European Journal of Epidemiology (2019) 34:259–265
https://doi.org/10.1007/s10654-018-0438-0

DIABETES MELLITUS

Cancer incidence among Finnish people with type 2 diabetes during 1989–2014

Katri Saarela[1] · Jaakko Tuomilehto[1,2,3,4] · Reijo Sund[5,6] · Ilmo Keskimäki[7,8] · Sirpa Hartikainen[9] · Eero Pukkala[7,10]

Received: 22 September 2017 / Accepted: 28 August 2018 / Published online: 4 September 2018

Abstract

Diabetes and cancer are common diseases both with enormous impact on health burden globally. The increased risk of several types of cancer among people with type 2 diabetes mellitus has been indicated repeatedly. This study aimed at exploring and describing the association between type 2 diabetes and cancer incidence. A cohort of 428,326 people with type 2 diabetes was identified from the Finnish National Diabetes Register and followed up through a register linkage with the Finnish Cancer Registry for cancer incidence during 1988–2014. A total of 74,063 cases of cancer occurred in this cohort in 4.48 million person-years. This accounted for 16% more than the expected cancer incidence in the Finnish general population; the standardized incidence ratio (SIR) was 1.16 (95% confidence interval [CI] 1.15–1.16). There was a statistically significant excess of cancers of lip (SIR = 1.40, CI = 1.28–1.53), liver (SIR = 2.44, CI = 2.35–2.53), pancreas (SIR = 1.75, CI = 1.70–1.79), stomach (SIR = 1.22, CI = 1.18–1.26), colon (SIR = 1.22, CI = 1.19–1.25), gallbladder and bile ducts (SIR = 1.29, CI = 1.21–1.36), non-melanoma skin (SIR = 1.18, CI = 1.15–1.22), kidney (SIR = 1.42, CI = 1.37–1.47), bladder (SIR = 1.17, CI = 1.13–1.21), and thyroid (SIR = 1.22, CI = 1.12–1.31). There was a small statistically significant decrease in prostate cancer incidence (SIR = 0.95, CI = 0.93–0.96). This study showed an association between type 2 diabetes mellitus and the incidence of cancer at numerous sites in the Finnish population.

Keywords Diabetes · Cohort study · Record linkage · Cancer

Introduction

Numerous epidemiological studies have indicated strong positive associations between type 2 diabetes mellitus (T2DM) and the incidence of several cancer types [1, 2], and mortality [3, 4]. The strength of association depends on cancer site. The most considerable associations have been demonstrated for pancreatic cancers [5–7], and liver [8], but there are observations of increased risks of colorectal [9], breast [10], endometrial [11], and kidney cancers [12]. A reduced risk of prostate cancer in diabetic males have documented in many studies. This effect has noticed

✉ Katri Saarela
katri.saarela2@thl.fi

[1] Chronic Disease Prevention Unit, National Institute for Health and Welfare, PO Box 30, 00271 Helsinki, Finland

[2] Department of Public Health, University of Helsinki, Helsinki, Finland

[3] Dasman Diabetes Institute, Dasman, Kuwait

[4] Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia

[5] Department of Social Research, University of Helsinki, PO Box 33, 00014 Helsinki, Finland

[6] Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland

[7] Faculty of Social Sciences, University of Tampere, Tampere, Finland

[8] Department of Health and Social Care Systems, National Institute for Health and Welfare, Helsinki, Finland

[9] School of Pharmacy, University of Eastern Finland, PO Box 1627, 70211 Kuopio, Finland

[10] Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Unioninkatu 22, 00130 Helsinki, Finland

especially strong among diabetic men with high body mass index (BMI) [13, 14].

The connection between diabetes and cancer has been explored extensively, but the observed associations are not completely understood. It has been suggested, that possible underlying mechanisms could associate with insulin resistance and its accompanying hyperinsulinemia, hyperglycemia, and chronic inflammation [8, 15, 16]. Hormonal factors, low testosterone levels in particular, have been suggested to explain the reduced risk for prostate cancer among male diabetics [17].

