Juvenile Diabetes Mellitus is a Risk Factor of Different Types of Cancers: Systematic Review

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Abstract

Introduction: Diabetes mellitus (DM) is a common endocrine condition affecting people worldwide. 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.

Methodology: PubMed, Web of Science, Science Direct, EBSCO, and Cochrane Library were searched. Study articles were screened by title and abstract using Rayyan QCRI, then implemented a full-text assessment.

Results: Eight studies were included, with 49276 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.

Conclusion: Type 1 diabetes (T1D) is a chronic disease resulting in the loss of the beta cells of the pancreas due to an autoimmune reaction, and its prevalence seems to be rising. Given the enormous number of people worldwide who have the condition, even slight increases in the RR of cancer incidence and/or mortality among this population will significantly raise the overall burden of cancer. Interestingly, few studies reported that overall cancer risks are reduced, likely due to the diabetes patients' healthier lifestyles regarding smoking and alcohol use, as well as a potential link between prostate cancer and lower testosterone levels in men with diabetes with a marginally elevated risk of cancer incidence in women, especially breast cancer.

Keywords; Type 1 diabetes, cancer, risk, systematic review

Introduction

According to the WHO, diabetes is currently the sixth leading cause of death worldwide and ranks second among all human illnesses in terms of prevalence. With a wide range of etiologies, diabetes mellitus (DM) is characterized by insulin resistance and a dysfunctional glucose homeostasis system. Complex systems are the cause of diabetes. Type 1 and Type 2 diabetes are the two varieties. The lack of pancreatic insulin production brought on by beta cell loss is what distinguishes juvenile diabetes/insulin-dependent diabetes mellitus (IDDM) type 1 from other forms of diabetes. Many young individuals, including children, teenagers, and young adults, are impacted by it. Adult-onset type 2 diabetes, or T2DM, is often referred to as non-IDDM because it develops when cells or tissues fail to respond to insulin as it should [1].

Numerous anatomical regions are associated with a higher risk of cancer in diabetes, according to extensive epidemiologic data. Only a few research have, however, provided results backed by solid evidence thus far [2]. The only cancers for which there was unambiguous proof of a correlation were those of the breast, endometrium, and colon, according to a thorough assessment of meta-analyses of observational research on the relationship between diabetes and cancer at various anatomic sites [3].

Even though the pathophysiologic processes underlying this link are still being investigated, experimental data suggest that hyperglycemia, hyperinsulinemia, insulin

resistance, and chronic inflammation play important roles [4]. According to various studies, there may be a correlation between insulin levels and the risk of developing several malignancies. High glucose levels may play a role in cancer risk, according to studies of fasting glucose levels or glycated hemoglobin (HbA1c) in relation to cancer risk [5, 6]. HbA1c testing is non-fasting, highly reproducible, and unaffected by changes in blood glucose levels during the day. It also displays the typical glucose level throughout the course of two to three months [7].

The role that sex hormones, hyperglycemia, inflammatory cytokines, and insulin resistance play in the development of neoplasms is the focus of potential molecular explanations for the association [8]. Insulin is a growth factor that can directly promote cancer by activating insulin receptors in tissues. More bioactive insulin-like growth factor I (IGF-I), which has potent mitogenic effects on preneoplastic and neoplastic cells, may also have an indirect effect. The synthesis of sex hormone binding globulin (SHBG), which elevates free oestradiol and testosterone (in women but not in men) [9, 10], is downregulated by higher insulin and bioactive IGF-I levels in diabetes.

Literature review

Noto et al. conducted a systematic review and meta-analysis to study how diabetes mellitus affects the occurrence and mortality of cancer at any anatomic site. Insofar as the exponentially rising prevalence of diabetes will have significant clinical and public health consequences on a global scale, cancer prevention, and early detection by appropriate screening methods in patients with diabetes should be important components of clinical management and investigation [11].

