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Associations between diabetes and cancer: A 10-year national population-based retrospective cohort study

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ABSTRACT

Aims: To investigate the risk of cancer in people with diabetes compared to the population without diabetes and to gain insight into the timely association between diabetes and cancer at national level.
Methods: A retrospective cohort study was conducted to analyse the role of diabetes in the development of cancer, based on service utilisation and antidiabetic dispensing data of the population between 2010 and 2021. Univariate and multivariate Cox regression were used to examine how diabetes status, in relationship with age and sex are related to the time to cancer diagnosis.
Results: Examining a population of 3 681 774 individuals, people with diabetes have a consistently higher risk for cancer diagnosis for each cancer site studied. Diabetes adds the highest risk for pancreatic cancer (HR = 2.294, 99 % CI: 2.099; 2.507) and for liver cancer (HR = 1.830, 99 % CI: 1.631; 2.054); it adds the lowest – but still significant – risk for breast cancer (HR = 1.137, 99 % CI: 1.055; 1.227) and prostate cancer (HR = 1.171, 99 % CI: 1.071; 1.280).The difference in cancer rate is driven by the younger age group (40–54 years: for patients with diabetes 5.4 % vs. controls 4.4 %; 70–89 years: for patients with diabetes 12.7 % vs. controls 12.4 %). There are no consistent results whether the presence of diabetes increases the risk of cancer diagnosis differently in males and females. The cancer incidence starts to increase before the diagnosis of diabetes and peaks in the year after. By the year after the start of the inclusion date, the incidence is 114/10,000 population in the control group, vs 195/10,000 population in the group with diabetes. Following this, the incidence drops close to the control group.
Conclusions: Screening activities should be revised and the guidelines on diabetes should be complemented with recommendations on cancer prevention also considering that the cancer incidence is highest around the time of the diagnosis of diabetes. For prostate cancer, our results contradict many previous studies, and further research is recommended to clarify this.

1. Introduction

There are many similarities between the risk factors of diabetes and cancer, this alone does not seem to explain the coexistence of the two diseases. Several studies have shown that diabetes is an independent risk factor for multiple cancer sites [1–3].

A meta-analysis of 151 cohorts attempted to estimate the likelihood of causality between diabetes and cancer. It indicated a strong causal

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association between Type 2 diabetes and liver, pancreatic, and endometrial cancer incidence, and pancreatic cancer mortality, a likely to be causal association with gallbladder cancer incidence. In contrast, the associations with kidney, colorectal, and thyroid cancer incidence were less robust. Finally, it found that the association between Type 2 diabetes and leukaemia, prostate, breast, bladder, stomach, ovarian, Non-Hodgkin lymphoma, melanoma, lung, or esophageal cancer is unlikely to be causal. It even showed that Type 2 diabetes was associated with a decreased risk of prostate cancer (RR: 0.83; 0.79, 0.88) [4].

For Type 1 diabetes, the results are not so clear. According to the review by Zhu et al, while there are studies indicating that cancer incidence of liver, pancreas, kidney, esophagus, stomach, lung, thyroid, squamous cell carcinoma and leukaemia are increased in Type 1 diabetes, some researches found no significant associations between them [5].

Contradictory results have also been found when analysing the association between sex-related cancers and diabetes [5].

However, according to a meta-analysis of 121 cohorts, females with any type of diabetes have around 6 % greater risk for cancer than males with diabetes. Differences vary by location of cancer, showing greater risk in females than males for oral, stomach, and kidney cancer and leukaemia, but lower risk for liver cancer [6].

Numerous studies have investigated the mechanism between diabetes and cancer. These include genetic researches [5,7,8], studies on common risk factors such as obesity, inflammation, hyperglycaemia or hyperinsulinaemia, sex hormones and the related molecular mechanisms [3,5,8–12], researches examining the role of antidiabetics [5,8,11–13] and nutrition [8].

Until recently, the time to onset of cancer relative to the diabetes diagnosis seems to be a less studied and therefore less evidence-based area. Lega et al. revealed that patients with diabetes had a significantly higher risk of most cancers ten years before and immediately after a diabetes diagnosis [14]. The increased risk just after the diabetes onset was also shown by Johnson et al. in the case of different sites of cancers, with only the risk of colorectal, liver, endometrial, and pancreatic cancer remaining elevated in later periods [15]. Furthermore, Carstensen et al. found that the rate ratio for all cancers was also the highest in the period just after the diagnosis of diabetes in both insulin users and non-users [16]. At the same time, Hu et al. found that when comparing the cohorts with and without diabetes, the hazard ratio (HR) for cancer was the highest at approximately eight years after the diagnosis of Type 2 diabetes, and the relationship with Type 2 diabetes duration was similar for different sites of cancers [17].

Within a Central European population, we investigated the relationship of diabetes and multiple cancer sites with two major objectives. First, to determine the risk of developing cancer in patients with diabetes compared to the non-diabetic population. Second, to examine how the time of cancer diagnosis is related to the time of diabetes diagnosis.

2. Material and methods

Data from five sources were provided by the Hungarian National Health Insurance Fund Administration (NHIFA) for our study: data on primary care, outpatient specialty care, hospital utilisation, demographic dataset of the population with a social security number (SSN, SSN dataset), and the stock of dispensed prescriptions. All datasets contain individual utilisation records in which individuals are identified by their SSN. The unique personal identifiers in the datasets were converted to depersonalized identifiers by the National Infocommunications Ltd, keeping them linkable, while individuals in the datasets could not be identified.

NHIFA collects data on all publicly financed healthcare services. This includes the date of service utilization, the diagnoses related to the service based on the 10th version of the International Classification of Diseases (ICD-10), and the tests and procedures performed. However, the datasets do not contain the results of diagnostic tests. The datasets provided to us contain data on service utilization from 2010 to 2021. NHIFA registers the date of birth, sex, date of death, citizenship, and validity of SSN for individuals with a Hungarian SSN in its SSN dataset. The provided dataset includes all individuals who were alive on 1st January 2010.

