* [26]	Retrospective cohort	Finland	4,758	*	42.6-60.1 (range)	T1DM	Thyroid cancer	T1DM individuals have a 2.7 times higher prevalence of thyroid cancer, with poor glycemic control linked to increased risk.	High
Fredriksson *et al.* [27]	Prospective cohort	UK	18,724	52.8	20-35	T1DM	Various types of cancer	Women with childhood-onset T1DM have a slightly higher cancer risk, while men show no such trend.	Moderate

Diabetes and cancer are two chronic conditions with rising global prevalence. The relationship between these two diseases, both from an epidemiological and physiological perspective, has been increasingly recognized. Type 2 diabetes (T2DM) in particular is strongly associated with a higher risk of developing a variety of cancers [28].

This review reveals that many cancer cases in patients with T2DM have been documented. In the early stages of T2DM, insulin resistance occurs, leading to hyperinsulinemia, which plays a significant role in tumor progression. Hyperinsulinemia promotes tumor growth by activating insulin receptors directly on cancer cells, as well as indirectly via the insulin-like growth factor 1 (IGF-1) receptor. Many cancer cells express both insulin and IGF-1 receptors, which promote cell growth, reduce cell death (apoptosis), increase cell movement, and enhance the ability of cells to invade surrounding tissues [29, 30].

As a result, exogenous insulin or high endogenous insulin levels may contribute to the development of cancers. This is supported by a recent meta-analysis indicating that high insulin or C-peptide levels are strongly associated with a greater risk of several types of cancer [31].

Diabetes is linked with an increased risk of various cancer types, including lung, biliary tract cancer (BTC), esophageal, stomach, colorectal, liver, pancreatic, bladder, kidney, endometrial, and breast cancers. Specifically, diabetes and poor glucose tolerance are implicated in approximately 80% of pancreatic cancer cases [32]. A meta-analysis of 88 cohort studies showed that individuals with diabetes have a 94% greater chance of developing pancreatic cancer compared to those without diabetes [33]. The relationship between diabetes and pancreatic cancer is complex, with impaired glucose metabolism potentially playing a role in cancer development.

The connection between diabetes and stomach cancer has been inconsistent in various studies. However, a meta-analysis of 22 cohort studies involving over 8.5 million people found that diabetes significantly increases the risk of stomach cancer, especially in men [34]. Research by Lin *et al*. suggests that hyperglycemia may cause an imbalance in energy metabolism and immune system dysfunction, both of which can contribute to gastric cancer [35].

The relationship between diabetes and colorectal cancer (CRC) has been extensively studied, and numerous meta-analyses have confirmed a strong association between T2DM and an elevated risk of CRC. A synthesis of eight studies revealed a 1.21-fold increased risk of CRC in individuals with T2DM [36]. While the biological mechanisms are not fully understood, it is believed that factors such as hyperglycemia, insulin resistance, and IGF signaling contribute to the progression of CRC.

For women, the evidence indicates that diabetes is associated with a higher risk of breast cancer, a leading cause of morbidity and mortality worldwide. Diabetes-related factors such as insulin resistance, hyperinsulinemia, and

alterations in hormone signaling may influence the risk of breast cancer. Studies suggest that women with T2DM have a 20% higher risk of developing breast cancer [37, 38]. Additionally, a meta-analysis by Hardefeldt *et al*. found that women with diabetes are at a significantly higher risk of breast cancer compared to those without diabetes [39].

Two studies have indicated that diabetes mellitus (DM) is linked to a reduced risk of prostate cancer. The relationship between prostate cancer and diabetes, as well as other types of cancer, has produced varied outcomes. A meta-analysis by Kasper and Giovannucci [40] found that men with diabetes had a significantly lower risk of developing prostate cancer. These conflicting results may be attributed to lower levels of testosterone and sex hormone-binding globulin (SHBG) in men with diabetes [41]. To minimize biases related to cancer staging and risk, Lee *et al*. [42] conducted a meta-analysis that focused on the mortality rate of prostate cancer in men already diagnosed with diabetes. In their analysis, no statistically significant association was found between pre-existing T2DM and prostate cancer mortality when considering subgroups of individuals with T2DM. Given the heterogeneity of the results, further studies are necessary to clarify the relationship between diabetes and prostate cancer.

While the biological mechanisms linking diabetes to cancer remain poorly understood, there is a clear association between diabetes and a higher incidence of various cancers. The global increase in diabetes rates, particularly due to rising obesity and an aging population, is expected to accelerate the incidence and mortality of cancer worldwide. Additionally, healthcare providers must recognize that individuals with diabetes are at greater risk of developing cancer and encourage appropriate cancer screenings and preventive measures [43].

Preventive strategies, including weight management and lifestyle modifications, will play a key role in improving the outcomes for individuals with both diabetes and cancer. Moreover, governments and international health organizations should implement policies to foster environments that promote healthy diets and lifestyles, thus helping reduce the global burden of diabetes and cancer while improving overall public health [43].

Conclusion

This review highlights the increased risk of cancer in individuals with diabetes, as evidenced by the studies included. Most studies reported that diabetes increases the likelihood of developing cancer; however, it was also noted that diabetes is associated with a reduced risk of prostate cancer. The exact causal relationship between diabetes and cancer remains unclear, and further research is needed to definitively determine how diabetes contributes to cancer development.

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