In recent years, attention has also been paid on the potential role of several anti-diabetic drugs on cancer risk [18–20], but the results are inconsistent. Some studies but not all have suggested that insulin analogs may increase the cancer risk [20], and that the biguanide metformin apparently reduces the risk of many cancer types [21, 22], but these findings have not confirmed in all studies, and causality has not been proven.

The aim of this study was to describe the cancer risk pattern among the Finnish T2DM patients. Special attention was paid to the cancers with a priori suspected associations with diabetes.

Materials and methods

Persons diagnosed with diabetes in Finland during 1988–2007 were identified from the nationwide FinDM II database, which comprises persons with diabetes identified from: (1) the Register of Persons Eligible for Special Reimbursement of Medication for chronic conditions including diabetes (years 1964–2007); (2) the Prescription Register including all reimbursed medicines purchased from the Finnish pharmacies (years 1994–2007); (3) the National Hospital Discharge Registers including all inpatient care (years 1969–2007) and outpatient hospital visits (years 1998–2007); (4) the Causes-of-Death Register (1971–2007); and (5) the Medical Birth Register (1987–2007). The unique Finnish personal identity code assigned to all residents in Finland allowed the deterministic record linkage. More detailed description of the study population is available elsewhere [23].

Persons were considered to have diabetes if they had started antidiabetic medication or had been hospitalized with a diagnosis of diabetes. We excluded from our analyses women with gestational diabetes only and people, who were not permanent residents in the country. The high reimbursement level for antidiabetic medication has resulted in a high coverage of diabetic persons in the medication registers. The completeness of the Hospital Discharge Register is confirmed by the law for every hospital in the country to report on the inpatient episodes. A very good coverage of diabetic patients in the FinDM II database was demonstrated in a study, where the database was compared to a local Diabetes Register of the Helsinki metropolitan area; only some diabetic persons aged 65 years or more treated in outpatient primary care settings without antidiabetic medication were missing [24].

The precise etiological classification into type 1 (T1DM) and T2DM was not possible with the current register-based data. Therefore, we determined the diabetes type based on age at diagnosis of diabetes: persons diagnosed before the age of 30 years were considered to have T1DM and the rest T2DM.

The follow-up for cancer incidence through the files of the national Finnish Cancer Registry and for vital status and emigration through the Population Register was performed using the personal identity code as the key. The follow-up for cancer incidence started at the date of diagnosis of the diabetes or on 1st of January 1989, whichever was later, and ended at death or emigration, or on December 31, 2014, whichever occurred first. The follow-up of 204,724 male and 223,602 female T2DM patients produced altogether 4.48 million person-years (Table 1). The mean length of follow-up of a person was 10.5 years.

The numbers of observed cases and person-years at risk were counted by 5-year age groups, separately for calendar periods (1989–1994, 1995–1999, 2000–2004, 2005–2009 and 2010–2014). The expected numbers of cases for total cancer and specific cancer types were calculated by multiplying the number of person-years in each age group by

Table 1 Number of type 2 diabetic patients under follow-up (N) and number of person-years at follow-up up to 31 December 2014, by sex and age

Sex	N[a]	Person-years
Age		
Males + Females	428,326	4,477,315
30–44 years	33,185	170,726
45–59 years	122,536	989,092
60–74 years	172,008	1,932,497
≥ 75 years	100,597	1,385,000
Males	204,724	2,160,811
30–44 years	20,461	99,651
45–59 years	75,188	609,641
60–74 years	80,143	1,001,174
≥ 75 years	28,932	2,160,811
Females	223,602	2,316,504
30–44 years	12,724	71,075
45–59 years	47,348	379,451
60–74 years	91,865	934,655
≥ 75 years	71,665	934,655

[a]Age in the N column defined at the beginning of follow-up

the corresponding average cancer incidence in all of Finland during the period of observation. The specific cancer types selected a priori for the analysis included the cancer sites with known or suspected exceptional (increased or decreased) risk in T2DM patients in earlier studies, and other common cancer types to give the whole picture of the cancer situation among Finnish T2DM patients.