Based on this dataset, a retrospective cohort study was conducted to analyse the role of diabetes (Type 1 and Type 2) in the development of cancer. Inclusion criteria were Hungarian citizenship, a valid SSN, age at inclusion date of at least 40 years and below 90 years. Individuals with diabetes were identified based on dispensation of antidiabetic drugs (ATC: A10A, A10B): individuals who had dispensed at least one antidiabetic drug were considered patients with diabetes. Only those patients with diabetes were included in the study whose first antidiabetic drug dispensation date according to prescription records was in 2014 or 2015. Since prescription records in the dataset were available from 2010, we could verify that for these patients, there were no antidiabetic drug dispensations from 2010 to 2013: therefore, diabetes was with great certainty indeed diagnosed in 2014 or 2015. The date of the first dispensation was considered as the date of the first diagnosis of diabetes, and in the group with diabetes, as the inclusion date in the study. For individuals without diabetes (control group), the inclusion date was defined as 1st January 2014. In addition, the following individuals were excluded from both groups: those who had a pregnancy-obstetric code (ICD-10: “O” category and Z31-Z37) or a diagnosis of polycystic ovary syndrome (PCOS, ICD-10: E2820) documented in their primary care or specialty care records at any time during the study period. Finally, for Study 1 only, we excluded those who had recorded cancer diagnosis of the studied site (back until 2010) before the inclusion date.

The date of cancer diagnosis was identified as the date of the first relevant diagnosis code recorded in outpatient or inpatient specialty care. The analysis covered all ICD codes for cancer and six specific sites (Colorectal: C18-C21, Liver: C22, Pancreatic: C25, Breast (female): C50, Prostate: C61, and Kidney cancer: C64). Time to cancer diagnosis was calculated from the inclusion date (ie, date of first antidiabetic drug dispensation for patients with diabetes and from 1st January 2014, for the control group). Study individuals were followed – based on utilisation and mortality data – until death or the end of the study period, 31st December 2021.

In Study 1, the first diagnosis of cancers in different sites in the period *after* the inclusion date was examined. The composition of the analysed population was characterized by descriptive statistical data. Time to cancer diagnosis (all cancer, and by cancer site) in the group with diabetes vs the control group was investigated by univariate Cox regression, in different subgroups (age group [40–54 years, 55–69 years, and 70–89 years], sex); results are presented in a Forest plot. Time to cancer diagnosis (all cancer, and by cancer site) was also investigated using multivariate Cox regression, with diabetes status, age (as continuous variable), and sex as independent variables. The HR values by sex and age for each cancer site in patients with diabetes were determined using the Cox proportional hazard regression model. Interaction of diabetes status with age and with sex was included, unless not statistically significant. Other potential influencing factors, such as obesity or smoking, were not included in the analyses due to lack of data. Due to the large sample size, a significance level of 1 % was chosen (consistently, 99 % confidence intervals are presented). The only exceptions are the interactions in the multivariate Cox model, where a significance level of 5 % was used.

In Study 2, the time of first cancer diagnosis was investigated in retrospect and prospectively with respect to the inclusion date. We investigated the yearly incidence of cancer diagnosis from 3 years before the inclusion date until 6 years after the inclusion date. (Three years before was chosen due to limited data availability before 2011; 6 years after was chosen because that is the maximum available follow-up for those who dispensed prescribed antidiabetics on 31st December 2015.) The incidences in the retrospective period are relative to the number of patients included in the study; for the incidences in the prospective

period, at each timepoint, the population included only those still at risk (ie, excluded those who passed away or were diagnosed with cancer by that time).

Statistical analyses were performed using IBM SPSS v27.0 software.

3. Results

3.1. Study 1

Table 1 summarizes the descriptive results, separately for the control group and group without diabetes. There were 3 681 774 individuals (with diabetes and without diabetes in total) included in the analysis, none of them had cancer diagnosis before 2014 (control group) or before the date of the first prescribed antidiabetics dispensation (group with diabetes). Of these, 3 595 237 individuals did not fill prescribed antidiabetics during the observation period (control group). The other 86 537 individuals dispensed their first prescribed antidiabetics in 2014–2015 (group with diabetes). The proportion of males is similar in the control group and in the group with diabetes (45.6 % and 46.7 %, respectively). However, in the group with diabetes, the average age (61.4 years) and the proportion of those older than 70 years (23.7 %) is higher than that in the control group (average age: 58.0 years; 70+: 19.6 %).

Cancer diagnosis was recorded during the observation period in 8.6 % of the individuals in the control group (males: 9.3 %, females: 8.0 %), and in 10.1 % of the individuals in the group with diabetes (males: 11.3 %, females: 9.2 %). The difference in cancer rate between the group with diabetes vs control group is driven by the younger age group (40–54 years: for patients with diabetes 5.4 % vs. controls 4.4 %; 70–89 years: for patients with diabetes 12.7 % vs. controls 12.4 %). Among those for whom cancer diagnosis was recorded during the observation period, the proportion of males was higher, and the average age was higher in both the control group and the group with diabetes (Table 1).

The results by cancer site are more or less consistent with those for all cancer. For each cancer site the proportion of those for whom cancer diagnosis was recorded during the observation period is higher in the group with diabetes vs. the control group. This is true by sex as well. In addition, in both groups, in cancer sites that are relevant in both sexes (pancreatic, renal, kidney, liver and colon), the raw incidence of cancer diagnosis is higher in the males – (Table 1).

Fig. 1 shows the time to cancer diagnosis HR for the group with diabetes vs the control group by subgroup (based on univariate Cox proportional hazards model). The point estimates of all HR's are higher than 1; further, for most cancer sites and subgroups, even the lower limit of the 95 % confidence interval (CI) is higher than 1. This indicates that for each cancer site, in most investigated subgroups (by sex, by age), the group with diabetes has consistently higher risk for cancer diagnosis. Regarding age: with the exception of breast cancer, for each cancer site, the presence of diabetes increases the risk of cancer diagnosis in the youngest group (40–54 years) the most. Consistently: with the exception of breast and pancreatic cancer, for each cancer site, the presence of diabetes increases the risk of cancer diagnosis in the oldest group (≥70 years) the least. In the cancer sites that can occur in both sexes, there is no consistent pattern for HR within the males vs within the females: the male vs female HR is similar for colorectal cancer; higher in males for liver (and pancreatic) cancer, and is higher in females for kidney cancer (Fig. 1).

In the multivariate analysis, in all cancer sites, all investigated independent variables (diabetes, age, sex [if applicable]) significantly influenced the time to cancer diagnosis: the presence of diabetes, higher age, and sex of male (if applicable) are risk factors in developing cancer. Diabetes adds the highest risk for pancreatic cancer (HR = 2.294, 99 % CI: 2.099; 2.507) and for liver cancer (HR = 1.830, 99 % CI: 1.631; 2.054); it adds the lowest – but still significant – risk for breast cancer (HR = 1.137, 99 % CI: 1.055; 1.227) and prostate cancer (HR = 1.171, 99 % CI: 1.071; 1.280). Females have significantly lower risk to develop cancer: the HR's for sex range between 0.470 (kidney cancer) and 0.718 (pancreatic cancer). Age significantly increases the risk of cancer diagnosis: one year of age increment increases the risk of cancer diagnosis with 1.7 % (breast cancer) to 8.3 % (prostate cancer) (Table 2).