Another epidemiological evidence to assess the overall risk of cancer among diabetic patients in Japan. Four cohort studies and one case-control study identified 22,485 cancer cases altogether. With the use of these five findings, a meta-analysis of the risk of all cancers in both men and women revealed that people with diabetes had a higher risk than those without diabetes (OR 1.70, 95% CI 1.38-2.10). Increased risks for incident hepatocellular carcinoma (OR 3.64, 95% CI 2.61-5.07) and endometrial cancer (OR 3.43, 95% CI 1.53-7.72) were seen in a study of site-specific malignancies. Asians with diabetes are more likely to develop incident cancer than those without diabetes, just like in Western nations. Given the exponentially rising prevalence of diabetes, which has significant effects on public health and professional practices, cancer prevention and early detection should be key facets of diabetes care [12].

Hope et al. conducted a systematic review to determine whether diabetes patients or not the association between HbA1c and malignancies. Eight studies examined the results of all cancer locations. According to four of these investigations, all malignancies had greater incidence rates and/or mortality risks when HbA1c levels were higher. According to one study, there is a U-shaped correlation between cancer incidence and death and HbA1c. The chance of developing colorectal, pancreatic, pulmonary, and female genital tract malignancies increased with rising HbA1c levels. For gastrointestinal, urological, or breast cancers, no higher risk was seen. The complex relationship between HbA1c and cancer requires more research in order to completely comprehend the association between HbA1c and cancer incidence and/or mortality [13].

Vissers et al. aimed to provide guidelines for future research and provide an overview of the present literature on the potential implications of having both cancer and diabetes on patient-reported outcomes (PROs). Although having both cancer and diabetes led to worse PROs than having either of the diseases alone, it was difficult to draw firm conclusions due to the significant heterogeneity of the included studies. Future research is required because this field of study has received little attention. Future studies should examine the effects of these diseases on other PROs, such depression, patient empowerment, and self-management, as the bulk of the included studies were on HRQoL [14].

Aim of the study

The coexistence of DM and the rising burden of cancer on the global population have spurred an increasing interest in discovering the epidemiological and molecular links between both disease conditions. To conclusively demonstrate the link between T1DM and cancer, additional research is required because the bulk of study results are confusing and conflicting. The risk of developing cancer in people with diabetes is examined in this systematic review of newly available literature.

Methodology

This systematic review will follow established guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA) [11].

Study Design and Duration

This was a systematic review conducted on July 2023.

Study condition

This review investigated recently published literature regarding the risk of the development of cancer in patients with T1DM.

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 English and 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," "Insulin-dependent diabetes mellitus," "IDDM," "Cancer," "Carcinoma," "Tumour," "malignancy," "hazard," and "risk." The appropriate keywords were paired with "OR" and "AND" Boolean operators. The search results comprised English, full-text publications, freely available articles, and human trials.

Selection criteria

Inclusion criteria

We considered the following criteria for inclusion in this review:

- Any study designs that investigate recently published literature regarding the risk of cancer development in patients with T1DM.
- No age limits were restricted
- Study articles conducted between 2018 to 2023.
- English language.
- Free accessible articles.

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) [12] 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 papers' whole texts that satisfy the inclusion requirements. 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, 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 [13]. The reviewers looked into and corrected any anomalies in the quality evaluation.

Strategy for data synthesis

Summary tables were produced with the information gathered from the eligible studies 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

Search results

A total of 330 study articles resulted from the systematic search, and then 44 duplicates were removed. Title and abstract screening were conducted on 286 studies, and 234 studies were excluded. Fifty-two reports were sought for retrieval, and only 7 articles were not retrieved. Finally, 45 studies were screened for full-text assessment; 20 were excluded for wrong study outcomes, and 17 for the wrong population type. Eight eligible study articles were included in this systematic review. A summary of the study selection process is presented in **Figure 1.**

