

# Diabetes Mellitus as a Risk Factor for Different Types of Cancers: A Systematic Review

## Abstract

Diabetes mellitus (DM) is a common endocrine condition that affects people all over the world. Numerous clinical research has looked into the relationship between diabetes and cancer and how it may be caused. This review investigates the recently published literature regarding the risk of the development of cancer in patients with DM. PubMed, Web of Science, Science Direct, EBSCO, and Cochrane library were searched. Study articles were screened by title and abstract using Rayyan QCRI then a full-text assessment was implemented. Fifteen studies were included, with 1,080,106 diabetic patients who developed different types of cancers. Most of our included studies reported that DM increases the risk of cancer development; however, it is reported that DM was related to a lower risk of prostate cancer. This review revealed a potential link between cancer and diabetes. However, most of the studies' findings are ambiguous and contradictory, necessitating further investigation to establish the relationship between diabetes and cancer.

**Keywords:** *Diabetes mellitus, Cancer, Malignancy, Systematic review*

## Introduction

Diabetes is now the sixth greatest cause of mortality globally and is one of the most common human illnesses after cardiovascular disorders (WHO). Diabetes mellitus (DM) has a diverse etiology and is defined by insulin resistance and impaired glucose homeostasis. Diabetes is brought on by intricate systems. There are two forms of diabetes: Type 1 and Type 2. Juvenile diabetes/insulin-dependent diabetes mellitus (IDDM) type 1 is defined by the pancreas' inability to produce insulin as a result of beta cell death. It affects a lot of people when they are young, including kids, teenagers, and young adults. Type 2 diabetes, or T2DM, is adult-onset and is also known as non-IDDM since it results from cells' or tissues' failure to react appropriately to insulin [1].

According to large-scale epidemiologic research, numerous anatomic areas are linked to an increased risk of cancer in diabetes. However, only a small number of studies to date have offered conclusions supported by reliable data [2]. Indeed, a comprehensive assessment of meta-analyses of observational research on the relationship between diabetes and cancer at

conclusion that the only malignancies for which there was conclusive evidence of a correlation were those of the breast, endometrial, and colon [3].

Experimental evidence suggests that hyperglycemia, hyperinsulinemia, insulin resistance, and chronic inflammation have critical roles in the relationship of diabetes with cancer, even if the pathophysiologic mechanisms underlying this association are still being studied [4]. The risk of certain cancers may be positively correlated with insulin levels, according to several research. Studies of fasting glucose levels or glycated hemoglobin (HbA1c) in relation to cancer risk provide evidence that high glucose levels may have a role in cancer risk [5, 6]. HbA1c may be tested in a non-fasting condition, has great reproducibility, and is unaffected by daily glucose fluctuations. It also reflects the average glucose concentration over a period of two to three months [7].

Potential molecular explanations for the connection center on the part played by sex hormones, hyperglycemia, inflammatory cytokines, and insulin resistance in the development of neoplasms [8]. Insulin is a

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various anatomic sites came to the  
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growth agent that, by activating insulin receptors in tissues, can directly cause tumorigenesis. It might also have an indirect effect by producing more bioactive insulin-like growth factor I (IGF-I), which has strong mitogenic effects on preneoplastic and neoplastic cells. Furthermore, elevated levels of insulin and bioactive IGF-I in diabetes downregulate the synthesis of sex hormone binding globulin (SHBG), which raises free oestradiol and testosterone (in women but not in males) [9, 10].

A growing interest in establishing the epidemiological and molecular connections between both medical disorders has been sparked by the coexistence of DM and the increasing burden of cancer on the world's population. The majority of the studies' findings are ambiguous and contradictory, necessitating further investigation to definitively establish the relationship between diabetes and cancer. This systematic review investigates the recently published literature regarding the risk of development of cancer in patients with DM.

## Materials and Methods

The established guidelines were followed in conducting this systematic review (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA).

### Study design

This was a systematic Review.

### Study duration

From November to December 2022.

### Study condition

This review investigates recently published literature regarding the risk of the development of cancer in patients with DM.

### Search strategy

To find the relevant literature, a comprehensive literature search was done in five main databases, including PubMed, Web of Science, Science Direct, EBSCO, and Cochrane Library. Our search was restricted to the English language, and it was customized as needed for each database. The following keywords, which were converted into Mesh terms in PubMed, were used to identify the appropriate studies; "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," "Tumour," "malignancy," "hazard," and "risk." The appropriate keywords were paired with "OR" and "AND". The search results comprised English, full-text publications, freely available articles, and human trials.

### Selection criteria

#### Inclusion criteria

The subjects will be chosen for addition founded on their applicability to the research, which has the following criteria; diabetic patients who developed any type of cancer. We included the published articles in the last 5 years.