The interaction of diabetes with sex (if applicable) and with age was also investigated within each cancer site and in total. At 1 % significance level, there was no difference by sex in how the presence of diabetes influences the risk of cancer diagnosis in any of the cancer sites. However, at 5 % significance level, for kidney cancer, the presence of diabetes increases the risk of cancer diagnosis more for females (ratio of hazard ratio [RHR] = 1.257; at age 40, HR females: 2.478, HR males: 1.972); while for liver cancer, the presence of diabetes decreases the risk of cancer diagnosis less for females (RHR = 0.831; at age 40, HR females: 2.126, HR males: 2.559). At 1 % significance level, for kidney, prostate, and colon cancer, the presence of diabetes increases the risk of cancer diagnosis less as age increases. This is most relevant for kidney cancer, where the RHR for 10 years of increase in age is 0.843 (eg, for females, HR at age 40: 2.478, at age 50: 2.090). The presence of diabetes increases for the risk of diagnosis of pancreatic and breast cancer similarly across all ages (Table 3).

3.2. Study 2

The year of the first appearance of cancer diagnosis relative to the inclusion date has also been investigated. In this analysis, also individuals who had cancer diagnosis before the inclusion date (and were still alive at the inclusion date) were included. As for the previous analyses, those who did not dispensed prescribed antidiabetics during the observation period were assigned to the control group, and those who dispensed their first prescribed antidiabetics in 2014–2015 were assigned to the group with diabetes. Consistently with the previous analysis, the inclusion date is 1st January 2014 in the control group, and the date of the dispensing of the first prescribed antidiabetics (between 1st January 2014 and 31st December 2015) in the group with diabetes. We investigated the yearly incidence of cancer diagnosis from 3 years before the inclusion date until 6 years after the inclusion date.

Fig. 2a-g show the incidence of cancer diagnosis for each year before and after the start of the inclusion date. In total, regardless of cancer site, in both groups, the incidence starts to increase already before the start of the inclusion date, and peaks in the year after the start of the inclusion date. The rate of increase over time is relevantly higher in the group with diabetes: by the year after the start of the inclusion date, the incidence is 114/10,000 population in the control group, vs 195/10,000 population in the group with diabetes. Following that, the incidence in the control remains more or less constant (109/10,000–113/10,000), and the incidence in the group with diabetes drops close to the control group, but remains always higher (128/10,000–143/10,000). Most cancer sites follow a similar pattern; the peak in the year after the inclusion date appears to be most relevant in pancreatic and liver cancer. An exception is breast cancer, where there is no increase in the control group before the inclusion date, and the incidence of the group with diabetes in the later years is similar to that of the control group. Similarly, in prostate cancer, the incidence of the group with diabetes is similar to that of the control group starting from 4 years after the inclusion date.

4. Discussion

In our study, we analysed the relationship between diabetes and cancer for the whole Hungarian population using the most comprehensive available database with administrative data from the period of 2010–2021.

Diabetes was identified based on antidiabetic drug dispensing rather than based on diagnosis codes because it is assumed that a high proportion of individuals with diabetes diagnosis codes may not actually have diabetes. An example of this is the presence of pre-diabetic conditions for which no specific ICD diagnosis code is available, therefore

Table 1
Characteristics of the study population.

Study group	Characteristics		All cancers						Total			Cancer rate (%)		
			Not present			Present								
			Male	Female	All	Male	Female	All	Male	Female	All	Male	Female	All
Control	Number of cases (people)	All	1,485,620.0	1,800,861.0	3,286,481.0	152,862.0	155,894.0	308,756.0	1,638,482.0	1,956,755.0	3,595,237.0	9.3	8.0	8.6
	Age distribution (%)	40–54	52.5	39.5	45.4	20.5	23.9	22.2	49.5	38.3	43.4	3.9	5.0	4.4
		55–69	34.4	37.0	35.8	53.3	45.8	49.6	36.2	37.7	37.0	13.8	9.7	11.5
		70–89	13.1	23.5	18.8	26.1	30.2	28.2	14.3	24.1	19.6	17.1	10.0	12.3
	Mean age (year)		55.3	59.5	57.6	62.8	63.0	62.9	56.0	59.7	58.0			
	Proportion of males (%)			45.2			49.5			45.6				
Diabetes	Number of cases (people)	All	35,883.0	41,876.0	77,759.0	4,553.0	4,225.0	8,778.0	40,436.0	46,101.0	86,537.0	11.3	9.2	10.1
	Age distribution (%)	40–54	34.5	24.0	28.9	14.3	14.9	14.6	32.3	23.1	27.4	5.0	5.9	5.4
		55–69	48.2	48.1	48.1	59.0	52.2	55.7	49.4	48.5	48.9	13.4	9.9	11.6
		70–89	17.3	27.9	23.0	26.7	32.9	29.7	18.4	28.4	23.7	16.4	10.6	12.7
	Mean age (year)		59.1	62.7	61.1	63.8	64.7	64.3	59.7	62.9	61.4			
	Proportion of males (%)			46.1			51.9			46.7				

Study group	Characteristics		Colorectal cancer						Total			Cancer rate (%)		
			Not present			Present								
			Male	Female	All	Male	Female	All	Male	Female	All	Male	Female	All
Control	Number of cases (people)	All	1,662,161.0	2,027,258.0	3,689,419.0	37,386.0	33,168.0	70,554.0	1,699,547.0	2,060,426.0	3,759,973.0	2.2	1.6	1.9
	Age distribution (%)	40–54	48.9	37.8	42.8	17.6	15.0	16.4	48.2	37.4	42.3	0.8	0.6	0.7
		55–69	36.2	38.0	37.2	51.5	44.1	48.0	36.5	38.1	37.4	3.1	1.9	2.4
		70–89	14.9	24.2	20.0	30.9	40.9	35.6	15.3	24.5	20.3	4.4	2.7	3.3
	Mean age (year)		56.2	59.9	58.2	64.1	66.3	65.1	56.4	60.0	58.3			
	Proportion of males (%)			45.1			53.0			45.2				
Diabetes	Number of cases (people)	All	41,729.0	48,917.0	90,646.0	1,226.0	957.0	2,183.0	42,955.0	49,874.0	92,829.0	2.9	1.9	2.4
	Age distribution (%)	40–54	31.6	22.8	26.8	13.7	9.8	12.0	31.1	22.5	26.5	1.3	0.8	1.1
		55–69	49.3	48.7	49.0	56.0	51.4	54.0	49.5	48.7	49.1	3.2	2.0	2.6
		70–89	19.1	28.6	24.2	30.3	38.8	34.0	19.4	28.8	24.5	4.4	2.6	3.3
	Mean age (year)		59.9	63.0	61.6	64.6	66.6	65.5	60.0	63.1	61.7			
	Proportion of males (%)			46.0			56.2			46.3				

