Sex and gender differences in diabetes care

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Chapter 4

Increased cancer incidence around the time of type 2 diabetes diagnosis (ZODIAC-49)

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Abstract

Aim

This study aimed to investigate differences in the incidence of both all cancers combined and obesity-related cancers in men and women with type 2 diabetes (T2D) in the 5 years before, at the time of, and 5 years after diabetes diagnosis compared to the Dutch general population.

Methods

A dataset of patients with T2D who participated in the ZODIAC study between 1998 and 2012 was linked to the Netherlands Cancer Registry. Sex-specific standardized incidence ratio (SIR), corrected for year of diagnosis and age, were calculated with 95% confidence intervals (CI), using the Dutch general population as a reference.

Results

A total of 69.583 patients was included. The SIR (95%CI) for all cancer was 1.40 (1.31 to 1.48) in women and 1.01 (0.95 to 1.08) in men in the 5 years before diabetes diagnosis, 1.82 (1.60 to 2.03) in women and 1.63 (1.46 to 1.81) in men the year following diabetes diagnosis, and 1.67 (1.56 to 1.79) in women and 1.26 (1.17 to 1.35) in men from 1 to 5 years after diabetes diagnosis. The SIRs (95%CI) for obesity-related cancers were 1.77 (1.63 to 1.91) in women and 1.02 (0.90 to 1.13) in men in the 5 years before diabetes diagnosis, 2.21 (1.94 to 2.30) in women and 1.38 (1.11 to 1.64) in men the year following diabetes diagnosis and 2.12 (1.94 to 2.30) in women and 1.21 (1.07 to 1.35) in men from 1 to 5 years after diabetes diagnosis.

Conclusion

In both men and women cancer incidence peaked around diabetes diagnosis, probably due to increased detection. A clear difference between men and women was observed. Women with T2D had a higher cancer incidence compared to women without T2D in the general population as early as 5 years before diabetes diagnosis, in both all and obesity-related cancers. In men no increase in cancer incidence before diabetes diagnosis was observed.

Introduction

Patients with type 2 diabetes (T2D) have an increased risk of being diagnosed with cancer compared to the general population (1). This increased cancer risk in patients with T2D appears to be site specific (1-4), and has been reported for cancers of liver, pancreas, endometrium, colon, rectum, breast and bladder (4). The increased risk for these specific types of cancer in patients with T2D show a large overlap with obesity-related cancers, which include liver, kidney, colorectal, gallbladder, pancreas, ovarian, endometrial and advanced prostate cancer, post-menopausal breast cancer and esophageal adenocarcinoma (4, 5). Since a large proportion of patients with T2D are overweight or obese (6, 7), the incidence of obesity-related cancers could especially be increased in patients with T2D.

Cancer risk is probably not constant over time, however, and also depends on the timing of the diagnosis of diabetes (8). One study reported a HR of 1.28 (95%CI 1.04 – 1.58) for colon cancer before the onset of T2D in men, and a non-significant HR of 1.18 (95%CI 0.86-1.62) in women. Breast cancer risk has also been shown to be increased in the pre-diabetes phase (9-11).

Around the time of diabetes diagnosis, an increased detection of cancer has been reported (12, 13). This increased detection is possibly due to more anamnestic information and attention for clinical complaints brought forward by the newly-diagnosed patient and the use of additional diagnostic tests at the time of diabetes diagnosis. When increased detection occurs, this could be reflected by a higher incidence of cancer in T2D patients around and after the diagnosis of diabetes. However, little data are available on whether there is a peak in incidence of cancer around the diagnosis of diabetes (14).

Therefore, the aim of this study was to describe the incidence of all cancers combined, and specifically obesity-related cancers, 5 years before, around and 5 years after the diagnosis of diabetes and to compare these incidences to those among the general population. Furthermore, we focused on sex-specific differences in occurrence of cancer before and after diabetes diagnosis.

Methods

This study is reported according to the STROBE (Strengthening the reporting of observational studies in epidemiology) recommendations (15).

