International Journal of Cancer

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Journal:	*International Journal of Cancer*
Manuscript ID:	Draft
Wiley - Manuscript type:	Mini Review
Date Submitted by the Author:	n/a
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Key Words:	Diabetes, Type-1, Cancer, Mortality, Incidence

Epidemiological evidence of a relationship between Type-1 diabetes mellitus and cancer: a review of the existing literature

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Vanessa Gordon-Dseagu is funded by Diabetes UK (grant number- 08/0003752).

Article category: Mini-Review

Novelty and impact of this paper
Although there is an increasing amount of evidence relating to the relationship between type-2 diabetes and cancer, very little is known about the relationship between the latter and type-1 diabetes. This review is the first to gather together all the epidemiological evidence in this regard and explore whether or not there is consistent evidence of an association between the two diseases.

Word count: **3,408**

Figure count: 1 (included in separate document)

Table count: 1 (included in separate document and body of text)

Reference count: 47

Key words Type-1 diabetes mellitus, Cancer
Abbreviations T1DM, Type-1 Diabetes Mellitus, T2DM, Type-2 Diabetes Mellitus, IDDM, Insulin Dependent Diabetes Mellitus, SMR, Standardized Mortality Ratio, SIR, Standardized Incidence Ratio, RR, Relative Risk, HI Hazard Ratio, CI, Confidence Interval.

Abstract

This review explores the epidemiological evidence relating to type-1 diabetes (T1DM) and cancer incidence and mortality. Mortality rates among those with T1DM are higher in every age group compared with the general population; the majority of this mortality is due to factors related to the consequences of diabetes, such as cardiovascular and renal diseases. For over 100 years, researchers have explored the relationships between diabetes and cancer and although there is now a large body of work on the subject, consensus has not been reached. Such research has tended to focus upon type-2 diabetes (T2DM), with the result that very little is known about T1DM and cancer. As incidence of T1DM increases, by around 3% annually among children, the need for further research into its impact upon cancer incidence and mortality increases. Within this review, findings varied by study method utilised, T1DM definition used, study region and outcome measure explored. None of the case-control studies found a statistically significant link between the two diseases, while both of the meta-analyses did. Cohort studies produced mixed results. There were also mixed findings among research that defined T1DM in the same way (for example defining individuals with the disease as those diagnosed with diabetes before 30 years of age). The review found a number of studies which explored cause-specific cancer mortality among those with diabetes; such studies also had mixed findings. This inconsistency within results suggests the need for further research in order to understand better the potential relationships between T1DM and cancer.

Introduction

Type-1 diabetes mellitus is a chronic condition which typically develops in childhood and is caused by the destruction of the β-cells within the pancreas, which leaves the body deficient in insulin.(1) Because of this, individuals with the disease require the use of exogenous insulin for survival. This form of the disease accounts for around 5-15% of all cases of diabetes mellitus, equating to around 290,000 individuals in the UK and over 33 million globally.(2,3) Research also indicates that, Europe-wide and internationally, incidence of the disease in children is increasing by around 3% annually. Although the cause of this is unclear, contributing factors appear to relate to the interplay between genes and the environment, and to better diagnosis and monitoring of the disease within countries that previously did not undertake such work.(4,5) Type-1 diabetes is associated with an increase in mortality at every age, with some estimates placing it at five to ten times higher among those with the disease.(6) The excess mortality found within this group is related primarily to metabolic complications of diabetes which result in increased rates of cardiovascular and renal disease.(7)

Investigations attempting to detail the link between diabetes mellitus, hyperglycaemia and cancer started in the late 1800s with the work of Freund(8) and Tuffier(9). Since then, a wealth of epidemiological research has been undertaken with resultant mixed findings. Even though a definitive answer has not been found, it does appear that diabetes influences the incidence of a number of cancers. Included in this group are cancers with a considerable increase in incidence (endometrium, pancreas, and liver), those with a moderate increase (breast and bladder), others for which the findings are inconclusive (kidney and non-Hodgkins lymphoma) and those with a lower incidence (prostate).(10) The majority of the research to date has focussed upon the link between type-2 diabetes and its impact upon cancer incidence, with some commentators questioning the validity of extrapolating such findings to type-1 diabetes.(11) Other studies have focussed upon diabetes in general and have not differentiated between type-1 and type-2 diabetes. Research has also begun to explore the effect that the use of different types of exogenous insulin, and other diabetic drugs, have upon the risk of developing cancer, again with mixed findings.(12–14) This review was undertaken to enable greater awareness of the potential relationship between type-1 diabetes and cancer. The review concludes with a number of suggestions for the development of future epidemiological research in this area.

