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Does the duration of diabetes increase the risk of cancer? A nationwide population-based cohort of patients with new-onset diabetes and a matched reference cohort

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Abstract

Diabetes mellitus and cancer are both common health issues, but the correlation between these two diseases remains unclear. We investigated the association of cumulative exposure of diabetes mellitus as an indication of hyperglycemia in terms of disease duration on multiple cancer types. We hypothesized that the risk of cancer would increase over time after the onset of diabetes. The study population consisted of a population-based cohort of 398,708 people and it was constructed from the Finnish CARING project. The Diabetes group consisted of 185,258 individuals, and the non-diabetic reference group comprised 187,921 individuals. Over 4.1 million person-years were accumulated, and the median follow-up time was 10.55 years. In the diabetes group, 25,899 cancer cases were observed compared with 23,900 cancers in the non-diabetic group. We did not find a clear relationship between the duration of diabetes mellitus and most cancer types examined. However, for cancers of the pancreas, prostate gland, bronchus, and lungs, a temporal relationship was found. Furthermore, even within the cancer types where the relationship was detected, it did not change over time. These findings indicate that diabetes does not independently increase the risk of cancer. Instead, the development of diabetes may be attributed to shared risk factors with cancer, such as obesity and/or insulin resistance accompanied by hyperinsulinemia. Thus, it is likely that the clock for increased cancer risk starts ticking already before onset of diabetes and hyperglycemia.

KEYWORDS

cancer, cohort-study, diabetes mellitus

What's new?

Although type 2 diabetes is associated with an increased risk for certain cancer types, temporal relationships between onset and diagnosis of diabetes and cancer remain unclear. In this study, the authors examined relationships between diabetes and cancer incidence in a large population-based cohort in Finland. Analyses indicate that the duration of diabetes mellitus is unrelated to the onset of most cancer types. Exceptions include cancers of the pancreas, prostate, bronchus, and lungs, though

these associations are limited primarily to the time of diabetes diagnosis. The findings provide new insight into the pathophysiology underlying the relationship between diabetes and cancer.

1 | INTRODUCTION

Cancer and diabetes mellitus are among the major public health issues, especially in industrialized countries. According to a Danish study, 35% of the population are projected to develop diabetes in their lifetime, while 44% will be diagnosed with cancer and 15% will experience both.[1] Type 2 diabetes is associated with hyperinsulinemia and hyperglycemia, two factors known to promote tumor cell growth.[2] There is a growing body of evidence linking the occurrence of type 2 diabetes with cancer.[3–5] According to a meta-analysis, the pooled adjusted risk ratio (RR) for all cancer types combined among diabetes patients was significantly elevated with RR of 1.10.[5] The greatest excess risk was for cancers of the liver, pancreas, and endometrium, while the risks for cancers of the bladder, breast, rectum and colon were also moderately increased.[3] However, it has been argued that the majority of the studies do not provide robust supporting evidence without a risk of bias.[6] One potential source of bias is the temporal sequence of the diagnoses, and, therefore, it is important to assess the link between these two conditions over time.[7–9] Some studies have evaluated the temporal relationship, but the results have been inconsistent. A study by Lega et al. (2016) demonstrated that the diagnosis of type 2 diabetes was associated with elevated risks of pancreatic, endometrial, liver, and thyroid cancers during the first 3 months as well as up to 10 years after the onset of diabetes. On the other hand, the study showed no significant co-occurrence of diabetes and cancer overall after the first 3 months following diabetes onset.[10] A study by De Bruijn et al. (2014) also found that the excess risk of many cancer types appeared to be lower after the initial 3-month period following the diagnosis of diabetes.[11] Contradictory results have spurred discussion on their interpretation including potential biases, such as detection bias and protopathic bias.[10,11]

To clarify these conflicting results, we investigated the relationship between type 2 diabetes and cancer incidence in a Finnish population-based cohort. In particular, we aimed to assess the temporal relationship between diabetes and risk of various cancers. We hypothesized that the risk of cancer increases with time since the onset of diabetes, which is consistent with the cumulative effect of persistent hyperglycemia.

2 | MATERIALS AND METHODS

2.1 | Study population

The study population was constructed based on the CARING Project[12] in Finland. The study population consisted of 185,258 patients with diabetes mellitus (DM), defined as individuals who had purchased and received reimbursement for at least one insulin prescription (ATC code A10A)[13] and/or an oral antidiabetic (OAD) prescription (ATC A10B) between January 1, 1997, and December 31, 2010. We obtained prescription data with the date of purchase, amount, and ATC code from the Social Insurance Institution (SII) (permission Kela 16/522/2012). All insulin users in Finland during this period were included, as well as a 50% random sample of OAD users (the latter restriction was made by SII due to administrative reasons).