To calculate the standardized incidence ratio (SIR), the observed number of cases was divided by the expected number. The 95% confidence intervals (CI) for the SIR were based on the assumption that the number of observed cases followed a Poisson distribution.

Results

During the follow-up, 74,063 cases of cancer were diagnosed; the expected number was 63,870. Consequently, the total cancer incidence for adults with T2DM was 16% higher than expected (SIR = 1.16, CI = 1.15–1.16; Table 2).

Table 2 Observed (Obs) and expected (Exp) numbers of cancer cases and standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) among Finnish type 2 diabetic patients in 1989–2014, by site according International Classification of Diseases (ICD-10)

Primary site	ICD10 codes	Obs	Exp	SIR	95%CI
ALL SITES[a]		74,063	63,870	1.16	1.15–1.16
Mouth and pharynx	C00-14	1362	1174	1.16	1.10–1.22
Lip	C00	465	331	1.40	1.28–1.53
Tongue	CO1-02	242	205	1.18	1.04–1.33
Salivary gland	C07-08	114	121	0.95	0.78–1.12
Oral cavity (mouth, other)	C03-06	308	271	1.14	1.01–1.26
Pharynx	C09-14	233	246	0.95	0.83–1.07
Digestive organs	C15-26	19,875	14,283	1.39	1.37–1.41
Oesophagus	C15	735	675	1.09	1.01–1.16
Stomach	C16	2602	2129	1.22	1.18–1.26
Small intestine	C17	263	222	1.19	1.05–1.33
Colon	C18	4981	4083	1.22	1.19–1.25
Rectum, rectosigmoid, anus	C19-21	2760	2413	1.14	1.10–1.18
Liver	C22	2536	1038	2.44	2.35-2.53
Gallbladder, bile ducts	C23-24	1000	777	1.29	1.21–1.36
Pancreas	C25	4555	2609	1.75	1.70–1.79
Unspecified intestinal tract	C26	363	256	1.42	1.28–1.56
Respiratory organs	C30-39	7030	6879	1.02	1.00–1.04
Larynx	C32	263	293	0.90	0.79–1.00
Lung, trachea	C33-34	6588	6416	1.03	1.00–1.05
Bone	C 40-41	61	54	1.14	0.87–1.46
Skin, melanoma	C43	1869	1745	1.07	1.02–1.12
Non-melanoma skin	C44	4063	3431	1.18	1.15–1.22
Mesothelioma	C45	210	216	0.97	0.84–1.10
Breast	C50	7120	6881	1.03	1.01–1.05
Urinary organs	C64-68	6058	4761	1.27	1.24–1.30
Kidney	C64-65	2745	1931	1.42	1.37–1.47
Bladder, ureter, urethra	C66-68	3313	2830	1.17	1.13–1.21
Eye	C73	104	104	1.00	0.82–1.20
Brain, central nervous system	C70-72, D32-33, D42-43	1668	1535	1.09	1.04–1.13
Thyroid gland	C73	600	492	1.22	1.12–1.31
Lymphoid/haematopoietic tissue	C81-96	5843	5426	1.08	1.05–1.10
Non-Hodgkin lymphoma	C81	2538	2352	1.08	1.04–1.12
Hodgkin lymphoma	C82-85, C96	140	127	1.10	0.92–1.28
Myeloma	C90	965	905	1.07	1.00–1.13
Leukaemia	C91-95	1434	1310	1.09	1.04–1.15
Ill-defined or unknown	C76, C80	2571	1807	1.42	1.37–1.47

The incidence of 16 cancer types was statistically significantly elevated; cancer of lip, stomach, colon, rectum, liver (SIR = 2.44, CI = 2.35–2.53), gallbladder, pancreas (SIR = 1.75, CI = 1.70–1.79), unspecified intestinal tract, non-melanoma skin, kidney, bladder, brain and central nervous system, thyroid, non-Hodgkin lymphoma, leukaemia, and ill-defined or unknown (Tables 2, 3).