#### Exclusion criteria

All additional papers, recurring research, and reviews of research that do not possess one of these themes as their major end were disregarded.

#### Data extraction

We used Rayyan (QCRI) [11] to detect the duplicates of the search strategy outcomes. The researchers evaluated the appropriateness of the titles and abstracts by filtering the combined search results based on a list of inclusion/exclusion criteria. The reviewers assessed the whole texts of the papers that satisfied the requirements for inclusion. The authors discussed any differences to be settled. A data extraction form was designed in order to include the qualified study. The authors extracted data about the study titles, authors, study year, study design, participant number, gender, diabetes type, cancer type, and main findings.

#### Risk of bias assessment

To evaluate the quality of the included research, the qualitative data synthesis employed the non-randomized studies ROBINS-I technique [12]. The reviewers looked into and corrected any anomalies in the quality evaluation.

#### Strategy for data synthesis

Summary tables with the information gathered from the eligible studies were produced to give a qualitative overview of the included study components and results. Decisions regarding how to make the most of the data from the included study articles were made after the systematic review's data extraction process was complete. Studies that met the full-text inclusion criteria but did not provide any data on the risk of DM on cancer development were excluded.

## Results and Discussion

### Search results

A total of 844 study articles resulted from the systematic search, and then 97 duplicates were removed. Title and abstract screening were conducted on 747 studies, and 480 studies were excluded. 267 reports were sought for retrieval, and only 10 articles were not retrieved. Finally, 257 studies were screened for full-text assessment; 135 were excluded for wrong study outcomes, 80 for unavailable data on the role of MRI on pancreatic cancer, and 27 for the wrong population type. Fifteen eligible study articles were included in this systematic review. A summary of the study selection process is presented in **Figure 1**.

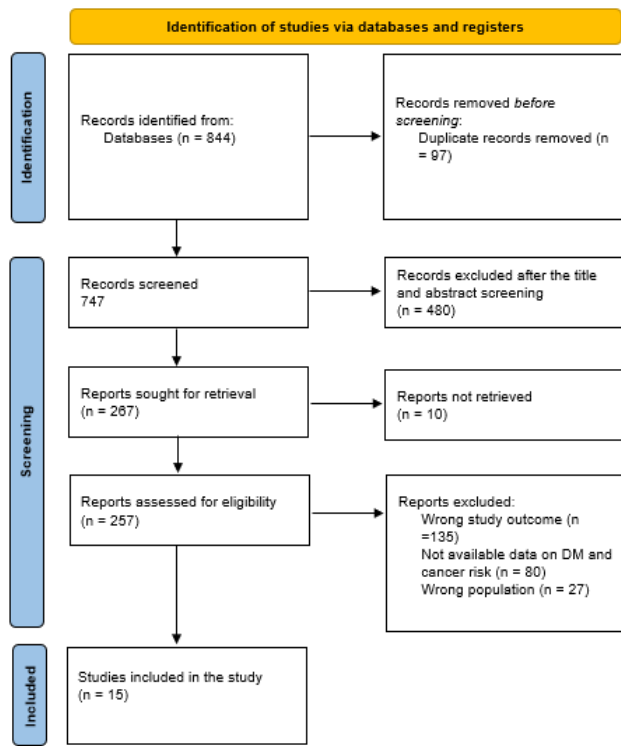


Figure 1. PRISMA flowchart summarizes the study selection process.

### Characteristics of the included studies

A total of 15 studies were included in this review, with 1,080,106 diabetic patients who developed different types of cancers. Seven studies were conducted in the USA [13-19], two in China [20, 21], one in Canada [22], one in the Australia [23], one in Lithuania [24], one in Poland [25] one in Finland [26] and one in the UK [27]. Regarding the studies’ designs; Eight studies were retrospective in nature [13, 16, 19, 20, 22, 24-26], four were prospective [14, 17, 23, 27], and two were case-control studies [15, 21]. Seven studies included patients with T2DM [16-19, 23-25], two studies included patients with T1DM [26, 27], and six studies included patients with both type1 and type2 DM [13-15, 20-22]. Lung cancer was reported in two studies [13, 19], prostate cancer [16, 22], thyroid cancer [21, 26], colorectal cancer [18, 25], different cancer types [14, 27], biliary tract cancer (BTC) [20], breast cancer [15], pancreatic cancer [23], endometrial cancer [24], and bladder cancer [17]. Most of our included studies reported that DM increases the risk of cancer development; however, two studies reported that DM was associated with a lower risk of prostate cancer [14, 22]. Some studies reported that the incidence of lung cancer [13], thyroid cancer [21], and bladder cancer [17] was not associated with DM.