The reference group was individually matched (1:1) to the DM group according to sex, age (±1 year), and region (hospital district). Individuals in this group had not purchased any insulin or OADs.

2.2 | Ascertainment of outcomes and covariates

Cancer cases were classified according to ICD-O-3 topological and morphological codes. We used the first-ever incidence of any cancer (C00-C97) as the outcome, apart from non-melanoma skin cancers, which were excluded from the analyses. Death was treated as a censoring event. The following covariants were used in the models: diabetes, 5-year age group, calendar year, follow-up period, and socioeconomic status.

We analyzed the most frequent cancer types separately, including stomach, colon, rectum, liver and intrahepatic bile ducts, pancreas, bronchus and lung, hematopoietic and reticuloendothelial systems, skin, kidney, bladder, breast, corpus uteri and prostate gland cancers.

2.3 | Follow-up

Follow-up for cancer incidence started on the date of the first diabetes medication purchase and ended on December 31, 2017, death, or on the date of cancer diagnosis, whichever occurred first. The same date was used for the individually matched control. The year prior to the start of follow-up (1996) was the initial wash-in period, so anybody with a prescription for antidiabetic medication within 1 year before the start of the follow-up was excluded.

The cancer data were obtained from the Finnish Cancer Registry. We received information on the histological subtype, primary site (ICD-O-3 codes), and date of diagnosis for all cancer cases. All individuals diagnosed with any cancer, except non-melanoma skin cancer, before the start of follow-up were excluded.

We obtained the information on socioeconomic status and deaths (the date and cause of death) from Statistics Finland (permission TK-53-214-12).

2.4 | Statistical analysis

The follow-up time was split into fixed time bands and analyzed using Poisson regression models that account for the

evolution of disease risk on multiple time scales.[14] Time break points were 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, and 18 years. We analyzed the cohort data separately for each endpoint. The results from the Poisson regression models were reported as incidence rate ratios (IRR). We checked the interaction between the time since the start of follow-up and diabetes using the likelihood ratio test. All results were reported with 95% confidence intervals (CIs). Analyses were carried out using R data-analysis language [20] with package Epi.[15]

TABLE 1 Basic characteristics of study population.

	Diabetes		
	No	Yes	Overall
N	187,921	185,258	373,179
Sex, female (%)	88,986 (47.4)	87,640 (47.3)	176,626 (47.3)
Socioeconomic group (%)			
Upper-level employees	18,014 (9.6)	13,133 (7.1)	31,147 (8.3)
Self-employed	12,745 (6.8)	11,113 (6.0)	23,858 (6.4)
Lower-level employees	27,019 (14.4)	23,131 (12.5)	50,150 (13.4)
Manual workers	28,982 (15.4)	28,236 (15.2)	57,218 (15.3)
Students	3549 (1.9)	3549 (1.9)	7098 (1.9)
Pensioners	79,584 (42.3)	85,782 (46.3)	165,366 (44.3)
Others	18,028 (9.6)	20,314 (11.0)	38,342 (10.3)
Age (mean [SD])	57.37 (17.60)	57.28 (17.64)	57.33 (17.62)