For women with T2DM, 34,199 cancer diagnoses were observed, which was 18% higher than expected. We found statistically significant increase for cancers of lip, stomach, colon, rectum, liver (SIR = 1.90, CI = 1.77–2.03), gallbladder, pancreas (SIR = 1.72, CI = 1.65–1.78), unspecified intestinal tract, non-melanoma skin, kidney, non-Hodgkin lymphoma, corpus uteri, and other female genital organs (Table 3).

Among men with T2DM, 39,864 cancer diagnoses were observed, which was 14% more than expected. Statistically significant increase in cancer incidence were seen for cancers of lip, oral cavity, stomach, colon, rectum, liver (SIR = 2.79, CI = 2.66–2.92), gallbladder, pancreas (SIR = 1.78, CI = 1.71–1.85), unspecified intestinal tract, non-melanoma skin, kidney, bladder, thyroid, and other male genital organs (C60, C63). The inverse effect was seen for prostate cancer only (SIR = 0.95, CI = 0.93–0.96); 10,692 men with T2DM developed prostate cancer, which was 5% less than expected (Table 3).

Discussion

The total cancer incidence among the 428,326 T2DM patients was 16% higher among people with T2DM compared with the expected average cancer incidence in the Finnish population. The increase in cancer incidence was seen both in women (18%) and men (14%).

We found an almost threefold increase in liver cancer incidence among men with T2DM and nearly twofold increase among women with T2DM compared with the general population. Similar findings have been observed in several studies earlier [1, 8, 25]. It has been speculated whether diabetes is a direct risk factor for liver cancer or whether there are other common risk factors involved, such as non-alcoholic fatty liver disease (NAFLD), steatosis or cirrhosis [26, 27].

For pancreatic cancer we observed a more than 70% increased risk in both men and women with T2DM. This result applies to what is already known about the relationship between T2DM and cancer of the pancreas [5–7]. Suggestions of the possible underlying mechanisms between diabetes and pancreatic cancer include elevated insulin concentrations acting as a tumor-growth promoting factor in pancreatic cells, hyperglycemia, insulin resistance and hyperinsulinemia [5, 16]. It also has been questioned whether the association is caused by reverse causality and diabetes is caused by liver or pancreatic cancer [4]. However, this does probably not explain increased risks in our data because of the temporal relations. Pancreatic cancer is generally known as quickly progressive and fatal, elevated incidence may be due to reverse causality only in the very short time frame (less than 6 months) following diabetes onset. Sometimes pancreatic cancer is misdiagnosed as diabetes, due to similar symptoms. Continuous increased risk of pancreatic cancer after longer periods of follow-up (up to 10 years after diabetes onset) is unlikely due to reverse causality [7, 15].

We found an increased risk of cancer of urinary organs, particularly kidney cancer, in persons with T2DM. This finding is similar to a meta-analysis of studies investigating the association between diabetes and kidney cancer incidence and mortality [12]. The association has been tried to be described by common risk factors, such as obesity and cigarette smoking, or medication. Influence of possible confounding or detection bias can not put aside, neither. Because diabetic patients are under increased medical surveillance, and the measurement of urinary specimens is recommended (mainly for detection of signs of diabetic nephropathy) it is possible that kidney cancer tend to be found at an earlier stage in diabetic patients than in non-diabetic people [28].

Although higher risk of breast cancer among type 2 diabetic patients has been indicated in many studies [10, 29], the connection was not seen in our data. Instead, we found an increase in cancers of female reproductive organs, such as cancer of corpus uteri, also known as endometrial cancer (50%), and cancers of vulva and vagina in diabetic women (24%). Endometrial cancer risk has reported to be higher among women with diabetes [11, 30], but this relationship may be confounded by body weight [31]. Nevertheless, a positive association between T2DM and endometrial cancer has still been seen after adjusting for possible confounding factors: physical inactivity and obesity [11].