Study design and data collection

For this study, two prospective cohorts were combined. A diabetes specific cohort, the observational ZODIAC (Zwolle Outpatient Diabetes project Integrating Available Care) cohort study, was merged with the Netherlands Cancer Registry (NCR). ZODIAC is a prospective primary care cohort study which was initiated in 1998. In this study, clinical data were sent annually to the Diabetes Centre by general practitioners (GPs) for benchmarking and research purposes. Patients included in the ZODIAC study were diagnosed with T2D and treated exclusively in primary care. Annually collected data includes date of birth, sex, date of diabetes diagnosis, HbA1c, height, weight, serum creatinine, albuminuria, cholesterol / HDL ratio, blood pressure, micro- and macrovascular complications, medication use (both diabetes specific and other medication), smoking status and alcohol use. Not only newly diagnosed patients were included, but also patients with previously diagnosed diabetes patients could participate. As a consequence, patients could have a date of diabetes diagnosis before 1998.

The NCR is a population based national registry and was founded in 1989 and records all malignancies based on notification by the National Pathology Archive (PALGA) and hospital discharge registries. Data is gathered by specially trained data-managers directly from the patients' files in all hospitals in the Netherlands. Data recorded includes incidence date, TNM stage, morphology, location and primary cancer treatment. Basal cell carcinoma of the skin, carcinoma in situ of the cervix, myelodysplastic syndrome, myeloproliferative disorders are not registered in the NCR database. Benign and borderline tumors are excluded, with the following exceptions; benign brain tumors (included from 1999), carcinoids of the appendix (included from 2001), borderline tumors of the ovaries (included from 2001), thymoma (included from 2001), phyloides tumors (included from 2001) and T-cell leukemia (included from 2004). All cancer events that occurred between 1989 and 2012 were linked to the data of the ZODIAC study via a trusted third party using postal code, full name, date of birth and sex. The NCR expects that the number of false-positive and the number false-negative for the ZODIAC-NCR linkage is both under 1%.

Patient selection

The combined ZODIAC-NCR database contained 71,648 patients of which 10,717 were diagnosed with a total number of 12,617 cancer events. In patients with more than one event, only the first diagnosis of cancer was included in the analysis. Patients were excluded from the present analyses when the cancer event occurred more than 5 years before the diagnosis of diabetes (n=2,065, 3.0%). For this study patients were followed up to 5 years after diagnosis of diabetes. A total of 69,583 (97.1%) patients were included in this study. Baseline date is the date of diabetes diagnosis, which could very well be

different to the time of entry into the ZODIAC study. Follow-up is calculated from first entry into the ZODIAC study until the last available check-up date.

Outcome measures

The primary outcomes were the sex-specific standardized incidence of all cancers combined and obesity-related cancers from 5 years before to 5 years after diabetes diagnosis compared to the expected incidence rates in the general Dutch population.

Statistical analysis

Using the date of diagnosis of diabetes and date of cancer events, cancer incidence was calculated for one-year intervals from 5 years prior to 5 years after the diagnosis of T2D. Patients from whom only the year (and not the month) of diabetes diagnosis was available in the ZODIAC study (n=5110, 6.9%), the first of July of that year was chosen as date of diagnosis of diabetes. Incidence rates were calculated for all cancer types combined (excluding Non-Melanoma Skin Cancer, NMSC) and for obesity-related cancer (liver, kidney, colorectal, gallbladder, pancreas, ovarian, endometrial and advanced prostate cancer, post-menopausal breast cancer and esophageal adenocarcinoma (5)). Sex-specific obesity-related cancer were defined as ovarian, endometrial and post-menopausal breast cancer in women and as advanced prostate cancer in men.

Incidence rates were calculated by dividing the number of cancer events in a one year time period by the amount of contributed time in this period. Reference data for all cancer and for obesity-related cancer incidence of the whole Dutch population were provided by the NCR. The Standardized Incidence Ratio (SIR), which is analogous to the commonly used standardized mortality rate, was calculated in order to compare the cancer incidence in the ZODIAC cohort to the general population. All analyses were standardized for age and year of cancer diagnosis.

Normality of baseline variables was evaluated using Q-Q plots. Standardized incidence rates with 95% confidence intervals adjusted for age, gender and year of cancer (in 5-year intervals) were calculated (16). Analyses were performed in STATA v14.

Ethics Statement

Patients consented with the anonymous use of their data for study purposes. The medical ethics committee of Isala, Zwolle, the Netherlands approved this study and the linking of the ZODIAC with the NCR (METC reference number 13.0765).