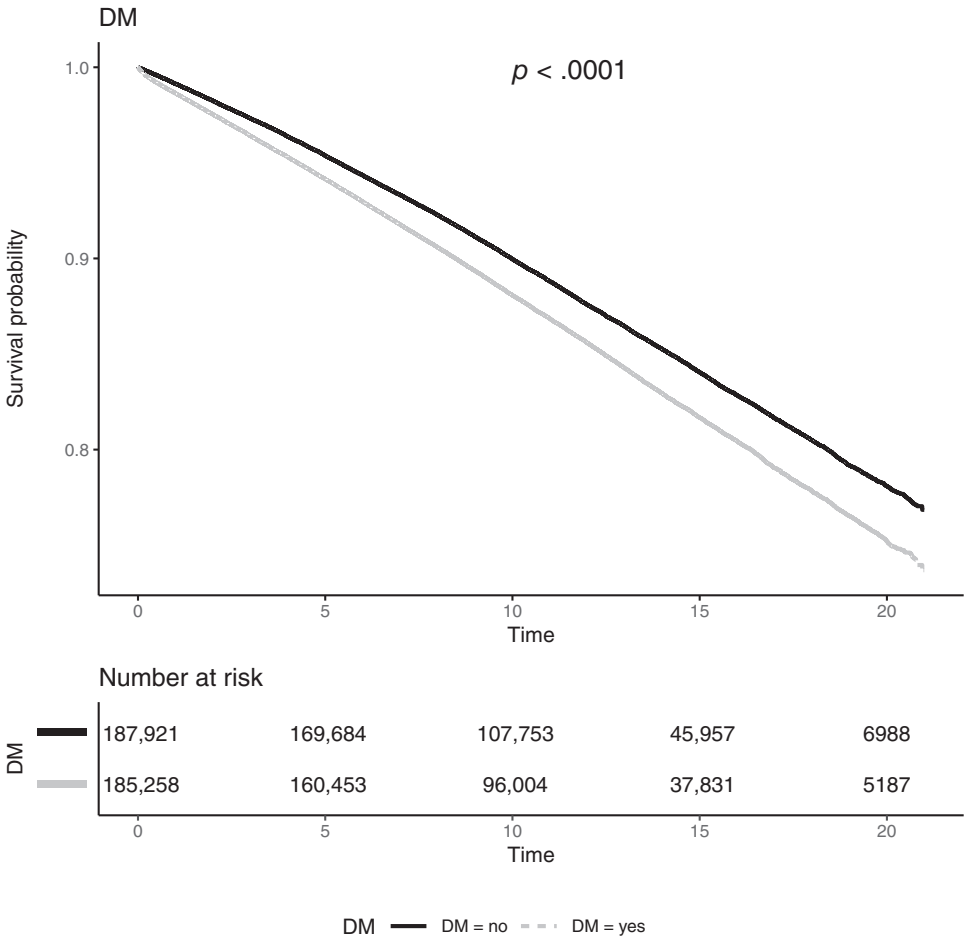

FIGURE 1 Kaplan–Meier curve for cancer incidence for diabetes and non-diabetic groups.

3 | RESULTS

The study population consisted of 398,708 individuals, with 196,553 men and 176,626 (47.3%) women who accumulated 4.1 million person-years of follow-up (Table 1). The diabetes group comprised 185,258 individuals and the comparison group included 187,921 individuals. The prevalence of diabetes mellitus was slightly higher in lower-level employees than in upper-level ones. Overall, the mean age at the start of the follow-up was 57.3 years. More accurate description of the age groups at the beginning of study can be found in the supplementary material (Supplementary table).

In total, 49,799 cancer cases were observed. Out of all cancers, 25,899 occurred in the diabetes group compared to 23,900 in the non-diabetic group. Of the cancers, 8720 cases were other than the 13 most frequent types of cancer mentioned in Section 2. The Kaplan–Meier curve showed that the overall risk for cancer was higher in the DM group than in the reference group (Figure 1).

The adjusted incidence for all-site cancers was significantly elevated in the DM group compared to non-DM group with incidence rate ratio (IRR) of 1.18 (95% CI 1.15–1.20). The IRRs for patients with DM were considerably elevated (>2.0) for cancers of the liver and intrahepatic bile ducts, and the pancreas (Table 2). In addition, moderately elevated IRRs (>1.5) were found in cancers of the corpus uteri and kidneys. The IRRs were slightly elevated (<1.5) for cancers of the stomach, colon, rectum, bronchus and lung, skin, and bladder. For prostate cancer, the IRR significantly decreased (0.92, 95% CI 0.88–0.96). No significant differences were found between the DM and reference groups for hematopoietic, reticuloendothelial, and breast cancers (Table 2).

We examined the temporal relationship between DM and various types of cancers. No clear pattern in relation to the time from diabetes onset was observed for most of the cancers examined, as the relationship remained fairly constant after diabetes diagnosis (Supplementary figures). However, a significant interaction between the DM group and the time since the start of follow-up was observed for cancers of the pancreas ($p < .0001$), bronchus and lung ($p = .0012$), and prostate ($p < .0001$) (Figure 2). For these three cancer types, the incidence increased immediately after the diagnosis of diabetes. For

TABLE 2 Number of cases, incidence rates (per 1000 person-years), univariate incidence rate ratios (IRR), and adjusted IRR.