Study group	Characteristics		Liver cancer						Total			Cancer rate (%)		
			Not present			Present								
			Male	Female	All	Male	Female	All	Male	Female	All	Male	Female	All
Control	Number of cases (people)	All	1,711,432.0	2,074,229.0	3,785,661.0	6,752.0	5,079.0	11,831.0	1,718,184.0	2,079,308.0	3,797,492.0	0.4	0.2	0.3
	Age distribution (%)	40–54	47.9	37.2	42.0	19.3	18.7	19.1	47.8	37.1	42.0	0.2	0.1	0.1
		55–69	36.5	38.1	37.4	54.8	46.9	51.4	36.6	38.1	37.4	0.6	0.3	0.4
		70–89	15.6	24.7	20.6	25.9	34.4	29.5	15.6	24.7	20.6	0.6	0.3	0.4
	Mean age (year)		56.5	60.0	58.4	62.9	64.6	63.6	56.5	60.0	58.4			
	Proportion of males (%)			45.2			57.1			45.2				
Diabetes	Number of cases (people)	All	43,350.0	50,305.0	93,655.0	335.0	187.0	522.0	43,685.0	50,492.0	94,177.0	0.8	0.4	0.6
	Age distribution (%)	40–54	30.8	22.4	26.3	14.0	12.3	13.4	30.7	22.3	26.2	0.4	0.2	0.3
		55–69	49.4	48.6	49.0	60.0	57.8	59.2	49.5	48.6	49.1	0.9	0.4	0.7

(*continued on next page*)

Table 1 (*continued*)

Study group	Characteristics		All cancers						Total			Cancer rate (%)		
			Not present			Present								
			Male	Female	All	Male	Female	All	Male	Female	All	Male	Female	All
		70–89	19.7	29.0	24.7	26.0	29.9	27.4	19.8	29.0	24.7	1.0	0.4	0.6
	Mean age (year)		60.1	63.1	61.7	63.9	64.5	64.1	60.2	63.1	61.8			
	Proportion of males (%)			46.3			64.2			46.4				

Study group	Characteristics		Pancreatic cancer						Total			Cancer rate (%)		
			Not present			Present								
			Male	Female	All	Male	Female	All	Male	Female	All	Male	Female	All
Control	**Number of cases (people)**	**All**	1,710,135.0	2,070,193.0	3,780,328.0	7,838.0	8,598.0	16,436.0	1,717,973.0	2,078,791.0	3,796,764.0	0.5	0.4	0.4
	Age distribution (%)	**40–54**	47.9	37.2	42.1	21.7	14.7	18.1	47.8	37.1	42.0	0.2	0.2	0.2
		55–69	36.5	38.1	37.4	50.4	43.1	46.6	36.6	38.1	37.4	0.6	0.5	0.5
		70–89	15.6	24.7	20.6	27.9	42.2	35.4	15.6	24.7	20.6	0.8	0.7	0.7
	Mean age (year)		56.5	60.0	58.4	62.9	66.6	64.9	56.5	60.0	58.4			
	Proportion of males (%)			45.2			47.7			45.2				
Diabetes	**Number of cases (people)**	**All**	43,073.0	49,887.0	92,960.0	454.0	438.0	892.0	43,527.0	50,325.0	93,852.0	1.0	0.9	1.0
	Age distribution (%)	**40–54**	30.9	22.5	26.4	15.0	8.9	12.0	30.7	22.4	26.2	0.5	0.3	0.4
		55–69	49.4	48.7	49.1	56.4	42.2	49.4	49.5	48.7	49.1	1.2	0.8	1.0
		70–89	19.7	28.8	24.6	28.6	48.9	38.6	19.8	29.0	24.7	1.5	1.5	1.5
	Mean age (year)		60.1	63.1	61.7	63.9	68.4	66.1	60.1	63.1	61.7			
	Proportion of males (%)			46.3			50.9			46.4				

Study group	Characteristics		Breast cancer						Total			Cancer rate (%)		
			Not present			Present								
			Male	Female	All	Male	Female	All	Male	Female	All	Male	Female	All
Control	**Number of cases (people)**	**All**	NA	1,972,493.0	1,972,493.0	NA	49,271.0	49,271.0	NA	2,021,764.0	2,021,764.0	NA	2.4	2.4
	Age distribution (%)	**40–54**	NA	37.8	37.8	NA	29.9	29.9	NA	37.7	37.7	NA	1.9	1.9
		55–69	NA	37.7	37.7	NA	44.8	44.8	NA	37.8	37.8	NA	2.9	2.9
		70–89	NA	24.5	24.5	NA	25.3	25.3	NA	24.5	24.5	NA	2.5	2.5
	Mean age (year)		NA	59.9	59.9	NA	61.1	61.1	NA	59.9	59.9			
Diabetes	**Number of cases (people)**	**All**	NA	47,366.0	47,366.0	NA	1,197.0	1,197.0	NA	48,563.0	48,563.0	NA	2.5	2.5
	Age distribution (%)	**40–54**	NA	22.9	22.9	NA	16.1	16.1	NA	22.7	22.7	NA	1.7	1.7
		55–69	NA	48.3	48.3	NA	55.6	55.6	NA	48.5	48.5	NA	2.8	2.8
		70–89	NA	28.8	28.8	NA	28.3	28.3	NA	28.8	28.8	NA	2.4	2.4
	Mean age (year)		NA	63.0	63.0	NA	63.7	63.7	NA	63.0	63.0			