Results

Baseline characteristics are shown in table 1. Among the 69,583 patients included, 49% were female. Women were older and had a higher BMI compared to men.

Table 1: Baseline characteristics.

	Men	Women
N	35.271 (50.5)	34.312 (49.5)
Age (years)	60.0 (±11)	63 (±12)
Diabetes duration (years)	2.1 (0.5 – 5.7)	2.5 (0.6 – 6.3)
HbA1c (mmol/mol)	49 (43 – 55)	49 (43 – 55)
BMI (kg/m2)	28.4 (26.0 – 31.5)	29.5 (26.3 – 33.7)
Cancer events		
All cancer	2139 (6.1)	2130 (6.2)
Obesity-related cancer	709 (2.0)	1344 (3.9)
Non sex-specific cancer	479 (1.4)	374 (1.1)

Values are depicted as n (%), mean (± SD), or median (25 - 75 percentiles).

Standardized incidence rates all cancers combined

The SIR (95%CI) for all cancers combined for men and for women are shown in figure 1 and table 2 and 3. Over the years, there was a gradual increase in SIR in both men and women, becoming significantly different from 1.0, 2-3 year prior to diagnosis of diabetes. The mean SIR (95%CI) for men and women together ranged from 1.05 (0.94 – 1.17) to 1.36 (1.24 – 1.48) between five and one year prior to the diagnosis of diabetes. A rise in cancer incidence is shown for men and women together at the time of diagnosis of diabetes (SIR 1.71, 95%CI 1.58-1.85). After diagnosis the SIR (95%CI) varied between 1.37 (1.24 – 1.50) (2-3 years after diagnosis) and 1.51 (1.37 – 1.66) (3-4 years after diagnosis).

Women had an increased cancer incidence, which started to increase from 4-5 years prior to diabetes diagnosis (SIR 1.26, 95%CI 1.08 – 1.45). At diagnosis of diabetes a significant rise in cancer incidence was observed (SIR 1.82, 95%CI 1.60 – 2.03). After diabetes diagnosis the SIR (95%CI) varied between 1.84 (1.61 – 2.07) at 1-2 years after diabetes diagnosis to 1.58 (1.36 – 1.80) at 2-3 years.

The mean SIR (95%CI) for men ranged from 0.88 (0.74 – 1.02) to 1.35 (1.19 – 1.51) at the 5 years prior to and 1 year prior to the diagnosis of diabetes. At the time of diagnosis of diabetes the observed SIR was 1.63 (95%CI 1.46 – 1.81). After the diagnosis of diabetes the SIR ranged from 1.22 (1.05 – 1.38) to 1.35 (1.17 – 1.53).

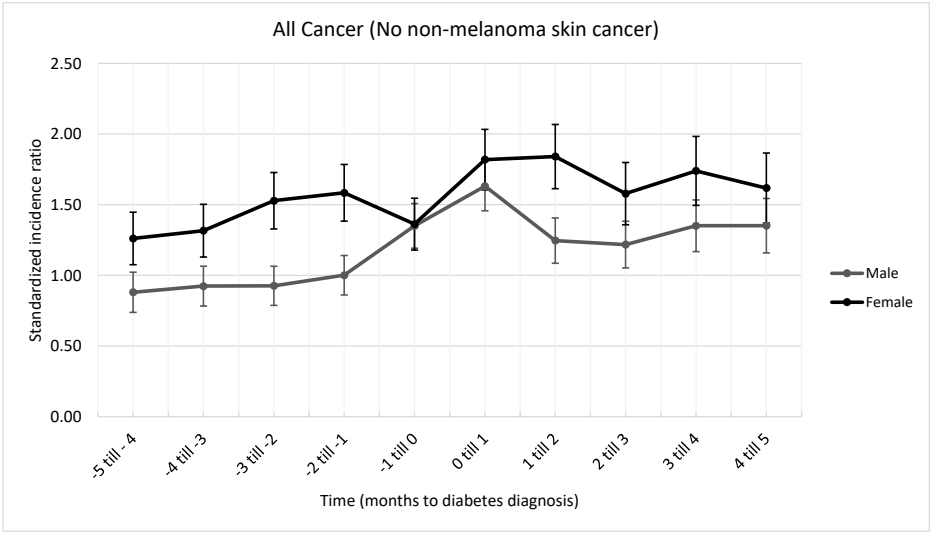

Figure 1: Standardized Incidence Ratio of all cancers combined (excluding non-melanoma skin cancer).