Material and methods

Study identification

A literature search was undertaken within PubMed and Google Scholar to identify research with a focus on diabetes mellitus and its impact upon cancer incidence and mortality. Searches utilised the terms “diabetes”, “type 1 diabetes” “insulin treated diabetes mellitus” “IDDM”, “early onset diabetes”, “juvenile onset”, “young onset”, or “type-1 diabetes mellitus” “T1DM”, and “cancer”, “neoplasm”, “malignancy”, “incidence” or “mortality”. The references cited within each article were then reviewed in order to elicit further relevant articles.

Inclusion/exclusion of reports

The review includes only those reports that document research specifically focussed upon exploring the link between type-1 diabetes and cancer. A large number of reports detail evidence relating to the excess all-cause mortality experienced by those with type-1 diabetes and the references for

these reports were also reviewed. Studies were excluded in instances when they did not analyse the two different types of diabetes separately, or when it was unclear which type of diabetes was under analysis. The only instances where studies of this nature have been included in the review is when the focus of the study was upon insulin use and the age group of the cohort was young enough to be composed mainly of those with type 1 diabetes. If two studies utilised the same cohort, the earlier study was excluded from the review. Studies were also excluded if they detailed the excess mortality of a type-1 diabetic cohort but did not specifically analyse cancer incidence or mortality compared with the general population, or other specified control group. Studies were excluded if they did not give information about the precision of their measurement, such as 95% Confidence intervals (CI) or p-values. Figure 1 details the literature selection.

Figure 1: Selection of articles

Results

As can be seen from table 1, there were mixed findings, depending on the study method used. Mixed results were found among cohort studies. None of the case-control studies found a statistically significant link between the two diseases, while both of the meta-analyses (which included both study designs) did. There were also mixed findings among research that defined type-1 diabetes in the same way. For example, three studies used diagnosis before the age of 30 as being indicative of the disease: two found no statistically significant relationship while one did. The rest of this section explores the results of the research found within this review, based upon the method used within the study.

Cohort Studies

A UK study found increased mortality among women with type-1 diabetes for ovarian cancer (SMR 2.90, 95% CI 1.45-5.19); the same was not found to be true for any other cancer site or all cancers combined, the latter gave an SMR 0.90 (95% CI 0.75-1.08).(15) A key limitation of this study was that a large proportion of their subjects (20,676 out of a total of 28,900) were under the age of 50 at follow up. This is known to be a period when cancer incidence is lower than in later life; 63% of

cancers are diagnosed in those over the age of 65 and only 5.4% of cancer in men, and 8.9% of those in women, occur under the age of 45.(16,17)

A Swedish study found a standardized mortality ratio (SMR) of 1.73 (95% CI 1.45-2.05) among its type-1 diabetic cohort compared with the general population.(18) In support of this, a New Zealand study found an SMR for cancer of 12.96 (95% CI 3.36-22.57) among those diagnosed with type-1 diabetes compared with the general population.(19) The CI is wide and this may be due to there being only seven observed cases of cancer among those diagnosed with diabetes under the age of 30 (the measure used within the study as indicative of type-1 diabetes). The US Allegheny County Type-1 Diabetes Registry cohort study investigated cause-specific mortality among its cohort of those with type-1 diabetes (n=1,043). They found no statistically significant association between the two diseases (SMR= 1.2, 95% CI 0.5-2.0) compared with the general population.(20) The lack of statistical significance in this study is likely to be heavily influenced by the small number of cancer deaths and the consequent effect on statistical power.