Study group	Characteristics		Prostate cancer						Total			Cancer rate (%)		
			Not present			Present								
			Male	Female	All	Male	Female	All	Male	Female	All	Male	Female	All
Control	**Number of cases (people)**	**All**	1,668,741.0	NA	1,668,741.0	28,904.0	NA	28,904.0	1,697,645.0	NA	1,697,645.0	1.7	NA	1.7
	Age distribution (%)	**40–54**	49.0	NA	49.0	9.3	NA	9.3	48.3	NA	48.3	0.3	NA	0.3
		55–69	36.3	NA	36.3	54.8	NA	54.8	36.6	NA	36.6	2.5	NA	2.5
		70–89	14.7	NA	14.7	35.9	NA	35.9	15.0	NA	15.0	4.1	NA	4.1

(*continued on next page*)

Table 1 (*continued*)

Study group	Characteristics		All cancers						Total			Cancer rate (%)		
			Not present			Present								
			Male	Female	All	Male	Female	All	Male	Female	All	Male	Female	All
	Mean age (year)		56.1	NA	56.1	66.2	NA	66.2	56.3	NA	56.3			
Diabetes	Number of cases (people)	All	42,086.0	NA	42,086.0	864.0	NA	864.0	42,950.0	NA	42,950.0	2.0	NA	2.0
	Age distribution (%)	40–54	31.7	NA	31.7	5.9	NA	5.9	31.2	NA	31.2	0.4	NA	0.4
		55–69	49.5	NA	49.5	60.2	NA	60.2	49.7	NA	49.7	2.4	NA	2.4
		70–89	18.8	NA	18.8	33.9	NA	33.9	19.1	NA	19.1	3.6	NA	3.6
	Mean age (year)		59.8	NA	59.8	66.1	NA	66.1	60.0	NA	60.0			

Study group	Characteristics		Kidney cancer						Total			Cancer rate (%)		
			Not present			Present								
			Male	Female	All	Male	Female	All	Male	Female	All	Male	Female	All
Control	Number of cases (people)	All	1,704,542.0	2,069,533.0	3,774,075.0	9,193.0	6,250.0	15,443.0	1,713,735.0	2,075,783.0	3,789,518.0	0.5	0.3	0.4
	Age distribution (%)	40–54	48.0	37.2	42.1	24.9	20.8	23.2	47.9	37.2	42.0	0.3	0.2	0.2
		55–69	36.5	38.1	37.4	49.6	47.2	48.6	36.5	38.1	37.4	0.7	0.4	0.5
		70–89	15.5	24.7	20.6	25.6	32.0	28.2	15.6	24.7	20.6	0.9	0.4	0.6
	Mean age (year)		56.5	60.0	58.4	62.0	63.9	62.7	56.5	60.0	58.4			
	Proportion of males (%)			45.2			59.5			45.2				
Diabetes	Number of cases (people)	All	43,198.0	50,095.0	93,293.0	303.0	228.0	531.0	43,501.0	50,323.0	93,824.0	0.7	0.5	0.6
	Age distribution (%)	40–54	30.8	22.4	26.3	20.1	17.5	19.0	30.7	22.4	26.2	0.5	0.4	0.4
		55–69	49.5	48.6	49.0	55.4	53.5	54.6	49.5	48.6	49.0	0.8	0.5	0.6
		70–89	19.7	29.0	24.7	24.4	28.9	26.4	19.8	29.0	24.7	0.9	0.5	0.6
	Mean age (year)		60.1	63.1	61.7	62.7	63.5	63.1	60.1	63.1	61.7			
	Proportion of males (%)			46.3			57.1			46.4				

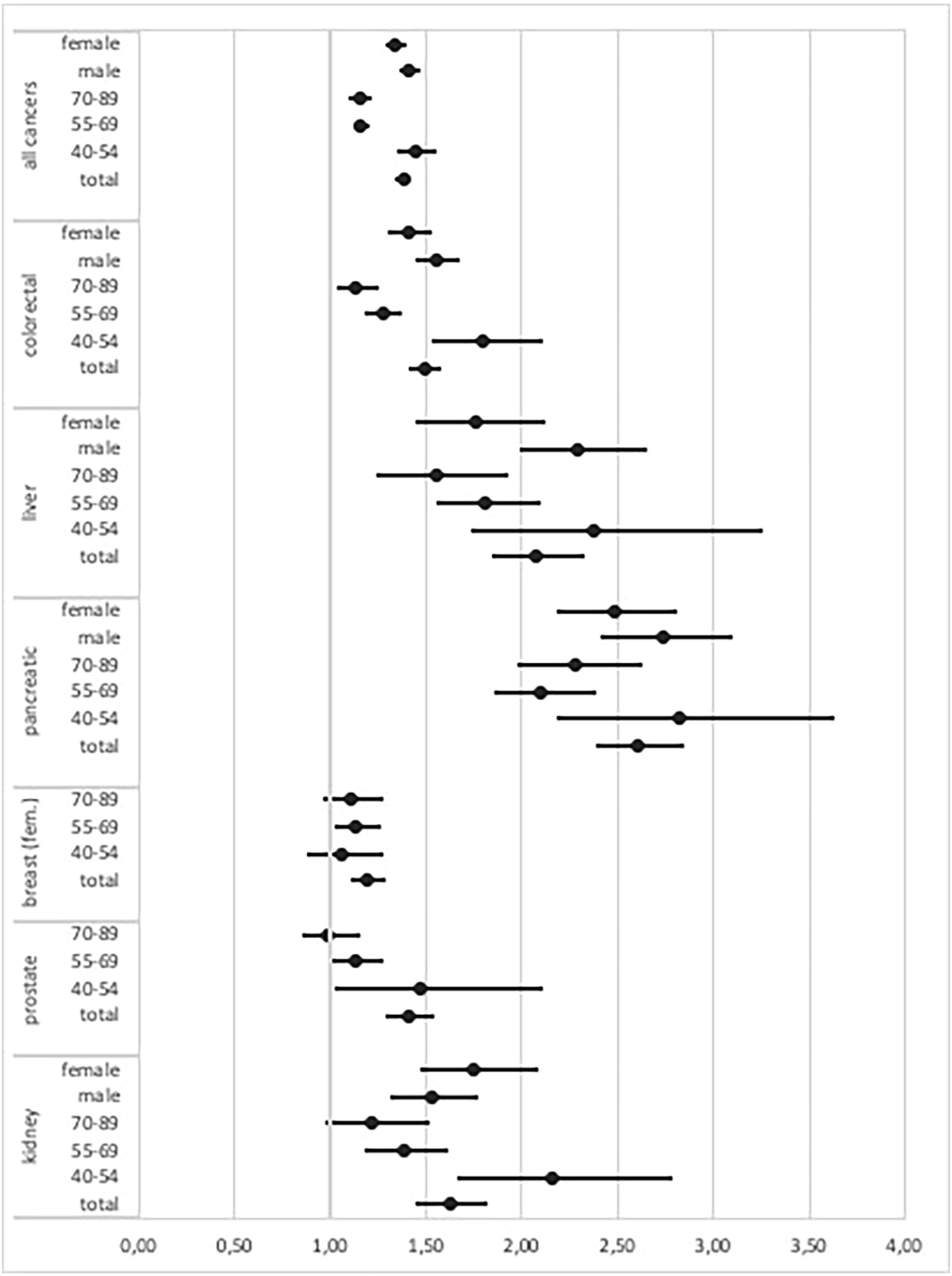

Fig. 1. Forest plot: The role of diabetes status in the development of cancer by cancer sites and subgroups using univariate Cox proportional hazard model (HR and 99% CI, based on univariate Cox regression separately for each cancer site and subgroup; modelled time to cancer diagnosis with diabetes status as sole independent variable.)