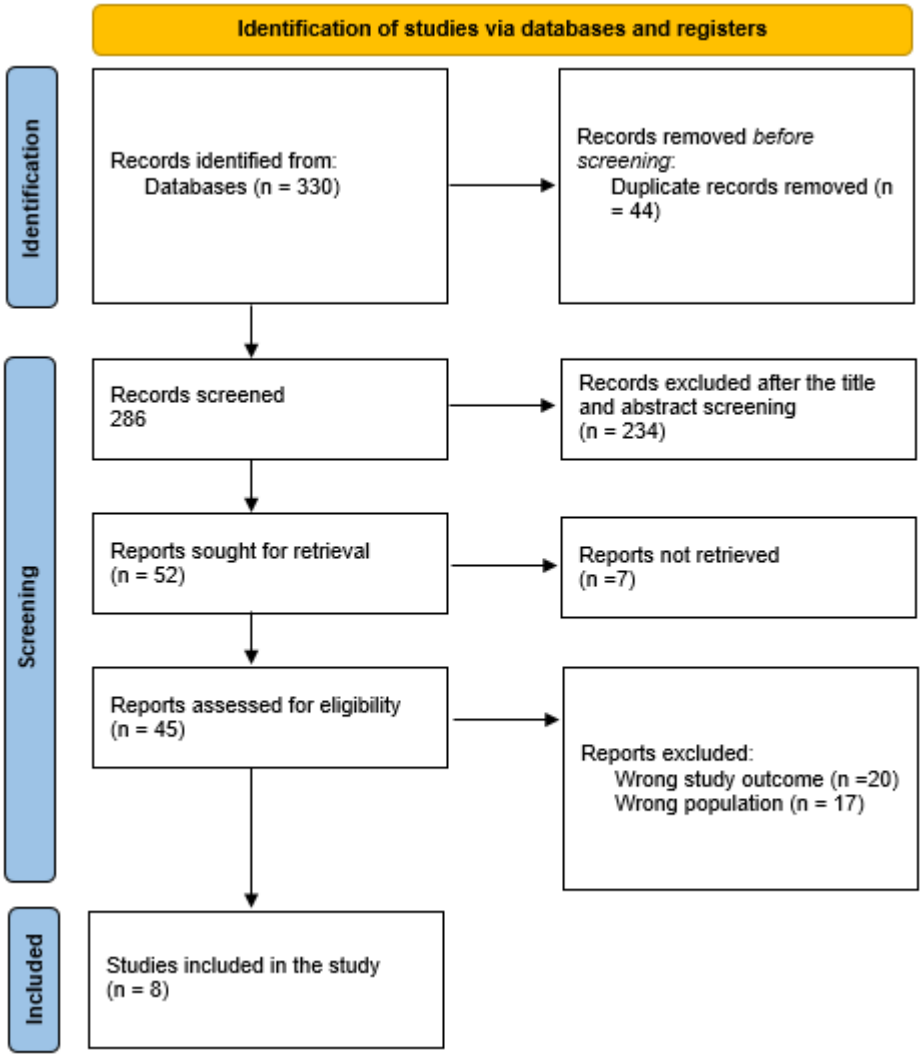

Figure (1): PRISMA flowchart summarizes the study selection process.

Characteristics of the included studies

Table (1) shows the sociodemographic characteristics of the included patients. A total of 8 studies were included in this review, with 49276 diabetic patients who had developed cancers. Three studies were conducted in the united kingdom (UK) [18, 19, 21], one in Italy [20], one in Finland [22], one in Iran [23], one in Taiwan [25], and one was multi-centered [24]. Regarding the studies' designs, three studies were cohorts [18, 20, 24], two were prospective in nature [19, 21], two were retrospective [22, 25], and one was a case-control study [23].

Table (2) shows the clinical characteristics. Most of our included studies reported that DM increases the risk of cancer development; however, one study reported that overall cancer risks are reduced, likely due to the diabetes patients' healthier lifestyles regarding smoking and alcohol use, as well as a potential link between prostate cancer and lower testosterone levels in men with diabetes [18]. When diabetes is diagnosed between the ages of 10 and 14, the typical age for puberty in the UK [18]. T1D women may be at higher risk for breast cancer [19]. Individuals with T1D have a prevalence of thyroid cancer that is 2.7 times higher and equally prevalent in both sexes [22]. **Fredriksson et al.** reported a marginally elevated risk of cancer incidence in women, particularly in those who started developing diabetes at a young age [21].