Table 2: Pooled standardized incidence ratio.

		Men and women				Men				Women			
	Time period (years)	**SIR**	**95%CI**			**SIR**	**95%CI**			**SIR**	**95%CI**		
All cancer	-5 till 0	1.18	1.13	to	1.23	1.01	0.95	to	1.08	1.40	1.31	to	1.48
	0 till 1	1.71	1.58	to	1.85	1.63	1.46	to	1.81	1.82	1.60	to	2.03
	1 till 5	1.43	1.36	to	1.49	1.26	1.17	to	1.35	1.67	1.56	to	1.79
Obesity-related cancer	-5 till 0	1.42	1.33	to	1.51	1.02	0.90	to	1.13	1.77	1.63	to	1.91
	0 till 1	1.80	1.59	to	2.01	1.38	1.11	to	1.64	2.21	1.88	to	2.54
	1 till 5	1.67	1.56	to	1.79	1.21	1.07	to	1.35	2.12	1.94	to	2.30
Non sex-specific obesity-related cancer	-5 till 0	1.38	1.23	to	1.52	1.52	1.31	to	1.72	1.20	1.00	to	1.40
	0 till 1	2.29	1.91	to	2.67	2.04	1.56	to	2.51	2.61	2.00	to	3.23
	1 till 5	1.88	1.69	to	2.08	1.80	1.54	to	2.05	1.99	1.68	to	2.29

Abbreviations: SIR: Standardized Incidence Ratio.

Table 3: Standardized incidence ratio all cancers combined.

	Men and women				Men				Women			
Time period (years)	**SIR**	**95%CI**			**SIR**	**95%CI**			**SIR**	**95%CI**		
-5 till - 4	1.05	0.94	to	1.17	0.88	0.74	to	1.02	1.26	1.08	to	1.45
-4 till -3	1.10	0.99	to	1.21	0.92	0.78	to	1.06	1.32	1.13	to	1.50
-3 till -2	1.19	1.08	to	1.31	0.93	0.79	to	1.06	1.53	1.33	to	1.73
-2 till -1	1.25	1.14	to	1.37	1.00	0.86	to	1.14	1.58	1.38	to	1.78
-1 till 0	1.36	1.24	to	1.48	1.35	1.19	to	1.51	1.36	1.18	to	1.55
0 till 1	1.71	1.58	to	1.85	1.63	1.46	to	1.81	1.82	1.60	to	2.03
1 till 2	1.50	1.36	to	1.63	1.25	1.09	to	1.41	1.84	1.61	to	2.07
2 till 3	1.37	1.24	to	1.50	1.22	1.05	to	1.38	1.58	1.36	to	1.80
3 till 4	1.51	1.37	to	1.66	1.35	1.17	to	1.53	1.74	1.50	to	1.98
4 till 5	1.46	1.31	to	1.62	1.35	1.16	to	1.54	1.62	1.37	to	1.87

Abbreviations: SIR: Standardized Incidence Ratio.

Obesity-related cancers

Incidence rates for obesity-related cancers are shown in figure 2 and table 4. In men and women combined the incidence of obesity-related cancer is elevated compared to the incidence in the general population at any time in the study period with the highest cancer incidence in the year after diabetes diagnosis (SIR 1.80, 95%CI 1.59 – 2.01).