they are coded for people with diabetes. Individuals over the age of 40 were included in the study because the incidence of cancer before this age is very low. People aged 90 and over were excluded because the population size in this age group was very low. As we did not want to investigate the association of gestational diabetes with cancer in our study, we excluded those individuals with a pregnancy code. We also excluded people with a PCOS code because they may have been prescribed metformin despite having diabetes. With these criteria, we assume that we have managed to specifically define the group of patients with diabetes. However, we did not group them by antidiabetic agent for lack of specific data. Six cancer sites were chosen to explore the relationship between the two diseases. We wanted to study cancer sites that were sufficiently presumed to be associated with diabetes (pancreas and liver), or which are relatively common, mostly primary cancer localisations – for accuracy of diagnosis – most of which are screenable and some of which are sex-related (colorectal, kidney, breast and prostate).

In our study, in multivariate analysis in each cancer site investigated, there was a significantly higher risk of cancer in the diabetic group vs the control group, with strongest association in pancreatic and liver cancer, the two cancer sites in which diabetes has been shown to play the

Table 2
Results of the Cox proportional hazard regression analysis.[a]

Cancer site	Independent variables											
	Sex (ref: male)				Age (continuous)				Presence of diabetes (ref: control)			
	Hazard ratio	Sig.	Conf.int (99 %)		Hazard ratio	Sig.	Conf.int (99 %)		Hazard ratio	Sig.	Conf.int (99 %)	
			lower	upper			lower	upper			lower	upper
All sites	0.697	***	0.690	0.703	1.045	***	1.045	1.045	1.223	***	1.189	1.258
Colorectal	0.568	***	0.557	0.579	1.059	***	1.058	1.060	1.300	***	1.229	1.375
Liver	0.503	***	0.479	0.527	1.048	***	1.046	1.050	1.830	***	1.631	2.054
Pancreatic	0.718	***	0.690	0.748	1.055	***	1.053	1.057	2.294	***	2.099	2.507
Breast (female)		NA			1.017	***	1.016	1.018	1.137	***	1.055	1.227
Prostate		NA			1.083	***	1.082	1.084	1.171	***	1.071	1.280
Kidney	0.470	***	0.451	0.491	1.043	***	1.041	1.044	1.442	***	1.287	1.616

[a] Based on multivariate Cox regression separately for each cancer site; modelled time to cancer diagnosis with independent variables of diabetes status, age (as continuous variable), and sex (where applicable).
*** $p < 0{,}001$.

Table 3
Interaction of sex and age with the presence of diabetes.[a]

Cancer site	sex * diabetes				age * diabetes			
	ratio of HR	Sig.	95,0% CI for ratio of HR		ratio of HR	Sig.	95,0% CI for ratio of HR	
			Lower	Upper			Lower	Upper
All sites		ns			0,994	***	0,992	0,996
Colorectal		ns			0,991	***	0,987	0,995
Liver	0,831	*	0,691	0,999	0,989	*	0,981	0,998
Pancreatic		ns				ns		
Breast (female)		NR				ns		
Prostate		NR			0,989	**	0,982	0,995
Kidney	1,257	*	1,053	1,499	0,983	***	0,975	0,991

* $p < 0{,}05$; ** $p < 0{,}01$; *** $p < 0{,}001$
reference sex: male
HR: hazard ratio
ns: non-significant
NR: non-relevant
[a] Based on multivariate Cox regression separately for each cancer site; modelled time to cancer diagnosis with independent variables of diabetes status, age (as continuous variable), and sex (where applicable); interaction of diabetes status with age and with sex (where applicable) was included, unless not statistically significant.

greatest role [1]. Although Tsidilis et al. only found significant association between diabetes and cancer in case of breast and colorectal cancer [18], there are many other reviews or national studies that support a significant association for several cancer sites. The different studies differ slightly in research design and details of the statistical analysis; however, their results seem to be more or less comparable.

For liver cancer, our result is similar to that of Ling et al. [19], but most of the studies showed higher HR values than ours [2,4,17,20–22]. Regarding kidney cancer, our result is not substantially different from that of previous studies [2,4,17,19–22], and this is also the case for colorectal cancer[2,4,17,19–22] and breast cancer [2,4,17,19–23], the results are in line with each other.

Of all cancer sites, our study found the strongest association in pancreatic cancer with diabetes. Previous studies mainly confirm the presence of significant association [2,4,17,19,21,22], while the UK Biobank Study measured a considerably lower [20], Zhang et al. a much higher value for the strength of the association [24].

In the vast majority of cases, studies revealed inverse association between diabetes and prostate cancer meaning that diabetes reduces the risk of prostate cancer [2,4,17,20–22,25,26] which is not consistent with our result where we received significant association in the other direction – though the HR for prostate cancer was indeed the lowest of all cancer sites (HR 1.17, 99 % CI: 1.07;1.28). Xu et al. found that diabetes was associated with a decreased risk of developing prostate cancer; the relative risk was a little bit stronger for low grade and localised disease [25]. Hong et al. even observed a significant positive association between diabetes and high grade prostate cancer, but the significance disappeared when analysing the association between diabetes and low grade prostate cancer [27]. In the Ohsaki Cohort Study, patients with diabetes showed higher risk only of advanced prostate cancer [28]. These findings raise the possibility that the strength and direction of the association between diabetes and prostate cancer may vary depending on the grade and advanced stage of the cancer. According to Kasper et al., the rate ratio for the pre-Prostate-Specific Antigen (PSA) testing era showed a less strong inverse association between diabetes and prostate cancer than for the PSA era [29], which makes it worthwhile to analyse screening participation in more depth and the possibility that the significant positive association observed in our results may be due to a higher proportion of advanced cancer. We should also mention that there was one study that was clearly in line with the direction of our results, in Asian population [30].