Only a few reports have focussed upon cause-specific mortality among those with type-1 diabetes; among these a smaller number still investigated cancer mortality. The reason for this is likely to be the excess of mortality among those with type-1 diabetes caused by complications of the disease itself, such as renal disease and cardiovascular disease.(21) A UK study linked cause of death data to a register of those with diabetes and found that those with type-1 diabetes only accounted for 18 (5%) of all deaths within the study; because of this they did not undertake separate analysis for cause of death among those with this form of diabetes.(22) Other studies were characterised by their inclusion of numbers of concurrent type-1 diabetes and cancer too small to elicit statistically viable results.(23–26)

A Danish study found no overall increase in cancer cases among those with type 1 diabetes compared with the general population.(27) More detailed analysis showed that, for site specific cancers, only that of the pancreas had a statistically significant increase (RR=2.53, 95% CI = 1.17-5.47). However, further analysis showed that, once cases were excluded where diabetes was an early indication of the presence of cancer, the relationship was no longer statistically significant (RR= 1.69, p=0.29). In terms of age and gender, only men between the ages of 0-54 had an increased risk of cancer (RR=2.04, 95% CI= 1.11-3.74); although this result may reflect the small numbers within the studies other groups rather than the real effect type-1 diabetes has upon cancer incidence.

There were also only a small number of cohort studies which focus upon type-1 diabetes and cancer incidence. A Swedish study found a 17% increase in cancer among those with type-1 diabetes compared with the general population.(28) At the same time, if analysis excluded specific time periods after diagnosis (based on either one or five years) no significant increase in standardized incidence ratio (SIR) was found. Exclusion of the first year (SIR 1.07, 95% CI 0.94-1.22) was similar to analysis for exclusion of first five years (SIR 1.09, 95% CI 0.96-1.25). This finding may support the reverse causality hypothesis-that diabetes is the result of an undiagnosed cancer, rather than the other way round or it could be the consequence of small numbers within the study. In terms of site-specific cancers the study found increased SIRs for those of the stomach (3.36, 95% CI 1.44-6.66), squamous cell carcinoma of the skin (4.96, 95% CI 2.83-8.07) and leukaemia (2.02 95% CI 1.15-3.29). These SIRs were those which excluded the first five years of follow up after diagnosis of type-1 diabetes, with significance remaining stable across all the three follow-up intervals of all cases, one year follow-up exclusion, and five years exclusion. Gender was a key factor in excess cancer

incidence. After exclusion of the first year following type-1 diabetes diagnosis, SIR only remained increased among women. This statistical significance was also only for cancers of the skin (SIR 9.40, 95% CI 5.12-15.82) and leukaemia (2.55, 95% CI 1.26-4.57). The number of visits an individual made to hospital was also found to be a risk factor for cancer, but the researchers were unsure whether this was due to the increased chance of a cancer being diagnosed within more frequent visits to hospital or because there was an association between type-1 diabetes and cancer.

A Danish cohort study found mixed results depending on cancer site.(29) Among those defined as having type-1 diabetes (hospitalised for diabetes within the study period before the age of 50) the SIR for all cancers was 1.1, 95% CI 1.0-1.2; only cancers of the mouth and pharynx (SIR 1.8, 95% CI 1.2-2.6) and liver (SIR 4.8, 95% CI 2.8-7.7) were increased among this group. For cancers of the pancreas, lung and kidney non-statistically significant increases were found (SIR 1.4, 95% CI 0.7-2.3, SIR 1.3, 1.0-1.6 and 1.6, 1.0-2.4 respectively). A third Swedish cohort study found an overall SIR for cancer of 1.2 (95% CI 1.0-1.3) among those with type-1 diabetes compared with the general population.(30) For site-specific cancers significant increases in SIR were found for those of the stomach (2.3, 95% CI 1.1-4.1), cervix (1.6, CI 1.1-2.2), and endometrium (2.7, CI 1.4-4.7).

