Sex and gender differences in diabetes care

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Chapter 5

Body mass index and obesity-related cancer risk in men and women with type 2 diabetes (ZODIAC-56)

Submitted as:
Hendriks SH, Schrijnders D, van Hateren KJJ, Groenier KH, Siesling S, Maas AHEM, Landman GWD, Bilo HJG, Kleefstra N. Body mass index and obesity-related cancer risk in men and women with type 2 diabetes (ZODIAC-56).

Abstract

Objective
Aim was to investigate the relationship between BMI and obesity-related cancers in men and women with type 2 diabetes.

Research Design and Methods
A dataset of patients with T2D who participated in the ZODIAC study between 1998 and 2012 was linked to the Netherlands Cancer Registry. Cox proportional hazards models were used to investigate cancer risk, adjusting for selected confounders. Analyses were performed for the total group of obesity-related cancers and for non sex-specific and sex-specific obesity-related cancers (in men: advanced prostate cancer, in women: ovarian, endometrial and postmenopausal breast cancer).

Results
A total of 52.044 patients was included (49% women). During follow-up from inclusion in the ZODIAC study, 689 men and 914 women were diagnosed with an obesity-related cancer. In men, BMI was associated with a higher risk of the total group of obesity-related cancers and non sex-specific obesity-related cancers (HR (per 5 kg/m2 increase) 1.12 (95%CI 1.02–1.23) and HR 1.18 (95%CI 1.06–1.31)). No association was found with prostate cancer. In women, an association between BMI and all obesity-related cancers combined and sex-specific obesity-related cancers was present (HR 1.15 (95%CI 1.08–1.22) and HR 1.22 (95%CI 1.14–1.32)). No association with non sex-specific cancers was found in women.

Conclusions
BMI is a risk factor for obesity-related cancers in men with T2D, except for advanced prostate cancer. The results of this study provide reason to reconsider the classification of advanced prostate cancer as an obesity-related cancer, at least in T2D. In women with T2D, BMI is a risk factor for the total group of obesity-related cancers and for sex-specific obesity-related cancers.

Introduction

Type 2 diabetes (T2D) is associated with an increased risk for cardiovascular morbidity and mortality (1,2). Furthermore, T2D is also related to a higher cancer risk (3,4). This increased cancer risk appears to be site-specific; a higher risk for liver, pancreas, endometrial, colorectal, breast and bladder cancer has been reported in patients with T2D (3). Whether this increased risk is directly related to T2D, caused by longer periods of hyperglycaemia and/or elevated insulin levels, or indirectly, due to common risk factors like obesity, is not clear (3).

According to the World Cancer Research Fund, being overweight or obese is related to an increased incidence of oesophageal, stomach (cardia), colorectal, liver, gallbladder, pancreatic and kidney cancer in both sexes in the general population. Furthermore, being overweight or obese is related to an increased incidence of ovarian, endometrial and postmenopausal breast cancer in women and to advanced prostate cancer in men (5).

Whether there is an association between BMI and excess risk of developing obesity-related cancers in patients with T2D is unclear. One previous study did not find an association between BMI and obesity-related cancers in T2D (6). Another study only investigated colon cancer and found a significant relationship when diabetes duration was taken into account (7).

Even more unclear is whether there is a sex difference in the association between BMI and obesity-related cancers in patients with T2D. A large prospective study from Sweden reported an association between being overweight and obesity with all cancers and gastrointestinal cancers in men. However, in women only an association with obesity and both cancer groups was found (8). This could indicate that the threshold for BMI to act as a risk factor for obesity-related cancer is lower in men compared to women with T2D. Therefore, the aim of the present study was to investigate the relationship between BMI and obesity-related cancers in men and women with T2D and specifically non sex-specific and sex-specific obesity-related cancers.

Methods

Study group

The study population consisted of patients who were included in the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study. This project started in 1998 and was part of a study at that time that primarily investigated the effects of shared care in patients with T2D treated in primary care in the Zwolle region of the Netherlands (9). This shared care initiative became the standard care for the Zwolle region in 2002 and

expanded to other regions in the Netherlands in the years thereafter. In these regions, general practitioners (GPs) provide data on an annual basis to the Diabetes Centre for benchmark and research purposes. Only T2D patients treated in primary care are included in the ZODIAC project. Patients with a very short life expectancy or insufficient cognitive capabilities are excluded from participation. At the start in 1998, 53 general practitioners (GPs) participated in this project, and this number increased to more than 700 GPs in 2012.