Based on the multivariate analyses, in all cancer sites, age and sex (where if applicable) significantly influenced time to cancer diagnosis: besides the presence of diabetes, higher age, and sex of male (if applicable) are risk factors in developing cancer. Age as a risk factor for cancer is generally known [31,32] and although the mechanism is not clear, the higher risk of male sex is also long known evidence [33–35].

However, our study also investigated how the association of diabetes and cancer differs by sex. Across all cancer locations, our study found no significant difference by sex. Specifically, for pancreatic and colorectal cancer, there was no difference between males vs females– ie, the presence of diabetes influences the risk of cancer diagnosis the same way for males and females. For kidney and liver cancer, we found significant difference (only at 5 % significance level): for kidney cancer, the

Fig. 2. Incidence of cancer for 10,000 individuals in the years before and after the inclusion date – for all cancer sites and by cancer sites.

presence of diabetes increases the risk of cancer diagnosis more for females; while for liver cancer, the presence of diabetes decreases the risk of cancer diagnosis less for females. This is partially consistent with the findings of Ohkuma et al.: although they showed that the excess risk of cancer associated with diabetes is slightly greater for females than males, but the direction and magnitude of sex differences varies by location of the cancer. Specifically, for kidney and for liver cancer, sex has significant role, and in the same direction as in our results [6]. For liver cancer, similar result was also shown by Fang et al. [36].

One of our important findings relates to the age factor. Multivariate analysis (including age as continuous variable) showed that for kidney, prostate, and colon cancer, the presence of diabetes increases the risk of cancer diagnosis less and less as age increases. This is most relevant for kidney cancer, where the RHR for 10 years of increase in age is 0.843 (eg, for females, HR at age 40: 2.478, at age 50: 2.090). Marginal significance (at 5 %) was observed in liver cancer. In the univariate analysis, for these four cancer sites, diabetes increased the risk of cancer most in the youngest age group (40–54 years), and least in the oldest age group (70+). Consistently, Tseng et al. also revealed the strongest association between diabetes and prostate cancer among the youngest (40–64 years) [37], while Yang et al. revealed that patients diagnosed with Type 2 diabetes before 50 years of age had the highest relative risk for overall and gastrointestinal cancer incidence [38]. For pancreatic and breast cancer, there was no significant interaction observed between the presence of diabetes and age as continuous variable. Univariate analysis shows that for pancreatic cancer, the change across age groups is not linear (though, relevantly, the highest HR can be observed in the youngest group); and for breast cancer, there is no relevant difference in HR across the 3 age groups. In case of breast cancer, to better understand the role of age, it may be worth looking at pre- and postmenopausal cases separately.

To study the temporal relationship between diabetes and cancer, cancer diagnoses between 2011 and 2021 was considered. We defined 2011 as the earliest possible date of cancer diagnosis rather than 2010, because in 2010, the first year for which we had data, all cancer cases appear as new cases. For all cancer sites, the incidence rate of cancer is consistently higher for diabetes patients across almost all timepoints. In the period before the reference year, the incidence of cancer is lower than the actual observed incidence rate because only patients who were still alive in the reference year were included. (ie, the population (denominator) was the same before the reference date.) The difference in cancer incidence between the diabetes and the control group might be influenced by the differences in age distribution between the two groups, among other factors. As a result, the rate from 2011 until the year after the reference year increase – nevertheless, it is valuable to observe that until the year after the reference year, the rate of increase over time is relevantly higher in the group with diabetes.

Our findings on temporality are consistent with those of Lega et al. as they also found a higher risk of cancer in the group with diabetes in the period before the diagnosis of diabetes, although they studied the 10 years before the diagnosis of diabetes as a single period. Though we only examined 3 years, we looked at the incidence by year, which highlighted the prominent period directly prior to the diagnosis of diabetes. The follow-up period after the diagnosis of diabetes is also shorter in our study, however both studies show that the period directly after diagnosis has a higher incidence of cancer among people with diabetes for pancreatic, liver, colorectal and prostate cancer [14]. Our findings are also in line with those of the Danish population-based study, where they also found the risk of cancer in patients with diabetes to decrease substantially for most cancer sites in the first two years after the diagnosis of diabetes [16]. In the Swedish national study, HRs for cancer incidence in case of those with one year of the diabetes diagnosis were also higher than in the entire cohort with the exception of prostate and liver cancer of the sites we have also examined [22]. In their study, Johnson et al. found that the cancer incidence was significantly higher among patients with diabetes compared to those without diabetes in 3 months after the onset of diabetes, but in many cases the cancer incidence also remained higher in the 3 months – 10 years period indicating that this association between the two diseases cannot be explained by detection bias only [39]. Ballotari et al. observed an increasing risk for developing cancer up to 10 years from the diagnosis of diabetes and a subsequent decrease to moderate-higher risk in the population of northern Italy [40]. Our findings support these results, given that in our study, an increase in the risk of developing cancer can be detected as early as 2 years before the diagnosis of diabetes, and for many cancers is still present 6 years after diagnosis.

Because of its high mortality and strong association with diabetes, studying of pancreatic cancer is also a priority in terms of timeliness. We found the same association between the duration of diabetes and the incidence of pancreatic cancer as Zhang et al., namely that the risk of pancreatic cancer is highest in the first 2 years after the presence of diabetes (the first year, according to our results). Though it's worth to note that our study also showed that the risk was already similarly high in the year before the diagnosis of diabetes as in the year thereafter [24]. In the study of Chari et al., 56 % of patients who developed pancreatic cancer in 3 years after the onset of diabetes were diagnosed with the cancer in less than 6 months from the onset of diabetes [41], which is consistent our results. They found that approximately 1 % of patients with new-onset diabetes aged >= 50 years are diagnosed with pancreatic cancer within 3 years. It means a 3-year incidence nearly 8 times that for the general population [41]. In our study, pancreatic cancer incidence in the diabetic group was 10 times that of the control in the year before the diagnosis of diabetes and around 6 times that of the control in the year following the diagnosis considering that these results have not been adjusted for age. This also supports closer monitoring of the development of the other disease, whichever comes first.