Table (1): Sociodemographic characteristics of the included study articles.

Study	Country	Study design	Participants	Mean age	Males (%)
Swerdlow et al., 2023 [18]	UK	Cohort study	28 531	0-49	15476 (54.2)
Xiong et al., 2023 [19]	UK	Prospective cohort study	575	53.4 ± 8.1	0
Vicentini et al., 2022 [20]	Italy	Cohort study	758	46.1 ± 14.6	410 (52.9)
Fredriksson et al., 2022 [21]	UK	Prospective cohort study	18724	20-35	9889 (52.8)
Mäkimattila et al., 2020 [22]	Finland	Retrospective cohort study	4758	42.6–60.1	NM
Soltani et al., 2019 [23]	Iran	Case-control	693	49.8 ± 14.6	346 (49)
Carstensen et al., 2016 [24]	Multi-centered	Cohort study	9149	43.5– 59.5	NM
Hsu et al., 2015 [25]	Taiwan	Retrospective cohort study	14619	NM	6867 (46.8)

Table (2): Clinical and sociodemographic characteristics of the included case reports.

Study	Objectives	Cancer type	Main findings	ROBINS-I
Swerdlow et al., 2023 [18]	To assess cancer incidence and mortality among T1DM patients	Different types of cancer	When diabetes is diagnosed between the ages of 10 and 14, the typical age for puberty in the UK, there is a significantly increased risk of ovarian and vulval cancers. However, overall cancer risks are reduced, likely due to the diabetes patients' healthier lifestyles regarding smoking and alcohol use, as well as a potential link between prostate cancer and lower testosterone levels in men with diabetes.	Moderate
Xiong et al., 2023 [19]	To assess the relationships between the risk of breast cancer and T1D.	Breast cancer	In the UK Biobank as a whole, they found no correlations between diabetes and breast cancer in women. Our results did, however, indicate that T1D or newly diagnosed T2D women may be at higher risk for breast cancer. Larger studies involving people of different races and ethnicities are required to learn more about the connection between T1D and breast cancer risk.	Moderate
Vicentini et al., 2022 [20]	To evaluate insulin's impact on cancer incidence in people with T1DM and T2DM.	Different types of cancer	Cancers of the liver, pancreas, bladder, and neuroendocrine systems appear to have the strongest associations. For those with T1D, there was also an excess for bladder cancer.	Moderate
Fredriksson et al., 2022 [21]	To investigate the increased risk of cancer in a	Different types of cancer	A marginally elevated risk of cancer incidence in women, particularly in those who started developing diabetes at a young age. Men had no higher risk than	

	sizable cohort of people who were diagnosed with T1D before the age of 15.		women. Further monitoring of the cohort is necessary.	High
Mäkimattila et al., 2020 [22]	To evaluate the increased risk of thyroid cancer in adults with long-term T1D in comparison to matched controls for sex and age.	Thyroid cancer	Individuals with T1D 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 T1D.	High
Soltani et al., 2019 [23]	To look into the relationship between the diagnosis of CRC, obesity, and diabetes in the chosen group of CRC patients.	Colorectal adenoma and cancer	This study shows a significant correlation between colon adenoma and familial history of colon cancer or positive T1D history. They confirmed that precancerous lesions are more likely in those with diabetes and obesity (BMI 25 kg/m2). Therefore, despite ongoing debates, such patients may consider getting screened for CRC earlier in life.	Moderate
Carstensen et al., 2016 [24]	To explain the connection between T1D and the likelihood of developing cancer	Different types of cancer	Multiple cancers occur more frequently in people with T1D. Particularly, people with T1D had lower rates of prostate cancer and higher rates of liver, pancreas, kidney, endometrium, and ovary cancers than those without the disease. The HRs of cancer were highest at the time of diabetes diagnosis and decreased over time, similar to the results for T2D.	Moderate
Hsu et al., 2015 [25]	To evaluate the incidence of cancer in T1DM patients overall and by site.	Different types of cancer	T1D was linked to a 13% increase in the incidence of all cancers. Patients with T1D should be encouraged to get screened for specific cancers.	Moderate

Discussion

Cancer and diabetes are chronic illnesses with rising prevalence rates around the globe. Epidemiologically and physiologically, diabetes and cancer have frequently been related to one another. Strong evidence links diabetes to a higher risk of developing a number of malignancies [25].