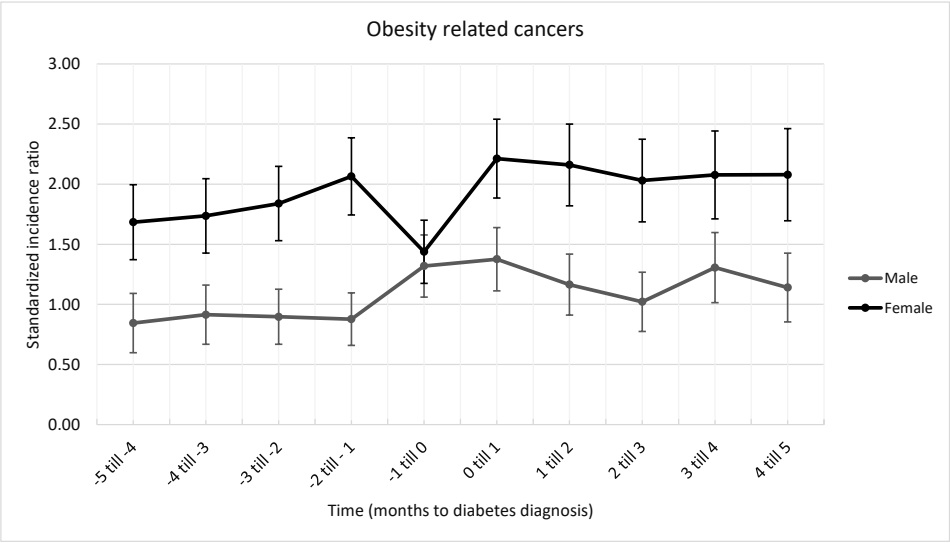

Figure 2: Standardized Incidence Ratio of obesity-related cancers.

In women, all 5 years prior to diabetes diagnosis, there was a significant increased incidence compared to women in the general population. The SIR gradually increased from 1.86 (95%CI 1.37 – 2.00) at 5 years prior to diabetes diagnosis to 2.06 (95%CI 1.74 –

2.39) at 2 to 1 year prior to diabetes diagnosis but decreases in the year before diagnosis of diabetes (SIR 1.44, 95%CI 1.17-1.70). The first year after diabetes diagnosis the SIR was highest(SIR 2.21, 95%CI 1.88-2.54) and remained increased in the 5 years after diabetes diagnosis.

In men no significantly increased cancer risk was observed in 5 to 1 year prior diagnosis of diabetes. In contrast, in the year prior and the year after diabetes diagnosis the SIR was significantly increased cancer risk compared to men in the general population, 1.32 (95%CI 1.06 – 1.58) and 1.38 (95%CI 1.11 – 1.64), respectively.

The SIR for obesity-related cancers was higher in women compared to men with T2D, with non-overlapping confidence intervals, except at one year before diagnosis of diabetes.

Table 4: Standardized incidence ratio of obesity-related cancers*.

	Men and women				Men				Women			
Time period (years)	**SIR**	**95%CI**			**SIR**	**95%CI**			**SIR**	**95%CI**		
-5 till - 4	1.31	1.11	to	1.52	0.84	0.60	to	1.09	1.68	1.37	to	2.00
-4 till -3	1.36	1.16	to	1.57	0.91	0.67	to	1.16	1.74	1.43	to	2.05
-3 till -2	1.40	1.20	to	1.59	0.90	0.67	to	1.13	1.84	1.53	to	2.15
-2 till -1	1.50	1.30	to	1.69	0.88	0.66	to	1.10	2.06	1.74	to	2.39
-1 till 0	1.38	1.20	to	1.56	1.32	1.06	to	1.58	1.44	1.17	to	1.70
0 till 1	1.80	1.59	to	2.01	1.38	1.11	to	1.64	2.21	1.88	to	2.54
1 till 2	1.67	1.46	to	1.88	1.16	0.91	to	1.42	2.16	1.82	to	2.50
2 till 3	1.53	1.32	to	1.74	1.02	0.77	to	1.27	2.03	1.69	to	2.37
3 till 4	1.69	1.46	to	1.93	1.31	1.01	to	1.60	2.08	1.71	to	2.44
4 till 5	1.61	1.37	to	1.85	1.14	0.85	to	1.43	2.08	1.70	to	2.46

* cancers included: liver, kidney, colorectal, gallbladder, pancreas, ovarian, endometrial and advanced prostate cancer, post-menopausal breast cancer and esophageal adenocarcinoma. Abbreviations: SIR: Standardized Incidence Ratio.

Sex-specific influences on obesity-related cancer incidence

Figure 3 and table 5 shows the SIR for obesity-related cancers when the sex-specific obesity-related cancer types (breast, ovarian and endometrial cancer in women and advanced prostate cancer in men) were excluded.

In women a significantly increased SIR before the diabetes diagnosis was only observed at 2 year before diagnosis (SIR 1.64, 95%CI 1.14-2.14). In the year following diabetes diagnosis a significantly increased SIR was observed (SIR 2.61, 95%CI 2.00-3.23) which remained significantly increased up to 5 years post diabetes diagnosis.