	DM	P-years (1/1000)	Events	Rate	Uni	Adj.
C16 (stomach)	No	2132.87	581	0.27 (0.25–0.30)	(Reference)	(Reference)
	Yes	1966.96	720	0.37 (0.34–0.39)	1.34 (1.20–1.50)	1.40 (1.25–1.56)
C18 (colon)	No	2132.87	1446	0.68 (0.64–0.71)	(Reference)	(Reference)
	Yes	1966.96	1722	0.88 (0.83–0.92)	1.29 (1.20–1.38)	1.35 (1.25–1.44)
C20 (rectum)	No	2132.87	700	0.33 (0.30–0.35)	(Reference)	(Reference)
	Yes	1966.96	793	0.40 (0.38–0.43)	1.23 (1.11–1.36)	1.28 (1.16–1.42)
C22 (liver and intrahepatic bile ducts)	No	2132.87	342	0.16 (0.14–0.18)	(Reference)	(Reference)
	Yes	1966.96	921	0.47 (0.44–0.50)	2.92 (2.58–3.31)	3.03 (2.67–3.43)
C25 (pancreas)	No	2132.87	826	0.39 (0.36–0.41)	(Reference)	(Reference)
	Yes	1966.96	1896	0.96 (0.92–1.01)	2.49 (2.29–2.70)	2.54 (2.34–2.76)
C34 (bronchus and lung)	No	2132.87	2155	1.01 (0.97–1.05)	(Reference)	(Reference)
	Yes	1966.96	2294	1.17 (1.12–1.22)	1.15 (1.09–1.22)	1.16 (1.10–1.23)
C42 (hematopoietic and reticuloendothelial systems)	No	2132.87	1164	0.55 (0.51–0.58)	(Reference)	(Reference)
	Yes	1966.96	1092	0.56 (0.52–0.59)	1.02 (0.94–1.10)	1.06 (0.98–1.15)
C44 (skin)	No	2132.87	2186	1.02 (0.98–1.07)	(Reference)	(Reference)
	Yes	1966.96	2163	1.10 (1.05–1.15)	1.07 (1.01–1.14)	1.16 (1.09–1.23)
C64 (kidney)	No	2132.87	656	0.31 (0.28–0.33)	(Reference)	(Reference)
	Yes	1966.96	965	0.49 (0.46–0.52)	1.60 (1.44–1.76)	1.63 (1.48–1.80)
C67 (bladder)	No	2132.87	678	0.32 (0.29–0.34)	(Reference)	(Reference)
	Yes	1966.96	799	0.41 (0.38–0.44)	1.28 (1.15–1.42)	1.34 (1.21–1.49)
C50 (breast)	No	1015.17	2884	2.84 (2.74–2.95)	(Reference)	(Reference)
	Yes	944.583	2615	2.77 (2.66–2.88)	0.97 (0.92–1.03)	0.99 (0.94–1.05)
C54 (corpus uteri)	No	1015.17	583	0.57 (0.53–0.62)	(Reference)	(Reference)
	Yes	944.583	899	0.95 (0.89–1.02)	1.66 (1.49–1.84)	1.67 (1.50–1.85)
C61 (prostate gland)	No	1117.70	5495	4.91 (4.78–5.05)	(Reference)	(Reference)
	Yes	1022.38	4453	4.36 (4.23–4.49)	0.89 (0.85–0.92)	0.92 (0.88–0.96)

Note: Adjusted for age, sex, socioeconomic group, calendar-year and time since start of follow-up.