Most of the included studies in this review reported that DM increases the risk of cancer development; however, one study reported that overall cancer risks are reduced, likely due to the diabetes patients' healthier lifestyles regarding smoking and alcohol use, as well as a potential link between prostate cancer and lower testosterone levels in men with diabetes [18]. 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 [26] lends weight to this notion.

Numerous studies revealed a tenuous link between the two illnesses among those studies that did discover an increase in the risk of cancer incidence and mortality among people with T1D when compared with the general population. This may be attributable to a real weakness in the association between T1D or it may have to do with inherent study-related issues. For instance, the sample size issue seems crucial given the low prevalence of T1D in a given area. Additionally, this

review may have been biased by studies that chose not to publish their results when they did not find an association.

When diabetes is diagnosed between the ages of 10 and 14, the typical age for puberty in the UK [18]. T1D or newly diagnosed T2D women may be at higher risk for breast cancer [19]. Postmenopausal women with diabetes have a slightly increased risk of breast cancer, according to previous meta-analyses and large cohorts [27, 28]. However, studies have shown significant heterogeneity, and many have not taken into account other potential confounding factors, such as BMI, which is strongly associated with diabetes and a known risk factor for postmenopausal breast cancer.

Individuals with T1D have a prevalence of thyroid cancer that is 2.7 times higher and equally prevalent in both sexes [22]. **Fredriksson et al.** reported a marginally elevated risk of cancer incidence in women, particularly in those who started developing diabetes at a young age [21]. When studies were grouped into those that focused on cancer mortality or incidence, the results were still inconsistent. Neither of the case-control studies found an association between T1D and cancer, but the meta-analyses did for both pancreatic and endometrial cancer (RR 2.0, CI 1.37-3.01 and RR 3.15, CI 1.07-9.92, respectively) [29, 30].

The findings' variability supports the need for additional research. The dearth of study in this field further emphasizes the necessity for research on the two diseases to be developed. Large-scale datasets with appropriate numbers of T1D cases and controls could be employed in future studies, for example, primary care records used in research like the General Practice Research Database or The Health Improvement Network in the UK. Notably, none of the studies included in this review confirmed T1D using biological (e.g., glycated hemoglobin) or immunological definitions (e.g., the presence of pancreatic autoantibodies or C-peptide levels). Future studies may use these techniques to define the T1D cohort more precisely. A better knowledge of a variety of important epidemiological topics regarding the connection between T1D and cancer will be made possible by such research. To comprehend the connection between T1D and overall cancer risk, a future study could be conducted.

Suppose a link between the two conditions is discovered. In that case, more investigation into the gender, racial, and other demographic and socioeconomic differences between T1D and cancer, as well as potential regional variations in the diagnosis and management of both conditions, may be needed. Although all people with T1D need exogenous insulin to survive, the type of insulin used may impact cancer risk differently. Nevertheless, some evidence suggests that people with diabetes who subsequently acquire cancer have a later diagnosis and may require a different course of therapy than people without the condition [31, 32].

Conclusion

T1D is a chronic disease resulting in the loss of the beta cells of the pancreas due to an autoimmune reaction, and its prevalence seems to be rising. Given the enormous number of people worldwide who have the condition, even slight increases in the RR of cancer incidence and/or mortality among this population will significantly raise the overall burden of cancer. Interestingly, few studies reported that overall cancer risks are reduced, likely due to the diabetes patients' healthier lifestyles regarding smoking and alcohol use, as well as a potential link between prostate cancer and lower testosterone levels in men with diabetes with a marginally elevated risk of cancer incidence in women, especially breast cancer.

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