In men, there was a significant difference in cancer incidence 3 years (SIR 1.50, 95%CI 1.06 – 1.94) and 1 year (SIR 1.96, 95%CI 1.49 – 2.42) prior to diabetes diagnosis compared to the general population. Cancer incidence was highest in the year after diabetes diagnosis

(SIR 2.04, 95%CI 1.56 – 2.51). The SIRs for non-sex-specific obesity-related cancers were not significantly different between sexes.

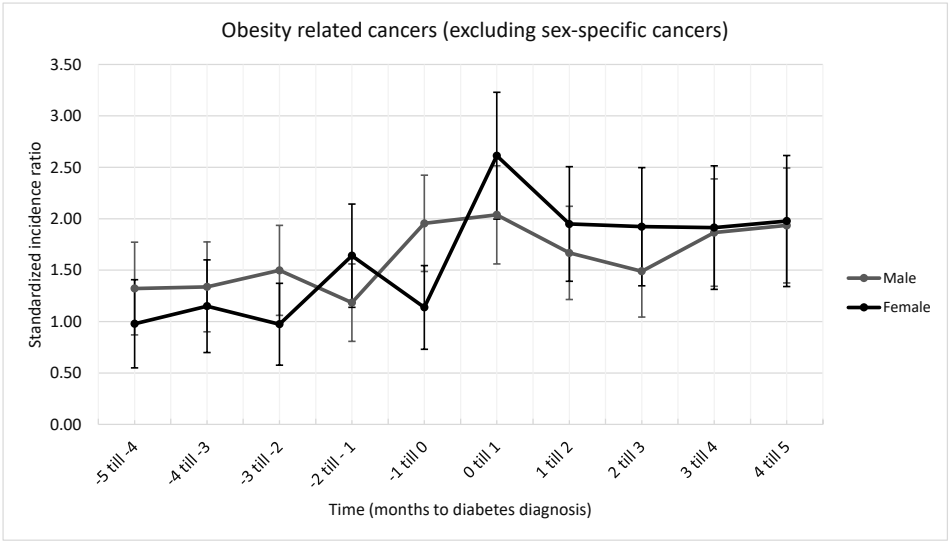

Figure 3: Standardized Incidence Ratio of obesity-related cancer excluding sex specific cancers.

Table 5: Standardized incidence ratio of obesity-related cancers excluding sex-specific cancers.

	Men and women				Men				Women			
Time period (years)	**SIR**	**95%CI**			**SIR**	**95%CI**			**SIR**	**95%CI**		
-5 till - 4	1.17	0.85	to	1.48	1.32	0.87	to	1.77	0.98	0.55	to	1.41
-4 till -3	1.25	0.94	to	1.57	1.34	0.90	to	1.77	1.15	0.70	to	1.60
-3 till -2	1.27	0.97	to	1.57	1.50	1.06	to	1.94	0.97	0.58	to	1.37
-2 till -1	1.38	1.08	to	1.69	1.18	0.81	to	1.56	1.64	1.14	to	2.14
-1 till 0	1.60	1.28	to	1.92	1.96	1.49	to	2.42	1.14	0.73	to	1.54
0 till 1	2.29	1.91	to	2.67	2.04	1.56	to	2.51	2.61	2.00	to	3.23
1 till 2	1.79	1.44	to	2.14	1.67	1.21	to	2.12	1.95	1.39	to	2.51
2 till 3	1.68	1.32	to	2.03	1.49	1.04	to	1.93	1.92	1.35	to	2.50
3 till 4	1.89	1.49	to	2.28	1.86	1.34	to	2.39	1.91	1.31	to	2.51
4 till 5	1.95	1.53	to	2.37	1.93	1.38	to	2.49	1.98	1.34	to	2.61

* cancer included: liver, kidney, colorectal, gallbladder, pancreas and esophageal adenocarcinoma.
Abbreviations: SIR: Standardized Incidence Ratio.