Case-control studies

A case-control study (7,713 cases, 38,518 controls) undertaken in the UK explored all-cause and cause-specific mortality among those with type-1 diabetes compared with the general population.(31) They found no difference in the hazard ratios for cancer mortality between the two groups (HR=1.05, 95% CI 0.72-1.52). An Italian case-control study exploring the link between endometrial cancer incidence and diabetes (type-1 diabetes and type-2 diabetes, assessed separately) found no link between type-1 diabetes and the disease (OR=1.0, 95% CI 0.3-3.4) but only four cases with type-1 diabetes were included in the study.(32) In support of this finding, a second study which included 14,000 individuals aged 30-89 with diabetes, found no statistically significant association (at the 5% level) between a range of site- specific cancers and the disease.(33)

Meta-analyses and systematic reviews

A meta-analysis of the link between diabetes and endometrial cancer found an association between the two diseases (RR=3.15, 95% CI 1.07-9.29).(34) This was based on three studies, one of which was a Swedish case-control study which had few women with type-1 diabetes (<10) and found a relative risk (RR) of 13.3, with a wide CI of 3.1-56.4.(35) The other two studies are those of Swerdlow (UK) et al and Zendehdel et al (Sweden), mentioned earlier in this review.(15,30)

A systematic review and meta-analysis focussed upon type-1 diabetes and the incidence of pancreatic cancer.(36) Within the meta-analysis a relative risk of 2.00 (95% CI 1.37-3.01) was found for pancreatic cancer among those with type-1 diabetes. The meta-analysis was based on 39 concurrent cases of the two diseases. The researchers themselves reported that the study was limited by the small number of studies published in this area; there were an even smaller number that were published with sufficient concurrent cases of type-1 diabetes and pancreatic cancer; Ekoe et al found only one case while La Vecchia found three.(37,38) Only two studies had more than five cases among those with type-1 diabetes; the first of these is the Wideroff study mentioned above and the second found an increased relative risk of pancreatic cancer among those with type-1 diabetes (RR 2.23, 95% CI 1.08-4.58.(39) Three of the studies included in the analysis had no concurrent cases of type-1 diabetes and pancreatic cancer.(33,40,41)

Table 1: Key findings of research exploring the relationship between type-1 diabetes and cancer

Study method	Country	Sample	Case definition (type-1 diabetes)	Outcome measure	Risk of cancer among T1DM participants (95% CI or p-value)	Risk of site-specific cancers (95% CI or p-value)
Cohort(27)	Denmark	1,499 insulin treated individuals	Insulin use	Incidence	Men RR=1.37 (1.03-1.83), Women RR=1.08 (0.77-1.51),	Pancreas RR=2.53 (1.17-5.47); RR=1.69 (p=0.29) once cases excluded where diabetes an indicator of cancer
Cohort(18)	Sweden	144,427 participants with diabetes	Hospitalisation for diabetes <age 40	Mortality	RR=1.73 (1.45-2.05)	N/A
Cohort(28)	Sweden	24,052 type-1 diabetic patients	Diagnosis <age 21	Incidence	RR=1.17 (1.04-1.33),	Stomach RR=3.36 (1.44-6.66), skin RR=4.96 (2.83-8.07), leukaemia RR=2.02 (1.15-3.29)
Cohort(19)	New Zealand	966 insulin treated participants including 427 with type-1 diabetes	Diagnosis <age 30	Mortality	SMR=12.96 (3.36-22.57)	N/A
Cohort(20)	USA	1,043 type-1 diabetic patients	Diagnosis <age 18	Mortality	SMR=1.2 (0.5-2.0)	N/A
Cohort(15)	UK	28,900 insulin treated diabetics including 23,834 with type-1 diabetes	Diagnosis <age 30	Mortality	SMR=0.90 (0.75-1.08),	Ovarian SMR=2.90, (1.45-5.19)
Cohort (29)	Denmark	109,581 individuals with diabetes	Hospitalised with diabetes < age 50	Incidence	SIR 1.1 (1.0-1.2)	Liver SIR= 4.8 (2.8-7.7), mouth and pharynx SIR=1.8 (1.2-2.6)
Cohort(30)	Sweden	29,187 diabetes patients	Hospitalisation for diabetes <age 30	Incidence	SIR=1.2 (1.0-1.3)	N/A
Case-control(31)	UK	7,713 cases of type-1 diabetes and 38,518 controls	Those currently on insulin and aged <35 at treatment or <35 years at diagnosis of diabetes	Mortality	HR=1.05 (0.72-1.52)	N/A
Case-control(32)	Italy	752 diabetic women with endometrial cancer and 2,606 admitted to the same hospitals	Diagnosis <age 40	Incidence	OR=1.0 (0.3-3.4)	N/A
Case-control(33)	USA	14,000 participants with diabetes aged 30-89	Diagnosed with diabetes < age 29	Incidence	Not statistically significant (at the p<0.05 level)	N/A
Meta-analysis(34)		I case-control and 2 cohort studies (15,30,35)		Incidence	N/A	Endometrial RR=3.15 (1.07-9.92)
Meta-analysis(36)		3 cohort and 6 case-control studies		Incidence	N/A	Pancreatic RR=2.00 (1.37-3.01)