Based on our results, one of the most important recommendations is to rethink and specialise screening activities. According to Ling et al., screening people with diabetes at an earlier age or more systematically can lead to earlier cancer diagnosis and longer survival [19]. The importance of this is further supported by our findings, namely that the association between diabetes and cancer was stronger at younger ages. This is particularly worth to consider in view of the fact that people with diabetes are less likely to receive cancer screening [42]. Furthermore, Lao et al. found that the probability of being diagnosed with advanced (stage III-IV) breast cancer was higher among females with diabetes (odds ratio (OR) 1.14) and females aged 45–69 years with diabetes were more likely to have screen-detected cancer than those without diabetes (OR 1.13) [43]. Given the high risk of pancreatic cancer in new-onset diabetes, closer monitoring of this patient group is recommended. A scoring system like that of Sharma et al. can help identify the high-risk patients [44]. As the prevalence of diabetes increases even with decreasing incidence due to better care of the classic complications of diabetes, more rigorous screening can reduce the burden on the care system and the cost of care through early detection of otherwise costly and sometimes high mortality diseases [45].

The onset of cancer before or shortly after the diagnosis of diabetes might support the role of hyperinsulinemia in the development of cancer [3,5,8–10]. Therefore, it may be worth considering focusing on screening for hyperinsulinemia rather than diabetes in some cases and considering the relevance of certain cancer screenings already at the stage of hyperinsulinemia preceding diabetes (for example, those for which screening is already available or a programme is in place, but which might be less frequent or would be carried out at a later age). Timely screening requires raising awareness among health care providers (and of course patients) of the link between diabetes and cancer. In many cases, even the guidelines for diabetes do not include cancer as a complication of diabetes, and screening for cancer (or at least the idea of it) is not really included in the monitoring activities in diabetes care. It would be useful to define who would be responsible for this, depending on how diabetes care works in a particular region, and to build this into care protocols. It is also essential to stress the importance of primary

prevention, which is probably the most effective way of reducing the individual and social burden of the two diseases, diabetes and cancer.

Setting up specific screening strategies will certainly require further research to clarify the value for resources invested in expanding screening activities at the population level. What can be done in any case, however, is to automatically ask about the history and results of cancer screening at the time of diagnosis of diabetes (possibly already in the case of hyperinsulinemia) and at each care visit and to inform the patient about the importance of screening and its availability in public or private care.

The main strength of our study is that we used population-based administrative health data covering more than 10 years. We were able to set up large cohorts with the diabetes cohort including the entire population above the age of 40 of incident diabetes in the years of 2014 and 2015. The large number of cases allowed us evaluate significance at 1 %. Besides analysing the risk for developing cancer in the cohorts, we also studied the temporal relationship between diabetes and cancers. However, unlike most studies of this kind, we also examined this before and after the diagnosis of diabetes with annual breakdowns. However, our study has limitations as well. Clinical data and information on prognostic factors and confounders were not available, so only age- and sex-adjusted calculations could be made. Due to the inaccuracy of the data, it was not possible to examine the different types of diabetes separately, mainly Type 1 diabetes and Type 2 diabetes, but it is assumed that the vast majority of the group with diabetes belongs to Type 2 diabetes. A further limitation is the possible inaccuracy of cancer diagnosis codes, although this affects both the control and the group with diabetes. In addition, although we excluded those with cancer diagnosis code before the diagnosis of diabetes, our data were only available from 2010 onwards, so we could not exclude cases with malignancies from earlier years, such as childhood, that were not already present in the codes of the period 2010–2013. The inclusion of untreated patients with diabetes in the control group may be a biasing factor. This is due to the fact that in our study, we only considered those as patients with diabetes who had dispensed antidiabetic medication. In addition, the database on antidiabetic dispensing included only medication prescribed with reimbursement, so people with diabetes taking other antidiabetics could also be included in the control group. According to Jermendy et al. this is not a significant number [46]. However, biasing factors that place people with diabetes in the control group do not weaken but strengthen our findings, meaning that the association between diabetes and cancer that our research suggests is underestimated and so probably even stronger in reality. However, it should be noted that due to the exclusion of those with pregnancy-obstetric code or PCOS code from both groups, our results cannot be interpreted for these population.

5. Conclusion

Although the link between cancer and diabetes has been the subject of research for some time, the translation of the results into care practice is not very visible. In our study, we wanted to examine this relationship at national level to use the results as input for appropriate improvements in care. We found that people with diabetes had a consistently higher risk for cancer diagnosis for each cancer site studied and the difference in cancer rate between the group with diabetes vs control group was driven by the younger age group (40–54 years). Regardless of cancer site, the cancer incidence starts to increase before the diagnosis of diabetes and peaks in the year after. Following this, the incidence drops close to the control group. Based on these, a diabetes-specific rethinking of screening activities is recommended while diabetes guidelines could be complemented with cancer prevention aspects.

Further research is needed to explore the inverse relationship between cancers and diabetes in the Hungarian population. In the case of breast cancer, it may be worth studying separately the pre- and post-menopausal cases to better understand the nature of the association with diabetes and to refine the prevention and intervention points. It is also recommended to explore the possible factors behind our data that contradict most of the findings in the literature. Therefore, males' higher risk of developing cancers could be studied. Due to the large sample size and strong significance, the positive association between prostate cancer and diabetes found in our study may change the existing picture of the relationship between the two diseases and the results of the related meta-analyses. In any case, it provides an opportunity to test the validity of theories that have so far explained the negative association between them. Moreover, as prostate cancer is the third most common cancer among male in Hungary [47], any new finding on the development of this disease could be an important intervention factor for us.

CRediT authorship contribution statement

Heléna Safadi: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **Ágnes Balogh:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Judit Lám:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Conceptualization. **Attila Nagy:** Writing – review & editing, Methodology, Conceptualization. **Éva Belicza:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Eva Belicza reports financial support was provided by National Research Development and Innovation Office. Judit Lam reports financial support was provided by National Research Development and Innovation Office. Helena Safadi reports financial support was provided by National Research Development and Innovation Office. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The data that supports the findings of this study are available from the authors but restrictions apply to the availability of these data, which were used under licence from the National Research, Development and Innovation Office for the current study, and so are not publicly available. Data are, however available from the authors upon request and with permission from the National Research, Development and Innovation Office.

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Contribution Statement

All authors contributed to the study conception and design. Material

preparation, data collection and analysis were performed by Éva Belicza and Ágnes Balogh. The first draft of the manuscript was written by Heléna Safadi, Éva Belicza and Ágnes Balogh and all authors commented on previous versions of the manuscript. The manuscript was supervised by Éva Belicza and Judit Lám. All authors read and approved the final manuscript.

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