Increased Cancer Mortality in Type 2 Diabetes (ZODIAC-3)

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Abstract. Background: It is unclear whether there is a relationship between type two diabetes and cancer mortality. It also is unclear whether obesity and body mass index (BMI) are associated with cancer in type 2 diabetes patients. Patients and Methods: In 1998, 1,145 patients with type two diabetes mellitus were enrolled in the Zwolle Outpatient Diabetes project Intergrating Available Care (ZODIAC) study. In this project, general practitioners (GPs) were assisted by hospital-based diabetes specialist nurses. Vital status was assessed in September 2004. The cancer mortality rate was evaluated using standardized mortality ratio (SMR) and its association with BMI (kg/m²) and obesity (>30 kg/m²) with the Cox proportional hazard ratio. Results: The median follow-up time was 5.8 years. A total of 335 patients had died, of whom 70 died from malignancy. The SMR for cancer mortality was 1.38 (95% CI 1.07-1.75). BMI and obesity were not associated with cancer death. Conclusion: An increased cancer mortality rate was found in type two diabetes mellitus patients but there was no significant association between BMI or obesity and cancer mortality.

Studies have shown conflicting results regarding the association between diabetes and cancer mortality (1-8). Some studies showed a comparable mortality rate for patients with diabetes and the general population (1-4) while others reported either a decreased (5, 6) or increased (6-10) cancer mortality risk.

There is increasing evidence that diabetes mellitus alters the risk of developing a variety of site-specific carcinomas (11-17). Patients with diabetes apparently experience increased mortality from cancer of the colon (17, 18), liver (17, 19), pancreas (17, 20, 21), female breast (17, 22), bladder (17, 23) and endometrium (24).

Furthermore, an association has been reported between obesity and cancer mortality (25). The proportion of all cases of death from cancer attributable to being overweight and obese might be as high as 14% in men and 20% in women.

The objectives of our study were to examine whether type two diabetes mellitus was associated with overall cancer mortality and whether there was an association between body mass index, obesity (BMI > 30), and cancer mortality.

Patients and Methods

In 1998, in the Zwolle region (the Netherlands), a large shared-care diabetes project was initiated, the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC). In this project, general practitioners (GPs) were assisted by hospital-based diabetes specialist nurses (DSNs), in their care of patients with type 2 diabetes. As part of this project, the patients with type 2 diabetes in 32 primary care practices consulted these DSNs annually. Patients with a very short life expectancy (including patients with active cancer) or insufficient cognitive abilities were excluded. A total of 1,269 patients were invited to participate of whom 1,149 (90.5%) agreed. Four patients were excluded because of insufficient baseline data. Details of the ZODIAC study have been published previously (26).

Baseline data were collected in 1998 and 1999 and involved a full medical history including macrovascular complications, medication use and tobacco consumption. Laboratory and physical assessment data were collected and included glycosylated hemoglobin (Hba1c), lipid profile, creatinine, albuminuria, blood pressure, weight, and height.

The ZODIAC study was approved by the local medical ethics committee.

Life status and cause of death were retrieved from records maintained by the hospital and the GPs. To study the cancer mortality incidence, standardized mortality ratios (SMR) were calculated using general mortality reference rates from the eastern part of The Netherlands (27).

To investigate whether BMI and obesity were associated with cancer mortality Cox proportional hazard modeling (28) was used. Seven variables were selected for their possible confounding effects in the relationship between cancer mortality and obesity: smoking status, age, gender, duration of diabetes, insulin therapy, Hba1c and macrovascular complications.
Results

The study population (n=1,145) consisted of 658 women and 487 men. The mean age at onset of diabetes was 69, average diabetes duration was 8 years. The mean BMI was 28.9 kg/m² (SD 4.8) with a range from 16 to 48. The median follow-up time was 5.8 years. The date of death could not be traced in 6 patients. The cause of death could not be confirmed for 20 patients.

Out of 335 deaths, 21% (n=70) were attributable to malignancies. Cancer of the digestive and respiratory tracts each accounted for 23% of deaths. Forty-three percent of the patients who died from cancer were female. The patients who died of malignancies were older and had lower average BMIs at baseline compared to those who did not die. The SMR for total cancer mortality was 1.38 (CI 1.07-1.75).

Baseline BMI was not associated with cancer mortality (HR 0.97; CI 0.91-1.28).

Obesity (defined as a BMI >30) was also not significantly associated with cancer mortality (HR 0.57 CI 0.32-1.02). Age and gender were confounders in the relationship between BMI and cancer mortality.

Discussion

The main findings of the present study were: mortality from cancer was moderately increased in type 2 diabetic patients in primary care, BMI was not associated with cancer death and obesity was not significantly associated with cancer mortality.

The results of this study did not confirm earlier findings reported by Calle et al. (25) and Reeves et al. (29) who reported that obesity was associated with increased cancer mortality.

A prospective study by Couglín et al. (17) reported diabetes to be an independent risk factor of cancer mortality. However, no significant differences were found across different levels of BMI. In agreement with this study, we found no relation between increased BMI and cancer mortality.

Although obesity was not significantly associated with cancer mortality (HR 0; 57, p=0.06), it would be interesting to repeat this analysis with longer follow-up and investigate any possible inverse relationship. Some studies have reported a reduced cancer rate among obese patients (5). A possible explanation for this finding may be that weight loss is often associated with cancer. This phenomenon has recently also been reported in other populations, and is referred to as the obesity paradox or reverse epidemiology (30).

The potential limitations of our study resulted primarily from the small number of observed patients, which made site and sex specific analyses impossible.

Another possible limitation stemmed from the use of death certificates as the source of establishing the cause of death in our reference population. Cancer mortality is subject to misclassification on death certificates although we are not aware of this phenomenon in The Netherlands (31, 31, 33).

The mortality characteristics of the population in the eastern part of the Netherlands was used for determining SMR. This may have led to an underestimation of the true SMR since patients with type two diabetes mellitus were also included in this reference population.

In conclusion, within the population studied, patients with type two diabetes mellitus appear to be at increased risk for cancer mortality.

Since our study population can be considered representative of the primary care population at large, we believe that our results may apply to other patients with type 2 diabetes mellitus being treated elsewhere within primary care.

References


Received November 1, 2007
Revised December 14, 2007
Accepted January 7, 2008