In contrast to the increased risk for many types of cancer, a 14% decreased risk of prostate cancer has been seen in pooled analysis of 45 studies [13]. In our study the diabetic males possessed 5% reduction in prostate cancer risk. This inverse relationship is not fully understood, but has been considered to result from lower testosterone levels in diabetic patients, as well as many more hormonal and metabolic factors related to lifestyle and medication. It has been suggested that diabetic men are more likely to be tested for prostate-specific antigen (PSA) levels, and this lead to an increased probability of detecting prostate cancer, opposite to the observed inverse association [14].

Cancer registration system in Finland is virtually complete nationwide and the computerized record linkage

Table 3 Observed (Obs) and expected (Exp) numbers of cancer cases and standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) among Finnish type 2 diabetic patients in 1989–2014, by sex and site according International Classification of Diseases (ICD-10)

Primary site	ICD10 codes	Females				Males			
		Obs	Exp	SIR	95% CI	Obs	Exp	SIR	95%CI
ALL SITES[a]		34,199	28,864	1.18	1.17–1.19	39,864	35,007	1.14	1.13–1.14
Mouth and pharynx	C00-14	533	467	1.14	1.05–1.24	829	707	1.17	1.09–1.25
Lip	C00	177	113	1.57	1.35–1.80	288	218	1.32	1.17–1.47
Tongue	C01-02	117	104	1.12	0.93–1.33	125	101	1.24	1.03–1.46
Salivary gland	C07-08	45	59	0.76	0.56–1.02	69	62	1.12	0.87–1.41
Oral cavity (mouth, other)	C03-06	139	134	1.04	0.87–1.21	169	137	1.24	1.06–1.43
Pharynx	C09-14	55	57	0.97	0.73–1.25	178	189	0.94	0.81–1.08
Digestive organs	C15-26	9433	7103	1.33	1.30–1.35	10,442	7180	1.45	1.43–1.48
Oesophagus	C15	272	266	1.02	0.91–1.14	463	410	1.13	1.03–1.23
Stomach	C16	1255	974	1.29	1.22–1.36	1347	1155	1.17	1.10–1.22
Small intestine	C17	118	100	1.18	0.98–1.40	145	122	1.19	1.00–1.39
Colon	C18	2519	2171	1.16	1.12–1.20	2462	1912	1.29	1.24–1.33
Rectum, rectosigmoid, anus	C19-21	1173	1043	1.13	1.06–1.19	1587	1370	1.16	1.10–1.21
Liver	C22	773	407	1.90	1.77-2.03	1763	631	2.79	2.66-2.92
Gallbladder, bile ducts	C23-24	628	519	1.21	1.12–1.30	372	258	1.44	1.30–1.59
Pancreas	C25	2425	1412	1.72	1.65–1.78	2130	1197	1.78	1.71–1.85
Unspecified intestinal tract	C26	225	161	1.40	1.22–1.58	138	95	1.45	1.22-1·70
Respiratory organs	C30-39	1807	1744	1.04	0.99–1.08	5223	5134	1.02	0.99–1.04
Larynx	C32	23	29	0.79	0.50–1.18	240	264	0.91	0.80–1.02
Lung, trachea	C33-34	1703	1638	1.04	0.99–1.08	4885	4778	1.02	0.99–1.05
Bone	C 40-41	24	23	1.03	0.66–1.53	37	30	1.22	0.86–1.68
Skin, melanoma	C43	797	765	1.04	0.97–1.11	1072	981	1.09	1.03–1.15
Non-melanoma skin	C44	1971	1754	1.12	1.07–1.17	2092	1678	1.25	1.19–1.30
Mesothelioma	C45	54	53	1.02	0.76–1.32	156	163	0.96	0.81–1.11
Breast	C50	7065	6836	1.03	1.01–1.05	55	44	1.24	0.93–1.61
Female genital organs	C51-58	4341	3329	1.30	1.27–1.34				
Cervix uteri	C53	280	232	1.20	1.07–1.34				
Corpus uteri	C54	2521	1681	1.50	1.44–1.55				
Ovary	C56	977	968	1.01	0.95–1.07				
Other	C51-52, C57	513	412	1.24	1.14–1.35				
Male genital organs	C60-63					10,827	11,345	0.95	0.94–0.97
Prostate	C61					10,692	11,241	0.95	0.93–0.96
Testis	C62					28	39	0.73	0.48–1.05
Other	C60, C63					107	66	1.63	1.33–1.94
Urinary organs	C64-68	2093	1568	1.34	1.28–1.39	3965	3194	1.24	1.20–1.28
Kidney	C64-65	1287	863	1.49	1.41–1.57	1458	1068	1.37	1.30–1.43
Bladder, ureter, urethra	C66-68	806	704	1.14	1.07–1.22	2507	2126	1.18	1.13–1.22
Eye	C73	48	49	0.98	0.72–1.29	56	55	1.03	0.77–1.33
Brain, central nervous system	C70-72,D32-33,D42-43	1002	897	1.12	1.05–1.18	666	638	1.04	0.97–1.12
Thyroid gland	C73	410	342	1.20	1.09–1.31	190	150	1.27	1.09–1.45
Lymphoid/haematopoietic tissue	C81-96	2891	2643	1.09	1.05–1.13	2952	2783	1.06	1.02–1.09
Non-Hodgkin lymphoma	C81	1295	1161	1.12	1.06–1.17	1243	1192	1.04	0.98–1.10
Hodgkin lymphoma	C82-85, C96	56	52	1.07	0.81–1.39	84	75	1.12	0.89–1.38
Myeloma	C90	492	459	1.07	0.98–1.16	473	446	1.06	0.97–1.15
leLeukaemia	C91-95	649	590	1.10	1.02–1.18	785	720	1.09	1.02-1.16
Ill-defined or unknown	C76, C80	1491	1079	1.38	1.31–1.45	1080	729	1.48	1.39–1.57

