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Diabetes and cancer mortality: A multifaceted association

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ABSTRACT

In a large cohort of subjects with diabetes cancer mortality increased by 30%, possibly due to lower survival, reverse causality, and an etiologic role of diabetes in cancer. A two-fold increased mortality from liver and pancreatic cancer was confirmed in both genders irrespective of follow-up period or disease duration.

1. Introduction

Evidence from the literature indicates an increased risk of cancer mortality from colorectal, breast, endometrium, kidney, liver and pancreas cancer among persons with diabetes [1–8]. It is, nevertheless, still unclear whether diabetes should be considered an independent risk factor for these neoplasms. To explain the increased cancer mortality among diabetic patients three main mechanisms can be hypothesized:

1. Diabetes is a well-recognized prognostic factor for cancer patients. One of the most widely applied comorbidity scores including diabetes, the Charlson index [9], was validated from survival data of women with breast cancer: patients with cancer carry a higher mortality risk if affected also by diabetes.
2. A new onset of diabetes is often considered by clinicians a marker of occult cancer, or of progression of a known disease (reverse causality: diabetes is a consequence of cancer). For example, there is debate as to whether diabetes increases the risk of pancreatic cancer, or if the onset of diabetes is due to a pre-clinical cancer [10].
3. Diabetes is etiologically associated with specific cancer sites: diabetes can be a cause of cancer, or a common etiologic pathway could lead to both diabetes and cancer (e.g., through overweight).

Aim of the study was to explore these hypotheses in a large cohort of diabetic patients.

2. Methods

Mortality was investigated in diabetic patients identified from the regional archive of subjects exempt from medical charges due to diabetes in the Veneto Region (North-Eastern Italy).

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Table 1 – Standardized mortality ratios (SMR) with 95% confidence intervals (CI) in a cohort of 167,621 diabetic patients followed-up for three years: analysis of the underlying cause of death.

Cause of death (ICD-10 codes)	Males		Females	
	n	SMR (CI)	*n*	SMR (CI)
All causes	9866	1.49 (1.46–1.52)	7268	1.53 (1.49–1.56)
All neoplasms (C00-D48)	3425	1.30 (1.26–1.34)	1893	1.32 (1.26–1.38)
All malignant neoplasms (C00-C97)	3300	1.31 (1.26–1.35)	1810	1.33 (1.27–1.39)
Malignant neoplasms of				
Lip, oral cavity and pharynx (C00-C14)	76	1.26 (0.99–1.58)	15	0.93 (0.52–1.53)
Esophagus (C15)	57	0.91 (0.69–1.18)	21	1.39 (0.86–2.12)
Stomach (C16)	151	1.14 (0.96–1.33)	78	1.25 (0.99–1.56)
Colon, rectum and anus (C18-C21)	328	1.22 (1.09–1.36)	188	1.13 (0.98–1.31)
Liver and intrahepatic bile ducts (C22)	486	2.40 (2.19–2.62)	140	1.86 (1.56–2.19)
Pancreas (C25)	343	2.16 (1.93–2.40)	237	1.95 (1.71–2.22)
Larynx (C32)	46	0.99 (0.73–1.33)	1	0.40 (0.01–2.21)
Trachea, bronchus and lung (C33-C34)	812	1.15 (1.08–1.24)	201	1.13 (0.98–1.30)
Melanoma of skin (C43)	24	0.97 (0.62–1.44)	12	1.00 (0.52–1.75)
Female breast (C50)			268	1.32 (1.17–1.49)
Uterus (C53-C55)			73	1.65 (1.30–2.08)
Ovary (C56)			65	1.10 (0.85–1.40)
Prostate (C61)	174	1.02 (0.88–1.19)		
Kidney and renal pelvis (C64-C65)	71	1.12 (0.88–1.42)	33	1.25 (0.86–1.76)
Bladder (C67)	101	1.10 (0.90–1.34)	22	1.13 (0.71–1.71)
Central nervous system (C70-C72)	47	1.03 (0.75–1.37)	26	0.93 (0.61–1.37)
Non-Hodgkin's lymphoma (C82-C85)	77	1.22 (0.96–1.52)	51	1.13 (0.84–1.49)
Multiple myeloma (C90)	43	0.98 (0.71–1.32)	40	1.28 (0.91–1.74)
Leukemia (C91-C95)	83	1.05 (0.83–1.30)	61	1.30 (0.99–1.67)

Details have been previously published [11]. Briefly, records of patients aged 30–89 years registered with diabetes in December 2007 were anonymized and linked with the archive of causes of death. Subjects were followed from January 1, 2008 either until death, 90 years of age, or December 31, 2010, whichever came first. The archive did not include the date of diagnosis, but that of diabetes registration. This date could follow the diagnosis by several years, but allowed us to identify a sub-cohort of subjects (registered before 2001) with at least seven years of diabetes duration at the beginning of the follow-up.

Standardized Mortality Ratios (SMR) with 95% confidence intervals based on the Poisson distribution were the ratios between cancer deaths observed in the cohort, and those expected according to age-gender-specific regional mortality rates. SMRs were assessed for the whole cohort, and for the sub-cohort with longer disease duration. Furthermore, SMRs were computed separately for each year of follow-up.

3. Results

167,621 subjects with diabetes (54.6% men) were identified in December 2007 and through follow-up 17,134 deaths (10.2% of the cohort) were recorded. Malignant neoplasms accounted for 29.8% of deaths. Both genders experienced a more than 30% increased risk of dying from malignant neoplasms overall, and a two-fold increased risk of dying from liver and pancreatic cancers (Table 1). Mortality from colorectal and lung cancer in males, and from breast and uterus cancer in females was significantly higher than that expected from regional rates.

The increased mortality risk from liver and pancreatic cancer did not decline through follow-up, while the excess risk of mortality from other-site cancers combined decreased from 26% to 9% (Fig. 1).

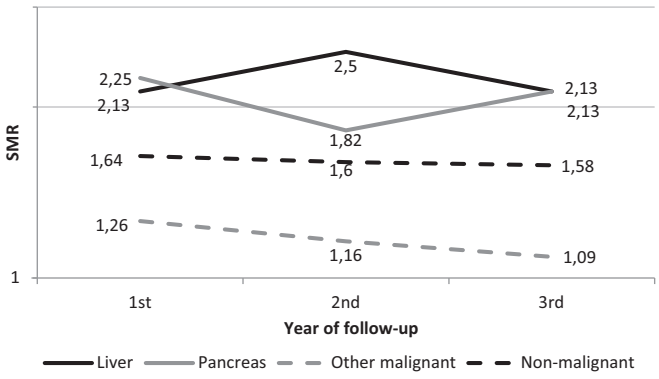

Fig. 1 – Standardized mortality ratios (SMR, logarithmic scale) for selected cancer sites in a cohort of 167,621 diabetic patients, by year since the beginning of follow-up.