The Relationship between Obesity and Cancer Mortality in Type 2 Diabetes: A Ten-year Follow-up Study (ZODIAC-21)

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Abstract. *Background: Patients with type 2 diabetes mellitus (T2DM) as well as patients with obesity have increased cancer mortality. In a previous paper we suggested that there was a trend for decreased mortality in obese individuals with T2DM. The aim of the new analyses was to investigate the same relationship after increasing our sample size and extending our follow-up period. Patients and Methods: 1353 patients were followed prospectively as part of the ZODIAC study. The cancer mortality rate was evaluated using standardized mortality ratio (SMR) and its association with BMI (kg/m^2) and obesity (>30 kg/m^2) with Cox proportional hazard analysis. Results: After a median follow-up time of 9.8 years, 570 patients had died, of whom 122 died from malignancy. The SMR for cancer mortality was 1.47 (95%CI 1.22-1.76). BMI and obesity were not associated with cancer death. Conclusion: The trend towards an inverse relationship between obesity and cancer mortality as reported previously disappeared after increasing sample size and follow-up to 9.6 years.*

Patients with type 2 diabetes mellitus (T2DM) have an increased cancer mortality risk (1, 2). Furthermore, an association is reported between obesity and cancer mortality (3). In our prospective observational study, published in 2008 (1), we confirmed the increased cancer mortality risk in T2DM and the association between obesity (defined as a BMI >30) and cancer mortality was certainly a possibility after a follow-up of 5.8 years. After adjustment for selected confounders, the HR for cancer mortality was 0.57 (95%CI 0.32-1.02) for patients with a BMI above 30 compared to the patients with a lower BMI. The so-called obesity paradox could be the cause of this phenomenon. The aim of this study was to investigate the same relationship after increasing our sample size and extending our follow-up period.

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Patients and Methods

This study is part of the ZODIAC (Zwolle Outpatient Diabetes project Integrating Available Care) study (1, 4). The study started in 1998 and baseline data were collected in 1998 and 1999. Laboratory and physical assessment data were collected annually, and included the following variables: HbA1c, non-fasting lipid profile, serum creatinine, urinary albumin and creatinine, blood pressure, weight, and height. At the beginning of 2009, life status and cause of death were retrieved from records maintained by the hospital and general practitioners from patients who started in 1998 and 1999. Eight baseline variables were selected for their possible confounding effects in the relationship between BMI and cancer mortality: smoking (yes or no), age, sex, diabetes duration, HbA1c, BMI, insulin use, and metformin use. To study the incidence of cancer mortality, standardized mortality ratios (SMR) were calculated for cancer mortality using general mortality reference rates from The Netherlands (http://statline.cbs.nl/StatWeb/). We used a Cox proportional hazard model to investigate the association between BMI, obesity and cancer mortality with adjustment of the selected confounders.

Results

The total number of patients included in the present study was 1353; the study population included 779 women (58%). Mean age at baseline was 68 (standard deviation (SD) 11.7 years) with median diabetes duration of 6 years (interquartile range 3-11). HbA1c was 7.5% (SD 1.2) on average and estimated creatinine clearance (Cockcroft-Gault formula) was 73.9 ml/min (SD 28.0). Macrovascular complications were present in 442 patients (33%) at baseline and 252 patients (18%) were smokers. After a median follow-up time of 9.6 years, a total of 570 (42%) patients had died. There were 122 (21%) cancer-related deaths, of which 26 (21%) were related to lung cancer and 21 (17%) to abdominal cancer. The cause of death was known for 541 (94%)

patients. The SMR for total mortality was 2.22 (95%CI 2.03-2.42) and 1.47 (95%CI 1.22-1.76) for cancer mortality. The hazard ratio for BMI as a continuous variable was 1.02 (95%CI 0.97-1.06) and for obesity 1.03 (95%CI 0.69-1.55).

Discussion

We found no evidence for an association between BMI and cancer mortality in patients with T2DM after 10 years of follow-up. Previous results concerning the relation between bodyweight and cancer mortality are not unequivocal (2, 3). The study that did find a relationship had not adjusted for a history of T2DM (4). Although both BMI and T2DM appear to be risk factors for cancer-related mortality, it remains unclear whether obesity itself increases the already increased cancer mortality induced by T2DM.

The trend towards an inverse relationship between obesity and cancer mortality in T2DM patients, as we reported previously, disappeared after sample size was increased and our follow-up was extended. After almost 10 years of follow-up, no association between BMI and cancer mortality in patients with T2DM was found. It is interesting to generate hypotheses as to why the results after 6 years were so different from the results after 10 years. First of all, it is possible that a number of patients had an undiagnosed malignancy when included in the ZODIAC study. Weight loss in patients with a malignancy may have caused the (non-significant) inverse relationship after six years of follow-up. However, additional analyses were performed in which the first three years of follow-up were excluded: the results did not change relevantly. Secondly, the relatively small number of patients may be another explanation for the differences in results. As a limitation, it should be mentioned that with the wide confidence intervals, the possibility that there was an association between bodyweight and cancer mortality could not fully excluded.

In conclusion, patients with T2DM, obese or not, are at increased risk for cancer mortality. Further research is needed to clarify whether BMI influences the already higher cancer mortality risk in patients with T2DM. Furthermore, the different results after 6 and 10 years of follow-up respectively, highlight the necessity for results of observational studies to be interpreted with caution and follow-up periods need to be extensive.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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