procedure based on the national personal identifier is precise [32]. Therefore, technical incompleteness of case ascertainment does not cause any bias in our results. However, confounding by lifestyle factors, such as physical inactivity, dietary habits and cigarette smoking, is possible [33]. The overall cancer incidence among working-aged Finnish men increases and among women decreases towards the lower social class [34]. Low socioeconomic status (SES) has been associated with late state diagnoses and T2DM is more common in people with lower SES, as well [35].

Other strengths of the study are, besides technical accuracy, relatively long-term follow-up and size of the data, due to record linkage. Finnish registers provide access to valuable data without time-consuming and expensive data collecting. Observed and expected frequencies of cancers are come from the same database. Most studies report associations between diabetes and cancer mortality. Compared to mortality, incidence is, nevertheless, a preferable indicator for cancer risk due to variation in cancer survival rates due to earlier diagnosis and better treatment.

Many studies investigating the association between diabetes and cancer incidence have not made a proper distinction between the two main types of diabetes. The precise etiological classification between T1DM and T2DM was not possible with our current register-based data, which might have led to misclassification, where group of T2DM includes persons who actually had other type of diabetes, but such a probability is small compared with the large number of people with T2DM [36].

It is very challenging to study associations between these heterogenous and complex diseases. T2DM shares several common risk factors with many cancer types, such as obesity, poor diet, ageing and physical inactivity. Thus confounding is likely to occur and the possibility of reverse causality could not be ignored, either. Risk factors for T2DM are similar to cardiovascular diseases (CVD), as well. Thus, a long follow-up shows negative correlation with cancer mortality, because of diabetic patients' high mortality on CVD [37]. Additionally, it has been speculated that if cancer is more common in diabetic patients, the relation between diabetes and cancer might be underestimated since T2DM, in fact, is underdiagnosed disease. Also, due to possible undiagnosed individuals with T2DM the cancer risk in the non-diabetic population might be higher than observed [8].