Discussion

This review of the epidemiological literature, relating to type-1 diabetes and cancer incidence and mortality, illustrates that there is still much we need to clarify about the relationship between the two diseases. The findings of the cohort studies were heterogeneous, for example the New Zealand study found an increased SMR of 12.96 (95% CI 3.36-22.57) while a UK study did not find an increase in cancer mortality among those with type-1 diabetes (SMR 0.09, 95% CI 0.75-1.08).(19,31) Neither of the case-control studies found an association between type-1 diabetes 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).(34,36) When studies were grouped into those that focussed upon either cancer mortality or incidence there was still no uniformity within the results.

Although a small number of reports have been specifically focussed upon the two diseases, many of these used different criteria to identify type-1 diabetes (related to age at first diagnosis or age at first hospitalisation for diabetes). The inclusion criteria for a case of type-1 diabetes within different studies ranged from disease diagnosis from ages <18 to those <40 years old. This makes comparison across studies difficult, although the use of similar criteria did not generate homogeneity within results. It is likely that the younger classification of type-1 diabetes is more likely to capture a cohort which most closely matches the true type-1 diabetic population. One study found that using diagnosis before the age of 21 years as the cut-off criterion was specific enough to create a cohort which contained only 2% with type-2 diabetes.(28) Future research should carefully consider the specificity of the criteria they use in this regard.

At the same time, studies which include younger cohorts are likely to contain fewer cases of cancer within a given follow-up period, thus reducing their statistical power considerably. One of the key issues with undertaking population based studies of the links between type-1 diabetes and cancer is that the former is relatively rare and, depending on the site of the cancer, the latter may also be relatively infrequent. The result has been that, when population-based studies have focussed specifically on cancer incidence and/or mortality, as well as differentiating between type-1 and type-2 diabetes, they produced small numbers of incident cancers among participants with type-1 diabetes.(42–44) Research could be improved through the use of larger cohorts and/or longer follow-up periods in order to generate enough concurrent cases of type-1 diabetes and cancer.

The study from Denmark, which found an increase in risk of cancer among men aged 0-54 years, is of particular interest.(27) This age group was most likely to represent those with type-1 diabetes in the study period (1970-1980s), and may represent the true rate of cancer among those with the disease. Although this study found no increase in cancer risk among women, further exploration is needed to clarify this result. The use of an exclusion period within some of the studies is also interesting to note in relation to the issue of reverse causality. Future research could explore the usefulness of this method in terms of exploring the causal pathway between diabetes and cancer (or whether or not it is vice-versa).

The heterogeneity of findings supports the need for further investigation. The paucity of research in this area further illustrates the need for the development of research focused upon the two diseases. Studies undertaken in the future could utilise large-scale datasets with sufficient numbers of cases with type-1 diabetes and controls, for example primary care records used for research such as the GPRD (General Practice Research Database) or THIN (The Health Improvement Network) in the UK. Such research would

enable a clearer understanding of a number of key epidemiological areas with respect to the relationship between type-1 diabetes and cancer. Future research could be undertaken to better understand the relationship between type-1 diabetes and:

- overall cancer risk,
- risk of site-specific cancers,
- cancer mortality,
- mortality after treatment for cancer, and
- the impact that the use of exogenous insulin, and other diabetic medications, have upon cancer incidence.