For the current study, available information on clinical variables from patients participating for at least one year in the ZODIAC project between 1998 and 2012 was linked to available information of the Netherlands Cancer Registry (NKR) to obtain data on cancer incidents in the years between 1989 and 2012. This national cancer registry started in 1989 and records all malignancies based on notification by the National Pathology Archive (PALGA) and hospital discharge registries in the Netherlands. Basal cell carcinoma of the skin, carcinoma in situ of the cervix, myelodysplastic syndrome, myeloproliferative disorders are not registered in the NCR database. Data on patient characteristics, tumor type and grade, and treatment are collected by specially trained data-managers directly from the patients' files in all hospitals in the Netherlands. The combined ZODIAC-NKR database contains 71.634 patients.

Data collection

The demographic and clinical data were collected as part of ZODIAC project and included: sex, age, diabetes duration, HbA1c, serum creatinine, BMI, smoking status and the use of metformin, sulfonylurea derivatives and insulin. Baseline was defined as the first year that a patient was included in the ZODIAC project.

Cancer characteristics provided and collected by the NKR were: cancer origin, incidence date, TNM stage, morphology and type of therapy.

Study procedure

The association between BMI and obesity-related cancer was investigated for three groups; total group of obesity-related cancers, non sex-specific obesity-related cancers and sex-specific obesity-related cancers. The non sex-specific cancer group consisted of gastric-cardia, colorectal, liver, gall bladder, pancreas and kidney cancer and adenocarcinoma of the esophagus. In men, the sex-specific cancer group was formed by advanced prostate cancers only (further referred to as prostate cancer). In women, the sex-specific cancer group consisted of ovarian, endometrial and postmenopausal breast cancer (further referred to as ovarian, endometrial and breast cancer). The total group of obesity-related cancers consisted of non sex-specific cancers and prostate cancer in men and of non sex-specific cancers and ovarian, endometrial and breast cancer in women. Post-menopausal

breast cancer was in the present study defined as breast cancer in women ≥ 55 years of age (10).

Patients with a BMI <18.5 kg/m2 were excluded in all analyses, as undiagnosed cancer may lead to becoming underweight (n= 130 (0.2%)). Furthermore, patients were excluded if they had only baseline data recorded (only one check-up by their care provider) (n= 18.643 (26.0%)). For the analyses of the total group of obesity-related cancers, patients diagnosed with a non sex-specific or sex-specific obesity-related cancer before entering the ZODIAC study were excluded (n = 2061 (2.9%)). For the non sex-specific analysis, only patients with a non sex-specific cancer before entering the ZODIAC study were excluded (n = 817 (1.1%)). For the sex-specific cancer analysis, only patients with a sex-specific cancer before entering the ZODIAC study were excluded (n = 1278 (1.8%)).

Clinical endpoint in all analyses was the first obesity-related cancer after baseline. Patients were not censored if they were diagnosed with a non-obesity-related cancer before during follow-up. The end of follow up for patients who were not diagnosed with cancer was based on the last check up by their general practitioner.

Statistical analyses

Statistical analyses were performed using SPSS version 23 for Windows (SPSS Inc., Chicago, Illinois, USA) and Stata version 14.0 for Windows (StataCorp, College Station, Texas, USA). Multiple imputation analysis was performed for missing data on the independent variables, assuming that data was missing at random (MAR) or completely at random (MCAR). Ten imputated datasets were created and the pooled results are presented. Baseline data are expressed as mean with standard deviation (SD) or median with interquartile range (IQR) for normally distributed and non-normally distributed data, respectively. Categorical variables are described in numbers and percentages. Normal distribution was assessed on the basis of histograms and QQ-plots. A two-sided $p<0.05$ was considered significant. Cox proportional hazard analyses were used to investigate the association between BMI as a continuous and categorical variable and obesity-related cancers in men and women with T2D, separately. Hazard ratios refer to a BMI increase of 5 m2/kg in the analyses for BMI as a continuous variable. For the analyses of BMI as a categorical variable, four BMI categories were used (18.5 - 25.0 kg/m^2, 25.0 - 30.0 kg/m^2, 30.0 - 35 kg/m^2, ≥ 35.0 kg/m^2). The lowest category was used as reference category. Age was used as the time-scale in all analyses, because the risk of cancer is not proportional with age. Patients entered the analysis at their baseline age and exited at their event/censoring age. Two models were used: an age-adjusted model (model 1) and a model additionally adjusted for diabetes duration, HbA1c, serum creatinine, smoking status and the use of metformin, SU-derivatives and/or insulin (model 2). Furthermore, the analyses for model 2 were stratified according to the year of inclusion in the ZODIAC

cohort. The assumption of proportional hazards for baseline predictors was investigated by visual inspection of the Schoenfeld residuals.