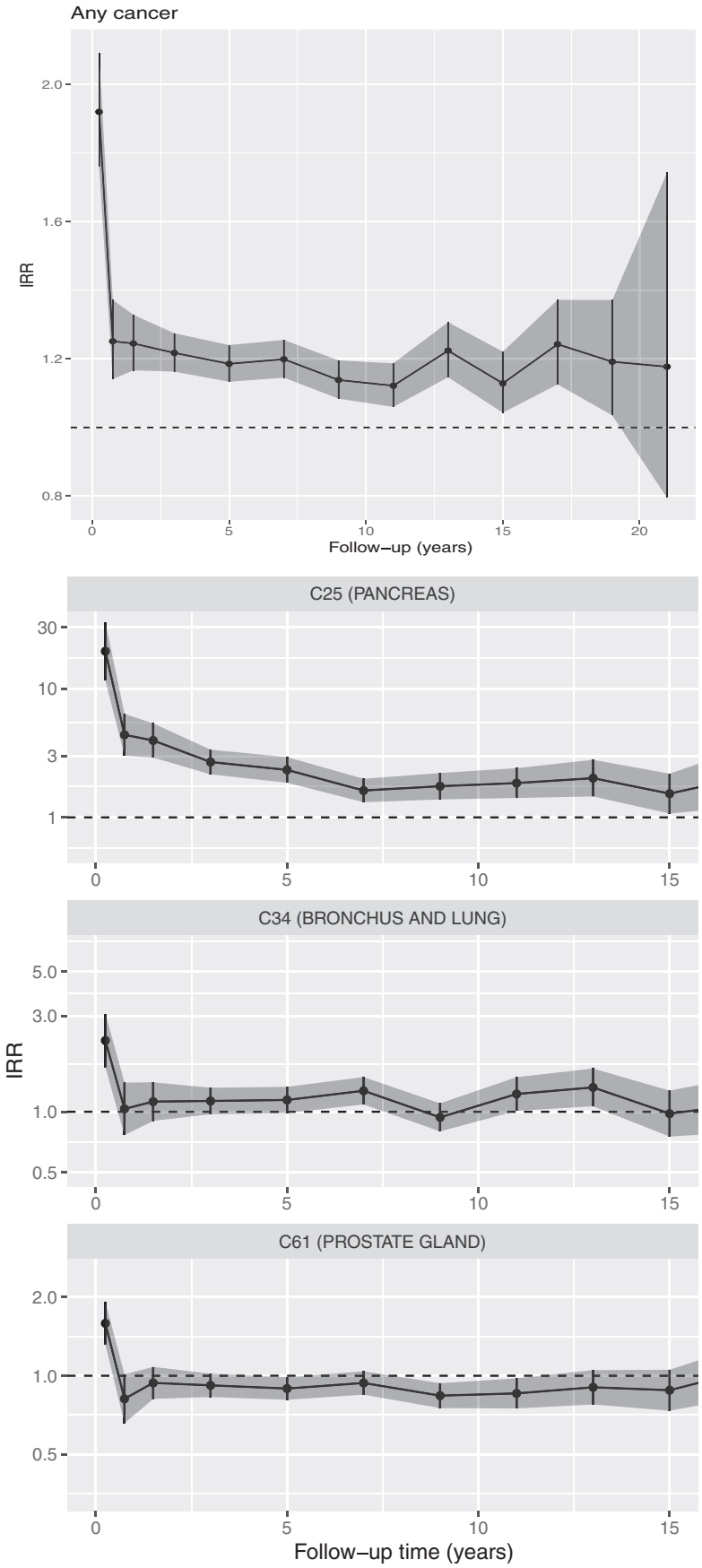

FIGURE 2 Incidence rate ratios with 95% confidence interval as function of time since start of follow-up comparing diabetes group to non-diabetic group.

pancreatic cancer, an IRR exceeding 10 was found after the start of follow-up, before plateauing at approximately twice the level in the reference group. Also for lung cancer, the IRRs remained elevated over time, whereas the IRR for prostate cancer decreased with time since the diagnosis of diabetes. Overall, no increased risk with the duration of diabetes was found for any cancer type apart from pancreatic cancer (Figure 2).

4 | DISCUSSION

In this study, we investigated the temporal relationship between diabetes onset and cancer incidence in a Finnish population-based cohort. As expected, the risk of several cancer types, including cancers of the liver and pancreas, was elevated in patients with diabetes, whereas prostate cancer showed a reduced risk. Over time, only three of the 13 examined cancer types, namely cancers of the pancreas, lung, and prostate, showed increased risks, which were largely limited to the time of diabetes diagnosis. We did not find an increasing trend in cancer risk over time after the onset of diabetes for any of the examined cancer types, except for pancreatic cancer.

We hypothesized that if there was a direct causal effect of diabetes on the incidence of cancer, it would lead to an increase in incidence over time after diagnosis of diabetes. In some cancer types, the incidence was elevated immediately after DM diagnosis but disappeared in almost all of the examined cancers, and no clear increase in IRR with the duration of diabetes was found. The only exception was pancreatic cancer, which had an elevated IRR for up to 15 years after the diagnosis of DM. Although this relationship was found, the IRR seems to decline over time after the onset of diabetes. Elevated risks of pancreatic, endometrial, liver, and thyroid cancers have been observed in previous studies during the first 3 months and up to 10 years after the onset of diabetes.[10] Likewise, incidence of individual cancers or cancer overall has been reported to decrease after the initial 3-month period. This has been suspected to reflect detection or protopathic bias.[10,11] Our findings suggest that there is no accumulation of cancer risk over time since the diagnosis of diabetes. This does not exclude a causal relationship between these two factors but speaks against a gradual accumulation of risk that could be expected if the excess risk in diabetes would be attributable to an incremental effect due to hyperglycemia or other metabolic effects of diabetes. However, we did not have information on glycemic control available in our study, which is a limitation.