If an association is found between the two diseases, then further research may be required which explores, in greater detail than previous studies, the differences in type-1 diabetes and cancer relating to gender, race and other demographic and socioeconomic factors; as well as the potential regional variations in diagnosis and treatment of both conditions. Although individuals with type-1 diabetes all require exogenous insulin for survival there may be differences in cancer risk dependent upon the type of insulin administered. At the same time, there is some evidence that individuals with diabetes who then go on to develop cancer are diagnosed at a later stage of the disease and may receive differing treatment regimens compared with those without diabetes.(45,46) The way that cancer is treated also differs by region and country, which will further impact upon cancer survival. All of these issues require further exploration. Research has begun to explore the biological basis for the increased all-cause and cause-specific mortality found among those with type-1 diabetes; key findings suggest that circulating adiponectin, the sharing of aetiological causes, complications caused by type-1 diabetes, and raised BMI may each contribute to increased mortality among those with type-1 diabetes compared with the general population.(10,47) Further research should also be undertaken which enables a better understanding of the biological causes of this differing mortality and enables interventions to be developed which address it.

Conclusion

Type-1 diabetes is a chronic condition relating to poor glycaemic control which appears to be increasing in incidence. Given the large number of individuals with the disease globally, even small increases in the relative risk of cancer incidence and/or mortality among this group will increase the total burden of cancer considerably. Those with the disease have increased mortality at every age following diagnosis, mainly due to complications of the disease itself and cardiovascular and renal disease. An understanding of the potential association between type-1 diabetes and cancer will become increasingly important as improvements are made in the control and prevention of cardiovascular disease, enabling those with diabetes to live longer lives (which in turn increases the risk of developing cancer). Better understanding of the relationship between the two diseases also enables the development of interventions to reduce potential excess mortality.

Current epidemiological research investigating the link between type-1 diabetes and cancer has resulted in mixed findings, which varied by the research methods used. Case-control studies have consistently not

found a statistically significant link between the two diseases, while meta-analyses have. Cohort studies have resulted in mixed findings and there appears to be heterogeneous results within studies that utilise the same criteria for a diagnosis of type-1 diabetes (such as being diagnosed with diabetes before the age of 30). Although there is heterogeneity within the results, it does appear that those with type-1 diabetes either have the same or an increased risk of cancer incidence and/or mortality from the disease. The inconsistency within study findings strongly suggests the need for further detailed research to be undertaken which explores the nature of the relationship between type-1 diabetes and cancer.

Acknowledgments

Vanessa Gordon-Dseagu is funded by Diabetes UK (grant number- 08/0003752) and wishes to thank them for their ongoing support. We thank Professor Sir Michael Marmot and Professor Daniel Hochhauser for their helpful comments on this literature review.

None of the authors declared any conflicts of interests in relation to this work.

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Figure 1: Selection of articles