Ethical approval

This study approved by the local medical ethics committee of the Isala, Zwolle, the Netherlands (METC reference number 13.0765).

Results

Total group of obesity-related cancers

Baseline results for the men and women who are included in the analyses for the total group obesity-related cancers are described in table 1. In these analyses, 25.811 men and 24.989 women were included. Mean age was 64.0 (SD 11.2) years in men and 66.6 (12.1) years in women. The median diabetes duration was higher in women. More men than women were current smokers and men had a lower BMI than women. A higher percentage of men used metformin whereas insulin use was more frequent in women. The median follow-up period for these patients was 3.1 (1.7 – 5.0) years in men and 3.1 (1.7 – 5.1) in women. During follow-up, 689 (2.7%) men and 914 women (3.7%) were diagnosed with an obesity-related cancer.

Table 1. Baseline characteristics of men and women.

Variable	Men	Women	P-value*
N	25811 (49.2)	24989 (50.8)	
Age (years)	64.0 (±11.2)	66.6 (±12.1)	< 0.001
Diabetes duration (years)	2.5 (0.7 – 5.8)	2.8 (0.8 – 6.3)	< 0.001
HbA1c (mmol/mol)	49 (43 – 55)	49 (43 – 54)	0.091
Creatinine (μmol/L)	83 (73 – 95)	68 (59 – 79)	< 0.001
Smoking	8029 (31)	4857 (19)	< 0.001
BMI (kg/m^2)	29.2 (±4.6)	30.4 (±5.7)	< 0.001
Use of metformin	14813 (57)	13539 (54)	< 0.001
Use of SU-derivatives	7977 (31)	7638 (31)	0.408
Use of Insulin	2135 (8)	2512 (10)	< 0.001

Values are depicted as n (%), mean (± SD), or median (IQR). Continuous data were analysed using independent t-tests or the Mann-Whitney U test. Categorical variables were analysed using chi square tests. * P-value for the difference between men and women.

The results of the association between BMI as a continuous variable and the total group of obesity-related cancers are described in table 2 for men and women separately. In both men and women, BMI was associated with a higher risk of obesity-related cancer in the age and fully adjusted analyses (in men: HR 1.11 (95% CI 1.01 – 1.22) and HR 1.12 (95% CI 1.02 – 1.23), in women: HR 1.14 (95% CI 1.07 – 1.21) and HR 1.15 (95% CI 1.08 – 1.22)). Analysis of BMI as a categorical variable showed that in men a BMI of 30.0 - 35.0 kg/m2 was associated with a higher risk of obesity-related cancer compared to the reference group. In women, a BMI of 30.0 - 35.0 kg/m2 and a BMI ≥ 35.0 kg/m2 were both associated with a higher risk of obesity-related cancer compared to the reference group (table 5).

Table 2. Regression analyses for all obesity related cancers in men and women.

Variable	Men		Women	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
BMI*	1.11 (1.01 – 1.22)	1.12 (1.02 – 1.23)	1.14 (1.07 – 1.21)	1.15 (1.08 – 1.22)
Diabetes duration		0.99 (0.97 – 1.01)		0.99 (0.97 – 1.00)
HbA1c		1.00 (0.99 – 1.01)		1.00 (0.99 – 1.00)
Creatinin		1.00 (0.99 – 1.00)		1.00 (1.00 – 1.00)
Use of metformin		0.94 (0.80 – 1.10)		0.98 (0.85 – 1.22)
Use of SU-derivatives		1.16 (0.98 – 1.37)		1.03 (0.88 – 1.19)
Use of insulin		1.14 (0.84 – 1.54)		1.09 (0.85 – 1.40)
Smoking		1.02 (0.86 – 1.22)		1.11 (0.93 – 1.33)

* per 5 kg/m2 increase in BMI. Abbreviations: HR (95% CI): hazard ratio with 95% confidence interval.

Non sex-specific obesity related cancers

In the analyses for non-sex specific obesity-related cancers, 25.945 men and 26.099 women were included. Baseline results for these patients did not significantly differ from the baseline results described in table 1 (data not shown). The median follow-up period was 3.1 (1.7 – 5.0) years in men and 3.1 (1.7 – 5.1) in women. During follow-up, 533 (2.1%) men and 385 (1.5%) women were diagnosed with a non-sex specific obesity-related cancer.

In men, BMI was associated with a higher risk of non-sex specific obesity-related cancer in the age and fully adjusted analyses (HR 1.17 (95% CI 1.05 – 1.30) and HR 1.18 (95% CI 1.06 – 1.31)) (table 3). In the categorical analyses, a BMI of 30.0 - 35.0 kg/m2 and a BMI ≥ 35.0 kg/m2 were also associated with a higher risk of non-sex specific obesity-related cancer in men (table 5). In women, no significant associations between BMI as a continuous or categorical variable and non-sex specific obesity-related cancers were found.