Discussion

This study is one of the first to investigate standardized cancer incidence in a 10-year time frame around diabetes diagnosis and to investigate whether sex differences were present. The results showed that women had already an increased all cancer and obesity-related cancer incidence in the 5 years prior to diabetes diagnosis. There was a marked dip in obesity-related cancer incidence in women the year prior to diabetes diagnosis. This decline seemed to be explained by sex-specific cancers, as this pattern was less obvious in the analyses which excluded sex-specific cancers. In men, there was a pronounced increase in all cancer and obesity-related cancer incidence around diabetes diagnosis. The increase in obesity-related cancer incidence was significantly higher in women than in men before and after diabetes diagnosis. The difference in obesity-related cancer incidence compared to the general population was largely related to sex-specific cancer types. In men, exclusion of prostate cancer substantially increased obesity-related cancer incidence.

The outcomes of this large Dutch T2D cohort are in accordance with results from previous studies that showed an increased cancer risk in the prediabetes phase (9-11, 14). A recent study from Canada showed that all cancer risk was elevated in the 10 years before (OR 1.23, 95%CI 1.19-1.27) and immediately (3 months) after diabetes diagnosis (HR 1.62, 95%CI 1.52-1.74) (14). These results support the results of the current study in which the increase in cancer incidence ranged from 5% to 36% before diagnosis of diabetes, and increased to 71% in the year following diagnosis of diabetes. An Austrian cohort study (n=5709 T2D patients) also reported an elevated SIRs for cancers of the pancreas (1.78, 95%CI 1.02 – 2.89) and corpus uteri (1.79, 95%CI 1.15 – 2.66) in women and for cancers of the liver (2.71, 95%CI 1.65 – 4.18) and pancreas (1.87, 95%CI 1.11 – 2.96) in men in the year after diagnosis of diabetes (17).

The studies that investigated the distribution of cancer incidence over the years prior and after diagnosis of diabetes did not, for the most part, perform sex-specific analyses (2, 14). However, studies that investigated site-specific cancers mostly focused on breast cancer and showed that breast cancer risk was already elevated in the pre-diabetes phase, (HR 1.16, 95%CI 1.03–1.31) (11) and (OR 1.13, 95%CI 1.09-1.18) (18). Postmenopausal breast cancer incidence has been related to obesity. It is plausible that women put on weight and developed cancer prior to diabetes diagnosis. This may result in a higher detection of breast cancer in screening programs prior to diabetes diagnosis in these women.

Part of the peak in cancer incidence around diabetes diagnosis could be explained by diabetes developing as a result of cancer, for example pancreas cancer (19). For this reason, we excluded pancreas cancer in a post-hoc analyses. This post-hoc analysis did not relevantly change results (see Table S1). However, increased detection could also play a role in the rise in cancer incidence immediately after diagnosis of diabetes in both men and women (12, 13). The previously mentioned study by Lega et al. included a sensitivity analyses to investigate the influence of detection bias, and found that it's likely that detection bias plays a role (14). Since the ZODIAC study does not record any other diseases, the current study was not able to include such sensitivity analyses. It is plausible that detection bias is also present in the current study, enhancing the peak in cancer incidence at diabetes diagnosis. This could in turn also explain the slight decrease in cancer risk seen in the 2 to 3 years after diabetes diagnosis in the present study which would be almost absent if there would not have been a peak. It is important to keep in mind that increased detection is not a negative effect and often directly results from increased contact with health care professionals (14). It is unlikely, however, that detection bias explained the increased incidence in the years before diabetes diagnosis.

The decline of the SIR in women 1 year before diabetes diagnosis was striking and has not been reported in previous studies. It could point to an influence of sex-specific cancers in women as when sex-specific cancers were excluded the dip disappeared. In women these cancers were primarily breast cancer. We considered several biological (20, 21), healthcare related (21-23) and methodological factors, but none seemed plausible. We have no causal explanation for this finding and in what way and why these sex-specific cancer influence incidence remains unclear. In addition, the dip was not present in men, likely excluding methodological errors as an explanation.

There appeared to be a difference in obesity-related cancer incidence between men and women. This difference disappeared when sex-specific obesity-related cancers were excluded. Exclusion of the sex-specific cancer types resulted in an increase of the SIR in men with T2D and a decrease of the SIR in women with T2D. The difference in men was caused by the exclusion of prostate cancer, which suggests that advanced prostate cancer might not be an obesity-related cancer. Previous studies have also reported that men with T2D have a lower risk of developing prostate cancer than men without T2D (19, 24). The decrease in SIR of women with T2D before diagnosis of diabetes was probably to a large extent the result of excluding breast cancer which incidence is increased in women with T2D compared to the general population. It has been suggested that this increased incidence is possibly due to increased aromatization of androgens to estrogens locally in fat tissue (25). Eventually, this could lead to increased ERα signaling in breast cancer

and possibly a greater risk of estrogen-dependent breast cancer (25). Indeed, especially estrogen receptor positive breast cancer risk is reported to be increased in women with T2D (26). Unfortunately, hormone receptor status of breast cancer was not available in the current combined ZODIAC-NCR dataset, but will be the subject of further studies.