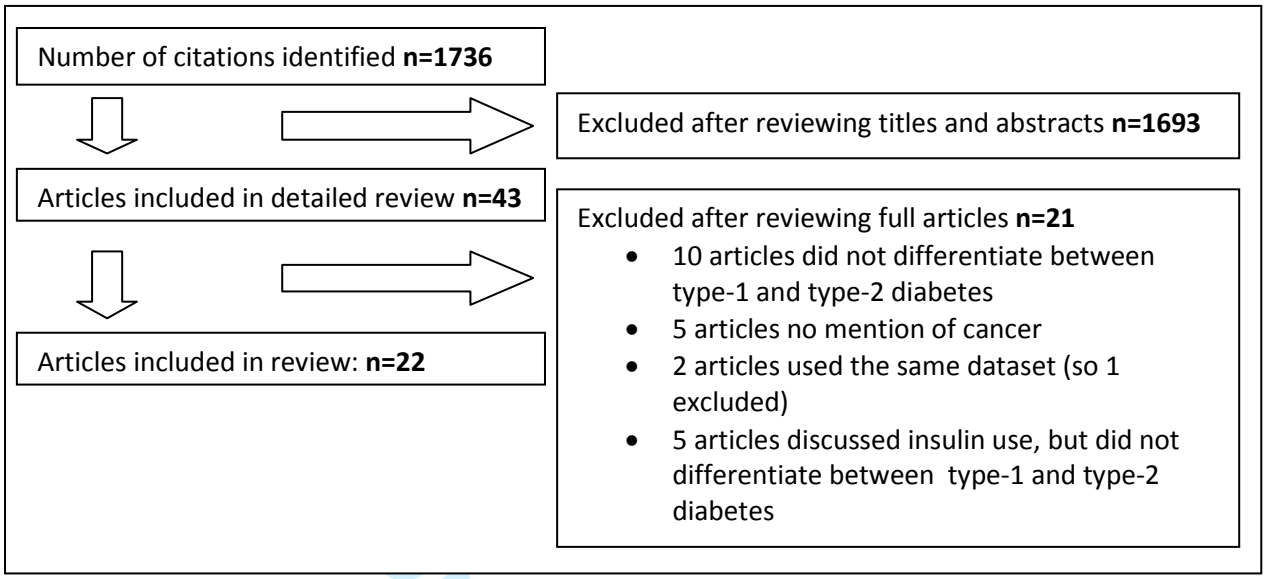

Table 1: Key findings of research exploring the relationship between type-1 diabetes and cancer

Study method	Country	Sample	Case definition (type-1 diabetes)	Outcome measure	Risk of cancer among T1DM participants (95% CI or p-value)	Risk of site-specific cancers (95% CI or p-value)
Cohort(27)	Denmark	1,499 insulin treated individuals	Insulin use	Incidence	Men RR=1.37 (1.03-1.83), Women RR=1.08 (0.77-1.51),	Pancreas RR=2.53 (1.17-5.47); RR=1.69 (p=0.29) once cases excluded where diabetes an indicator of cancer
Cohort(18)	Sweden	144,427 participants with diabetes	Hospitalisation for diabetes <age 40	Mortality	RR=1.73 (1.45-2.05)	N/A
Cohort(28)	Sweden	24,052 type-1 diabetic patients	Diagnosis <age 21	Incidence	RR=1.17 (1.04-1.33),	Stomach RR=3.36 (1.44-6.66), skin RR=4.96 (2.83-8.07), leukaemia RR=2.02 (1.15-3.29)
Cohort(19)	New Zealand	966 insulin treated participants including 427 with type-1 diabetes	Diagnosis <age 30	Mortality	SMR=12.96 (3.36-22.57)	N/A
Cohort(20)	USA	1,043 type-1 diabetic patients	Diagnosis <age 18	Mortality	SMR=1.2 (0.5-2.0)	N/A
Cohort(15)	UK	28,900 insulin treated diabetics including 23,834 with type-1 diabetes	Diagnosis <age 30	Mortality	SMR=0.90 (0.75-1.08),	Ovarian SMR=2.90, (1.45-5.19)
Cohort (29)	Denmark	109,581 individuals with diabetes	Hospitalised with diabetes < age 50	Incidence	SIR 1.1 (1.0-1.2)	Liver SIR= 4.8 (2.8-7.7), mouth and pharynx SIR=1.8 (1.2-2.6)
Cohort(30)	Sweden	29,187 diabetes patients	Hospitalisation for diabetes <age 30	Incidence	SIR=1.2 (1.0-1.3)	N/A
Case-control(31)	UK	7,713 cases of type-1 diabetes and 38,518 controls	Those currently on insulin and aged <35 at treatment or <35 years at diagnosis of diabetes	Mortality	HR=1.05 (0.72-1.52)	N/A
Case-control(32)	Italy	752 diabetic women with endometrial cancer and 2,606 admitted to the same hospitals	Diagnosis <age 40	Incidence	OR=1.0 (0.3-3.4)	N/A
Case-control(33)	USA	14,000 participants with diabetes aged 30-89	Diagnosed with diabetes < age 29	Incidence	Not statistically significant (at the p<0.05 level)	N/A
Meta-analysis(34)		I case-control and 2 cohort studies (15,30,35)		Incidence	N/A	Endometrial RR=3.15 (1.07-9.92)
Meta-analysis(36)		3 cohort and 6 case-control studies		Incidence	N/A	Pancreatic RR=2.00 (1.37-3.01)