Table 3. Regression analyses for non sex-specific obesity related cancers in men and women.

Variable	Men		Women	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
BMI	1.17 (1.05 – 1.30)	1.18 (1.06 – 1.31)	1.01 (0.92 – 1.12)	1.02 (0.92 – 1.13)
Diabetes duration		1.00 (0.97 – 1.02)		0.98 (0.96 – 1.01)
HbA1c		1.00 (0.99 – 1.01)		1.00 (0.99 – 1.01)
Creatinine		1.00 (0.99 – 1.00)		1.00 (0.99 – 1.01)
Use of metformin		0.88 (0.74 – 1.06)		1.16 (0.94 – 1.44)
Use of SU-derivatives		1.07 (0.88 – 1.30)		1.15 (0.92 – 1.44)
Use of insulin		1.04 (0.73 – 1.49)		1.19 (0.82 – 1.74)
Smoking		1.09 (0.90 – 1.33)		1.33 (1.01 – 1.76)

* per 5 kg/m2 increase in BMI. Abbreviations: HR (95% CI): hazard ratio with 95% confidence interval.

Sex-specific obesity-related cancers

In the analyses for sex-specific obesity-related cancers, 26.226 men and 25.357 women were included. Baseline results for these patients did not significantly differ from the baseline results described in table 1 (data not shown). The median follow-up period for these patients was 3.1 (1.7 – 5.0) years in men and 3.1 (1.7 – 5.1) in women. During follow-up, 170 (0.7%) men and 575 (2.3%) women were diagnosed with a sex-specific obesity-related cancer.

In men, no significant associations between BMI as a continuous or categorical variable and prostate cancer was found (table 4). In women, BMI was associated with a higher risk of ovarian, endometrial and breast cancer in the age and fully adjusted analyses (HR 1.22 (95% CI 1.13 – 1.31) and HR 1.22 (95% CI 1.14 – 1.32)). In the categorical analyses, a BMI of 25.0 - 30.0 kg/m2, a BMI of 30.0 - 35.0 kg/m2 and a BMI ≥ 35.0 kg/m2 were associated with a higher risk of ovarian, endometrial and breast cancer in women (table 5).

Table 4. Regression analyses for sex-specific obesity related cancers in men and women.

Variable	Men		Women	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
BMI (per 5 kg/m^2)	0.92 (0.74 – 1.15)	0.93 (0.75 – 1.16)	1.22 (1.13 – 1.31)	1.22 (1.14 – 1.32)
Diabetes duration		0.98 (0.95 – 1.02)		0.98 (0.96 – 1.01)
HbA1c		0.99 (0.98 – 1.01)		1.00 (0.99 – 1.01)
Creatinine		1.00 (0.99 – 1.00)		1.00 (1.00 – 1.00)
Use of metformin		1.17 (0.85 – 1.61)		0.86 (0.73 – 1.03)
Use of SU-derivatives		1.50 (1.07 – 2.09)		0.93 (0.77 – 1.13)
Use of insulin		1.34 (0.74 – 2.42)		1.05 (0.76 – 1.44)
Smoking		0.81 (0.55 – 1.19)		1.00 (0.79 – 1.27)

* per 5 kg/m2 increase in BMI. Abbreviations: HR (95% CI): hazard ratio with 95% confidence interval.

Table 5. Regression analyses with BMI categories for all obesity related cancer groups in men and women.

	Men			Women		
Variable	**All**	**Non-sex specific**	**Sex-specific**	**All**	**Non-sex specific**	**Sex-specific**
BMI (kg/m2)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
≥ 18.5 - < 25.0	Reference	Reference	Reference	Reference	Reference	Reference
≥ 25.0 - < 30.0	1.12 (0.89– 1.40)	1.12 (0.86 – 1.46)	1.07 (0.69 – 1.66)	1.24 (1.00 – 1.55)	0.98 (0.71 – 1.36)	1.46 (1.05 – 2.02)
≥ 30.0 - < 35.0	1.34 (1.04 – 1.73)	1.42 (1.05 – 1.90)	1.15 (0.71 – 1.86)	1.31 (1.03 – 1.65)	1.06 (0.77 – 1.46)	1.51 (1.08 – 2.12)
≥ 35.0	1.24 (0.86 – 1.78)	1.61 (1.10 – 2.36)	- *	1.61 (1.26 – 2.07)	1.07 (0.73 – 1.56)	2.09 (1.48 – 2.93)

* Only one event. Abbreviations: HR (95% CI): hazard ratio with 95% confidence interval.