Table 1. A summary of characteristics of the included study articles

Study	Study design	Country	Total Participants	Male (%)	Mean age (y)	Type of DM	Cancer type	Key findings	ROBINS-I
Leiter <i>et al.</i> , 2021 [13]	Retrospective cohort	USA	10819	56	59-68 (range)	T1DM & T2DM	Lung cancer	Lung cancer incidence and diabetes are not correlated. Additionally, there was no connection between diabetes and the histology of lung cancer.	Moderate
Park <i>et al.</i> , 2021 [20]	Retrospective cohort	China	829032	61.4	57.2 ± 12.0	T1DM & T2DM	BTC	Both diabetes and an elevated risk of BTC were strongly linked. A greater risk of BTC was linked to having diabetes over a longer period of time.	High
Peila <i>et al.</i> , 2020 [14]	Prospective cohort	USA	25544	61.2	59.4 ± 7.3	T1DM & T2DM	Esophageal, stomach, colon, liver, pancreatic, bladder, kidney, endometrial, lung cancers, and prostate cancer	Independent of other risk factors, diabetes is linked to an increased risk of esophageal, stomach, colon, liver, pancreatic, bladder, kidney, endometrial, and lung cancers as well as a lower risk of prostate cancer.	Moderate
Chen <i>et al.</i> , 2018 [22]	Retrospective cohort	Canada	80001	100	64.7 ± 9.4	T1DM & T2DM	Prostate cancer	Diabetes is associated with a reduced risk of developing a prostate cancer	High
Wang <i>et al.</i> , 2021 [21]	Case-control	China	2937	23	49.27 ± 1.19	T1DM & T2DM	Thyroid cancer	Although there is no correlation between overall diabetes and thyroid cancer, it is suggested that among people who have older age, female sex, higher BMI, and a positive family history of diabetes, diabetes and short diabetes duration are significantly linked to a lower risk of thyroid cancer.	High

Parada <i>et al.</i> , 2019 [15]	Case-control	USA	1508	0	59	T1DM & T2DM	Breast cancer	Genetic variations that raise the risk of diabetes may also raise the chance of BC development and death.	High
Davis <i>et al.</i> , 2022 [23]	Prospective cohort	Australia	1291	48.7	64.0 ± 11.2	T2DM	Pancreatic cancer	T2DM is linked to a doubled chance of developing incident of pancreatic cancer.	High
Zhu <i>et al.</i> , 2022 [16]	Retrospective cohort	USA	1303	100	60 ± 6.9	T2DM	Prostate cancer	High-risk prostate cancer was independently correlated with both obesity and diabetes mellitus.	High
Zabulitene <i>et al.</i> , 2021 [24]	Retrospective cohort	Lithuania	77708	0	40 – 70 (range)	T2DM	Endometrial cancer	In comparison to the general population, diabetic women have a significantly higher risk of developing EC.	Moderate
Mitek <i>et al.</i> , 2019 [25]	Retrospective cohort	Poland	967	47.5	65	T2DM	Colorectal cancer	The prevalence of colorectal adenomas is significantly associated with T2DM.	Moderate
Li <i>et al.</i> , 2020 [17]	Prospective cohort	USA	8381	0	50-79 (range)	T2DM	Bladder cancer	Among postmenopausal women, there is no correlation between diabetes, diabetes duration, diabetes treatment, and with risk of bladder cancer.	High
Ma <i>et al.</i> , 2018 [18]	Prospective cohort	USA	3000	40.3	67.7 ± 9.4	T2DM	Colorectal cancer	Men with T2DM have a slightly increased risk of developing CRC; women only showed a weaker, non-significant positive association.	Moderate
Kim <i>et al.</i> , 2020 [19]	Retrospective cohort	USA	14133	*	55 ± 7.7	T2DM	Lung cancer	People without DM had a lower risk of developing lung cancer, particularly men ever smokers and women nonsmokers.	Moderate
Mäkimattila <i>et al.</i> , 2020 [26]	Retrospective cohort	Finland	4758	*	42.6–60.1 (range)	T1DM	Thyroid cancer	Individuals with T1DM have a prevalence of thyroid cancer that is 2.7 times higher and equally prevalent in both sexes. The evidence points to an association between poor glycemic control and thyroid cancer risk in T1DM.	High
Fredriksson <i>et al.</i> , 2022 [27]	Prospective cohort	UK	18724	52.8	20-35	T1DM	Different types of cancer	Women with T1DM in childhood had a slight but noticeably higher risk of malignancy. For men, no such tendency was seen.	Moderate

Cancer and diabetes are chronic illnesses with rising prevalence rates around the globe. Epidemiologically and physiologically, diabetes and cancer have been related to one another frequently. There is strong evidence linking diabetes (especially type 2) to a higher risk of developing a number of malignancies [28].