It is still unclear, whether T2DM and its metabolic derangements (hyperglycemia, insulin resistance and hyperinsulinaemia) increase the risk of cancer directly or is the association indirect. There is a wide array of possible mechanisms related with cancer incidence in patients with T2DM. Due to the multiple and complex mitogenic effect of insulin, hyperinsulinaemia is a potential factor favouring cancer progression [38]. Increasing insulin levels activate the related insulin-like growth factor-I (IGF-I) that probably promotes cancer cell growth and proliferation. Impaired glucose tolerance is related to increased cancer risk without diabetes, too. Poor metabolic control leads to increasing oxidative stress causing a chronic pro-inflammatory state, resulting vulnerable cells predisposing to malignant transformation. Biological actions, common with degenerative diseases, such as T2DM, might accelerate carcinogenic processes [16].

We need more in-depth, well-designed follow-up studies to advance our knowledge of the complex association between T2DM and cancer incidence, and the underlying direct and indirect biological mechanisms. It is essential to explore the potential role of glucose-lowering treatments. The task is challenging, because of the diversity of therapies over time. A series of confounders and biases should be observed properly to ensure validity. Because of the growing, worldwide burden of diabetes, it is extremely important to acquire understanding to these questions to prevent cancer in diabetic patients.

Acknowledgements This study has been partly supported by the research Grants to JT from the Finnish Cancer Foundation, European Foundation for the Study of Diabetes and Sanofi-Aventis. JT is an advisory board member of Novo Nordisk and Merck KGaA. SH has received lecture fees from MSD.

Compliance with ethical standards

Conflict of interest Authors KS, RS, IK and EP declare that they have no conflict of interest.

References

1. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JPA. Type 2 diabetes and cancer: umbrella review of meta-analysis of observational studies. BMJ. 2015;350:g7607.
2. Noto H, Tsujimoto T, Sasazuki T, Noda M. Significantly increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis. Endocr Pract. 2011;17:616–28.
3. Gallagher EJ, LeRoith D. Obesity and diabetes: the increased risk of cancer and cancer-related mortality. Physiol Rev. 2015;95:727–48.
4. Harding JL, Shaw JE, Peeters A, Carstensen B, Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes: disentangling truth associations, detection bias, and reverse causation. Diabetes Care. 2015;38:264–70.
5. Song S, Wang B, Zhang X, et al. Long-term diabetes mellitus is associated with an increased risk of pancreatic cancer: a meta-analysis. PLoS ONE. 2015;10:e0134321.
6. Zhang C, Yang G, Ling Y, Chen G, Zhou T. The early diagnosis of pancreatic cancer and diabetes: what's the relationship? J Gastrointest Oncol. 2014;5:481–8.