We found considerably elevated risks (IRR >2) for cancers of the liver and intrahepatic bile ducts, and pancreas. These findings are in line with previous literature.[3] In the case of pancreatic cancer this might reflect impaired insulin secretion function of the Langerhans islet cells caused by the cancer.[16,17] It is important to note that DM is a risk factor but also an early warning sign of pancreatic cancer.[18] Some of the excess risk is also caused by shared risk factors for these diseases such as obesity.[19] Shared risk factors may be one of the reasons why IRR stays elevated for up to 15 years after diagnosis of DM. A moderately elevated IRR (1.5–2) for cancers of the corpus uteri and kidneys was also found. For kidney cancer, the previous literature is inconclusive,[3] whereas for corpus uteri cancer, a moderately elevated risk has been reported.[20] IRRs were also slightly elevated (IRR <1.5) for cancers of the stomach, colon, rectum, lung, skin, and bladder. Obesity is an obvious risk factor connecting diabetes with several of these cancer types, notably colorectal, kidney, breast, and endometrial cancer, as well as esophageal, ovarian, and pancreatic cancers, and previous studies have shown increased risks of cancers of the colon, rectum, and bladder among patients with diabetes.[3,21] On the other hand, no significant increases have been previously reported for lung or skin cancer.[3,22] Contrary to our findings, earlier literature suggests that DM has no clear effect on the incidence of stomach cancer.[23] Finally, we found that IRR for prostate cancer was materially decreased, which agrees with the previous studies.[3] We detected no difference in risk of hematopoietic and reticuloendothelial malignancies or breast cancer. We found no previous literature on lympho-hematological malignancies. Unlike our findings, an increased risk of breast cancer has previously been described among patients with DM.[3]

Our study has several strengths, including its large population-based cohort and comprehensive coverage of diabetes and cancer diagnoses from reliable national registries. This avoids selection and information bias. We were able to take into account several time scales simultaneously in the analysis, including calendar year, age, and time since the onset of diabetes.

The shortcomings of our study include the lack of detailed information on potential confounders, including shared risk factors for DM and major cancer types, as well as the inability to distinguish specific types of DM. Information on body mass index, diet, physical activity, smoking and alcohol consumption would have been useful since these factors affect the risk of DM and many cancers.[3] According to national surveys in the US, individuals with DM have similar smoking patterns as non-diabetic individuals but a higher body mass index.[24,25] In addition, the definition of diabetes depended on antidiabetic medication; therefore, new cases treated with behavioral and nutritional interventions were not included. The lack of information on the clinical details of DM, such as medications, blood glucose, and HbA1c measurements, is also a limitation. Yet, clinical practice in Finland has been shown to adhere to national guidelines with stepwise addition of medications, and therefore collinearity with diabetes duration would be unavoidable. Although the maximum follow-up time for the study was as long as 20 years, only a small proportion of the individuals were followed up for more than 10 years. We only used the baseline characteristics of DM and were not able to exclude people in the reference group who were later diagnosed with DM. Also there was a high probability of undiagnosed DM in the reference group, even at baseline. Finally, the Finnish population is ethnically rather homogenous, which may limit the generalization of our results.

In conclusion, we found an increased risk for several cancer types shortly after the onset of diabetes, but the risk declined over time and did not significantly deviate from the risk in the non-diabetic group in the long-term except for pancreatic cancer. For pancreatic cancer, the incidence remained elevated for the full follow-up period, although it was at a lower level after the initial post-diagnostic period. These

findings do not exclude causal effects between DM and cancer, but they suggest that common risk factors, protopathic bias, or detection bias may inflate the risk of cancer among patients with DM soon after diagnosis. Future studies with detailed long-term data on medications and glycemic control could shed more light on determinants of cancer risk in patients with diabetes.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions: conception and design (all), data acquisition and analysis (PL, JH, AA), and data interpretation(all). They all participated in drafting the article or revising it critically for important intellectual content, and all approved the final version. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data that support the findings are available from the authors upon reasonable request and with permission from Statistics Finland, Social Insurance Institution (SII), and the Finnish Cancer Registry.

ETHICS STATEMENT

The study plan was approved by the Faculty of Medicine, University of Helsinki Ethical Committee on January 17th 2012 (Ref 02/2012). All the data from the registers were anonymous, the researchers had no information about their identities, and there was no contact with the study population. According to Finnish law, no consent from patients in purely register-based studies is needed.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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