This review demonstrated that T2DM was reported in many cases with several cancers. In its early stages, T2DM is

characterized by insulin resistance and the ensuing hyperinsulinemia. The latter stimulates tumour cell development indirectly through the IGF-1 receptor, but it also stimulates tumour cell growth directly through insulin receptors. Insulin and IGF-1 receptors are also expressed by a large number of cancer cell lines. Enhanced cell proliferation, anti-apoptosis, increased cell motility, and invasion are characteristics that favor tumours [29, 30].

Therefore, it is possible that the administration of exogenous insulin and/or high endogenous insulin levels will promote the development of cancer. A recent meta-analysis that showed excessive serum insulin or c-peptide levels are linked to a significantly higher risk of several malignancies [31] lends weight to this notion.

Several cancer types, including lung, BTC, esophageal, stomach, colon, liver, pancreatic, bladder, kidney, endometrial, and breast cancers, were associated with increased incidence risk in diabetic patients. Diabetes and poor glucose tolerance are linked to pancreatic cancer in about 80% of cases [32]. A recent meta-analysis of 88 cohort studies found that people with diabetes have a 94% higher risk of developing pancreatic cancer than people without the disease [33]. Due to the possibility that impaired glucose homeostasis may be a contributing factor in pancreatic cancer development, the relationship between diabetes and pancreatic cancer is complicated.

Studies studying the link between DM and the chance of dying from stomach cancer have yielded conflicting results. Diabetes was found to be a predisposing factor that raised the incidence of stomach cancer in men in a meta-analysis of 22 cohort studies with data on 8,559,861 people [34]. According to Lin *et al.*, hyperglycemia may be responsible for the creation of an energy/metabolism imbalance and immune system damage that may eventually result in gastric cancer [35].

Numerous epidemiological investigations and published meta-analyses have clarified the relationship between diabetes and colorectal cancer (CRC) [4]. Compared to non-diabetics, diabetics are far more likely to develop CRC. Systemic analysis of 8 chosen research revealed a strong association between T2DM and the 1.21-fold increased risk [36]. It is currently unknown how diabetes and the prognosis for CRC are related biologically. Hyperglycemia, insulin resistance, and insulin/IGF are currently thought to play a role in the development of diabetes into CRC.

In females, there has been evidence of a link between diabetes and an increased risk of breast cancer. The most prevalent disease impacting the morbidity and mortality of women worldwide is breast cancer [37]. Breast neoplasm risk may be impacted by insulin resistance, hyperinsulinemia, and alterations in growth hormone and steroid hormone signaling linked to diabetes. Researchers have shown a 20% increase in the incidence of T2DM and breast cancer [38]. Similarly, Hardefeldt *et al.* meta-analysis of 43 papers, including 40 and 6 studies looking at breast cancer in men and women, discovered a considerably higher risk of breast cancer in women with diabetes [39].

Two studies have reported that DM is associated with a lower risk of prostate cancer. Prostate cancer and other types of cancer showed different outcomes in connection to diabetes. Men with diabetes had a considerably lower risk of acquiring prostate cancer, according to a meta-analysis by Kasper and Giovannucci [40]. These contradictory results may be due to

the reduced testosterone and SHBG levels in diabetic males [41]. Lee *et al.* conducted a meta-analysis to remove the bias in the stage of cancer diagnosis and its risk. They looked into the prevalence of prostate cancer deaths in males who already had diabetes [42]. Additionally, no statistically significant link was found between preexisting T2DM and mortality from prostate cancer when concentrating on subgroup analysis in T2DM in particular. Further research projects should be implemented to determine the relationship between diabetes and prostate cancer because the results are heterogeneous.

Although the underlying biological pathways are poorly understood, diabetes is often associated with an increased incidence and development of cancer. The global diabetes epidemic, which is spreading quickly, has several significant ramifications for the development and prevention of cancer. First, due in part to the rising obesity and diabetes epidemics, as well as population aging, the rate of increase in cancer incidence and mortality globally will quicken. Second, medical providers need to acknowledge that diabetic people are at a greater risk of developing cancer and should actively encourage them to follow the right cancer screening and preventive recommendations [43].

The outcomes of diabetes and cancer will be improved by preventive measures, including weight management and lifestyle changes. Finally, international organizations and national governments should implement public policies to enhance nutritional and constructed environments that enable people to choose a healthy diet and lifestyle in order to minimize the worldwide burden of diabetes and cancer and improve population health [43].

## Conclusion

The findings in this review suggest that diabetic people have an increased chance of acquiring cancer based on the survey of the published data. Most of our included studies reported that DM increases the risk of cancer development; however, it is reported that DM was associated with a lower risk of prostate cancer. On the other hand, it's still unclear if diabetes causes cancer. The cause of both diabetes and cancer needs to be specifically determined, which will require more investigation.

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## Conflict of interest

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