Discussion

The results of the present study showed that BMI was associated with the total group of obesity-related cancers in both men and women with T2D. Important differences between men and women were found. BMI was associated with non sex-specific obesity-related cancers in men, but not in women. Results concerning the sex-specific cancers showed the opposite. In these analyses BMI was associated with ovarian, endometrial and postmenopausal breast cancer in women, but not with advanced prostate cancer in men.

This is the first study which describes the association between BMI and the total group of obesity-related cancers in a large cohort of men and women with T2D. A study from Japan could not find an association between BMI and all obesity-related cancers (6). However, this was a study that included 2334 patients, and only 35 patients developed cancer during follow-up (6).

The absence of a significant association between BMI and non sex-specific obesity-related cancers in women may indicate that BMI (in contrast to men) is not a risk factor for this group of cancers. Only one study has previously described sex differences in the association between BMI and non-sex-specific obesity-related cancers in patients with T2D (8). A study from Sweden found that being overweight or obese was associated with a higher risk of gastrointestinal cancers in men, whereas in women only obesity but not overweight was found to be associated with gastrointestinal cancers (8). The sex difference in the association between BMI and non-sex specific obesity-related cancers could partly be the result of a sex difference in distribution of fat. In general, obese men have more intra-abdominal fat compared to obese premenopausal women. Although the sex difference in intra-abdominal fat is less apparent in patients with T2D, the amount of intra-abdominal fat is probably still higher in men (11). Especially this abdominal adiposity is associated with many metabolic abnormalities which may increases cancer risk. It might be that BMI was not accurate enough to represent the amount of abdominal fat especially in women with T2D. Using waist circumference as a marker of abdominal fat might have been more accurate.

In the present study, obese women had a 51% higher risk for ovarian, endometrial and, post-menopausal breast cancer compared to lean women with T2D during follow-up. Only one previous study has described an association between BMI and sex-specific cancers in women with T2D. Jonasson et al. described a 39% higher risk for postmenopausal breast cancer compared to lean women (8). The association of BMI

with these types of cancer might be attributed to an increase in oestrogen production in adipose tissue in overweight and obese women with T2D (12). Not only BMI but also T2D itself has been found to be related to a higher risk of endometrial and breast cancer (3). Taken this together, this indicates that especially obese women with T2D are at risk for the development of endometrial cancer and postmenopausal breast cancer. On the other hand, some researchers have questioned the relation between T2D itself and breast cancer. They have suggested that the higher risk of postmenopausal breast cancer in women with T2D could be completely explained by residual confounding by overweight and not by having a problem with metabolic disturbance related to glucose control (13).

In line with the results of the present study, Jonasson et al. could not find an association between BMI and prostate cancer in men with T2D (8). However, they included all prostate cancers, whereas only advanced prostate cancer is described by the World Cancer Research Fund to be related with BMI in the general population (5). Nevertheless, the International Agency for Research on Cancer (IARC) Working Group has recently described that evidence for a preventive effect of the absence of excess body fat for fatal prostate cancer is limited (14). The present study adds to the literature that a relation between BMI and advanced prostate cancer is not present, at least not in men with T2D. Advanced prostate cancer should therefore be reconsidered as being obesity-related.

The strengths of the present study were the prospective design and the use of a large cohort of T2D patients of which data on BMI was available. Some limitations of the present study should also be mentioned. Firstly, the clinical data and the data on medication use of the ZODIAC cohort were collected annually by practice nurses and general practitioners. The reliability of the data is therefore dependent on their accuracy. Secondly, data on BMI was missing for 9% of the patients. BMI values for these patients were estimated using multiple imputations. Thirdly, the grouping of obesity-related cancers could be discussed. All different cancers were taken together as the number of total events would be too small when investigating each of the obesity-related cancers separately. Finally, the follow-up period was relatively short for cancer epidemiology and therefore the number of events is relatively small.

In conclusion, BMI is a risk factor for the total group of obesity-related cancers and for non sex-specific obesity-related cancers in men with T2D. BMI is not related to advanced prostate cancer. The present study provides an extra reason for questioning advanced prostate cancer being obesity-related, at least in patients with T2D. In women, BMI is a risk factor for the total group of obesity-related cancers and for ovarian, endometrial and postmenopausal breast cancer. BMI is not related to non sex-specific obesity-related cancers in women with T2D.

Funding

This study was supported by a research grant (grant number 836041017) from the research programme Good Use of Medication the Netherlands Organization for Health Research and Development (ZonMw).

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Part 2

Gender differences