7. Huxley R, Ansary-Moghaddam A, Berrington de González A, et al. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer. 2005;92:2076–83.
8. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33:1674–85.
9. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97:1679–87.
10. Hardefeldt PJ, Edirimanne S, Eslick GD. Diabetes increases the risk of breast cancer: a meta-analysis. Endocr Relat Cancer. 2012;19:793–803.
11. Zhang ZH, Su PY, Hao JH, Sun YH. The role of preexisting diabetes mellitus on incidence and mortality of endometrial cancer: a meta-analysis of prospective cohort studies. Int J Gynecol Cancer. 2013;23:294–303.
12. Bao C, Yang X, Xu W, et al. Diabetes mellitus and incidence and mortality of kidney cancer: a meta-analysis. J Diabetes Complicat. 2013;27:357–64.
13. Bansal D, Bhansali A, Kapil G, Undela K, Tiwari P. Type 2 diabetes and risk of prostate cancer: a meta-analysis of observational studies. Prostate Cancer Prostatic Dis. 2013;16(151-8):S1.
14. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomark Prev. 2006;15:2056–62.
15. Johnson JA, Carstensen B, Witte D, et al. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. Diabetologia. 2012;55:1607–18.
16. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer. 2009;16:1103–23.
17. Xu H, Jiang HW, Ding GX, et al. Diabetes mellitus and prostate cancer risk of different grade or stage: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2013;99:241–9.
18. Tokajuk A, Krzyżanowska-Grycel E, Tokajuk A, Grycel S, Sadowska A, Car H. Antidiabetic drugs and risk of cancer. Pharmacol Rep. 2015;67:1240–50.
19. Ioannidis JP, Zhou Y, Chang CQ, Schully SD, Khoury MJ, Freedman AN. Potential increased risk of cancer from commonly used medications: an umbrella review of meta-analyses. Ann Oncol. 2014;25:16–23.
20. Karlstad Ø, Starup-Linde J, Vestergaard P, et al. Use of insulin and insulin analogs and risk of cancer—systematic review and meta-analysis of observational studies. Curr Drug Saf. 2013;8:333–48.
21. Yang T, Yang Y, Liu S. Association between metformin therapy and breast cancer incidence and mortality: evidence from a meta-analysis. J Breast Cancer. 2015;18:264–70.
22. Gandini S, Puntoni M, Heckman-Stoddard BM, et al. Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. Cancer Prev Res (Phila). 2014;7:867–85.
23. Sund R, Koski S. FinDM II. On the register-based measurement of the prevalence and incidence of diabetes and its long-term complications. A technical report. Tampere: Finnish Diabetes Association; 2009.
24. Sund R, Harno K, Ranta S, Tolppala EP. Comparing the case inclusion in two population-based diabetes registers. Finn J eHealth eWelfare. 2010;2:136–46.
25. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2012;28:109–22.
26. Raff EJ, Kakati D, Bloomer JR, Shoreibah M, Rasheed K, Singal AK. Diabetes mellitus predicts occurrence of cirrhosis and hepatocellular cancer in alcoholic liver and non-alcoholic fatty liver diseases. J Clin Transl Hepatol. 2015;3:9–16.
27. Tudzarova S, Osman MA. The double trouble of metabolic diseases: the diabetes-cancer link. Mol Biol Cell. 2015;26:3129–39.
28. Larsson SC, Wolk A. Diabetes mellitus and incidence of kidney cancer: a meta-analysis of cohort studies. Diabetologia. 2011;54:1013–8.
29. De Bruijin KM, Arends LR, Hansen BE, Leeflang S, Ruiter R, van Eijck CH. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. Br J Surg. 2013;100:1421–9.
30. Liao C, Zhang D, Mungo C, Tompkins DA, Zeidan AM. Is diabetes mellitus associated with increased incidence and disease-specific mortality in endometrial cancer? A systematic review and meta-analysis of cohort studies. Gynecol Oncol. 2014;135:163–71.
31. Luo J, Beresford S, Chen C, et al. Association between diabetes, diabetes treatment and risk of developing endometrial cancer. Br J Cancer. 2014;111:1432–9.
32. Pukkala E. Biobanks and registers in epidemiologic research on cancer. Methods Mol Biol. 2011;675:127–64.
33. Katzke VA, Kaaks R, Kühn T. Lifestyle and cancer risk. Cancer J. 2015;21:104–10.
34. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer—follow-up of 15 million people in five Nordic countries. Acta Oncol. 2009;48:646–790.
35. Kim YJ, Jeon JY, Han SJ, Kim HJ, Lee KW, Kim DJ. Effect of socio-economic status on the prevalence of diabetes. Yonsei Med J. 2015;56:641–7.
36. Lammi N, Taskinen O, Moltchanova E, et al. A high incidence of type 1 diabetes and an alarming increase in the incidence of type 2 diabetes among young adults in Finland between 1992 and 1996. Diabetologia. 2007;50:1393–400.
37. Gordon-Dseagu VL, Mindell JS, Steptoe A, et al. Impaired glucose metabolism among those with and without diagnosed diabetes and mortality: a cohort study using Health Survey for England data. PLoS ONE. 2015;10:e0119882.
38. Shikata K, Ninomiya T, Kiyohara Y. Diabetes mellitus and cancer risk: review of the epidemiological evidence. Cancer Sci. 2013;104:9–14.