Strengths and Limitations

A strength of this study is the size of the cohort of patients diagnosed with diabetes. Another strength is the long follow-up period of both the ZODIAC and NCR which made it possible to estimate incidence rates as early as five years before diagnosis of diabetes. This study sample represents the majority of primary care treated T2D patients in the Netherlands and has a high degree of generalizability.

There were also limitations. Some patients were selected with a date of diagnosis of diabetes occurring before 1994. In theory, patients could already have had a cancer event while diagnosed with diabetes before the NCR commenced in 1989, in the 5 years before diabetes diagnosis (the period between 1989 and 1994). However we expect this effect to be fairly negligible, since only 4.4% of in our data were diagnosed with diabetes before 1994. A second limitation was that patients included could be subject to a survival bias. Since the ZODIAC cohort only consists of patients diagnosed with type 2 diabetes, patients who died from, amongst others, cancer, could never be included in this cohort. Thirdly, the general population also includes people diagnosed with diabetes which could have led to an underestimation of the effect. Fourthly, the ZODIAC cohort was expanded to different regions in the Netherlands at several time points and both patients with known diabetes and newly diagnosed diabetes participated. For several patients already diagnosed with diabetes no date of diabetes diagnosis was present, or some inaccuracy of diabetes diagnosis could have occurred when patients were asked when they were diagnosed with diabetes. This could be subject to recall bias. In daily practice, when the patient could not remember the month, the first of January of that year was then chosen date of diagnosis of diabetes. By using the first of July in this analysis, it was attempted to minimize the size of effect of this bias. Unfortunately, an effect of this recall bias cannot be excluded although we have no reason to assume that this would be different in men or women.

Conclusion

In patients with T2D, both in men and women, cancer incidence peaked around the time of diabetes diagnosis. This is probably due, in part, to increased detection. Furthermore, a clear difference in elevated cancer risk was observed between men and women. Women

with T2D seem to have a higher incidence of cancer than women without diabetes, as early as 5 years before diabetes diagnosis. Breast cancer was probably mostly responsible for this increase. Exclusion of sex-specific obesity-related cancers resulted in a lower SIR in women and a higher SIR in men compared to the SIR in all obesity-related cancers. The latter might suggest a protective effect of diabetes on prostate cancer.

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Supplemental table 1: Standardized incidence ratio all cancers combined (excluding pancreas).

	Men and women				Women				Men			
Time period (years)	SIR	95%CI			SIR	95%CI			SIR	95%CI		
-5 till - 4	1.06	0.94	to	1.17	1.26	1.08	to	1.45	0.88	0.74	to	1.03
-4 till -3	1.10	0.99	to	1.22	1.32	1.13	to	1.51	0.93	0.78	to	1.07
-3 till -2	1.20	1.08	to	1.31	1.53	1.33	to	1.73	0.93	0.79	to	1.07
-2 till -1	1.24	1.13	to	1.36	1.56	1.36	to	1.75	1.00	0.86	to	1.14
-1 till 0	1.34	1.23	to	1.46	1.35	1.16	to	1.53	1.34	1.19	to	1.50
0 till 1	1.68	1.55	to	1.82	1.79	1.58	to	2.00	1.60	1.43	to	1.77
1 till 2	1.49	1.35	to	1.62	1.82	1.60	to	2.05	1.24	1.08	to	1.40
2 till 3	1.36	1.23	to	1.50	1.57	1.35	to	1.79	1.21	1.05	to	1.38
3 till 4	1.50	1.35	to	1.64	1.73	1.49	to	1.98	1.33	1.15	to	1.51
4 till 5	1.45	1.30	to	1.60	1.61	1.36	to	1.86	1.33	1.14	to	1.52

Abbreviations: SIR: Standardized Incidence Ratio.