Incidence of New-Onset Type 2 Diabetes After Cancer: A Danish Cohort Study

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For patients with cancer, prevalent type 2 diabetes at the date of cancer diagnosis is associated with increased cancer-specific and all-cause mortality (1,2). Yet, despite potential health implications, there is limited knowledge on whether cancer is also a risk factor for type 2 diabetes. Moreover, the impact of new-onset type 2 diabetes after cancer diagnosis on survival among cancer patients is unknown. We investigated the incidence of type 2 diabetes following a cancer diagnosis and evaluated the influence of new-onset type 2 diabetes in patients with cancer on overall survival.

We included 51,353 incident cancer case subjects diagnosed from 2004 to 2015 living in the Greater Copenhagen area without type 2 diabetes, defined according to one measurement of plasma or serum glucose ≥11 mmol/L or HbA_{1c} ≥6.5% (48 mmol/mol), at diagnosis, each with 10 cancer- and type 2 diabetes–free age- and sex-matched control subjects. In Denmark, health care is public and free for all residents. We sampled all 112 million tests from 1.3 million individuals, performed by the Copenhagen General Practitioners' Laboratory, contained in the Copenhagen Primary Care Laboratory Database (CopLab) (2015-57-0121) from 2000 to 2015, data for which were merged with data on incident cancer from the Danish Cancer Registry. Only cancer types with >1,000 incident cases with individuals aged >30 years were included. Individuals with diabetes prior to the cancer diagnosis were excluded. The median follow-up time was 2.34 years (interquartile range 0.70–5.53) for all case subjects and 4.41 years (2.04–7.40) for cancer-free control subjects.

We found an increased hazard of new-onset type 2 diabetes for all cancers (hazard ratio [HR] 1.09; 95% CI 1.03–1.14) (Fig. 1*A*). The hazard of new-onset type 2 diabetes for different cancer types in comparisons with control subjects was particularly strong for pancreatic cancer (HR 5.00; 95% CI 3.62–6.90), cancer of the brain and other parts of the nervous system (HR 1.54; 95% CI 1.22–1.95), and cancer of the corpus uteri (HR 1.41; 95% CI 1.10–1.84).

Patients diagnosed with lung (HR 1.38; 95% CI 1.14–1.66), urinary tract (HR 1.32; 95% CI 1.15–1.51), and breast (HR 1.20; 95% CI 1.08–1.34) cancers also had a significantly increased hazard of type 2 diabetes. Melanoma of the skin (HR 0.76; 95% CI 0.61–0.94) and lymphatic and hematopoietic tissue cancers (HR 0.83; 95% CI 0.71–0.98) were associated with reduced type 2 diabetes cause-specific hazard rate.

Having established an increased hazard for incident type 2 diabetes in patients with specific cancer types, we next investigated whether new-onset type 2 diabetes following cancer diagnosis influenced survival. To this end, we considered a subpopulation of 28,308 cancer patients who were still alive 2 years after diagnosis. Compared with cancer patients without type 2 diabetes, cancer patients with new-onset type 2 diabetes in this 2-year period had a 21% higher all-cause mortality (HR 1.21; 95% CI 1.04–1.41) (Fig. 1*B*).

To our knowledge, this study is the largest cohort study addressing the effect of cancer on the risk of subsequent new-onset type 2 diabetes in adults. This advantage comes from the use of a large amount of high-quality data in combining a clinical database with information from population-based registries containing information on all residents in the catchment area free of selection or recall bias.

Our results align with a smaller study of 15,130 incident cancer survivors (3) where investigators observed an overall 35% increase in the hazard of diabetes following a cancer diagnosis. We included more than three times the number of incident cancer cases and observed similar effects; thus, our findings bolster the evidence for associations that was previously less strongly supported. The

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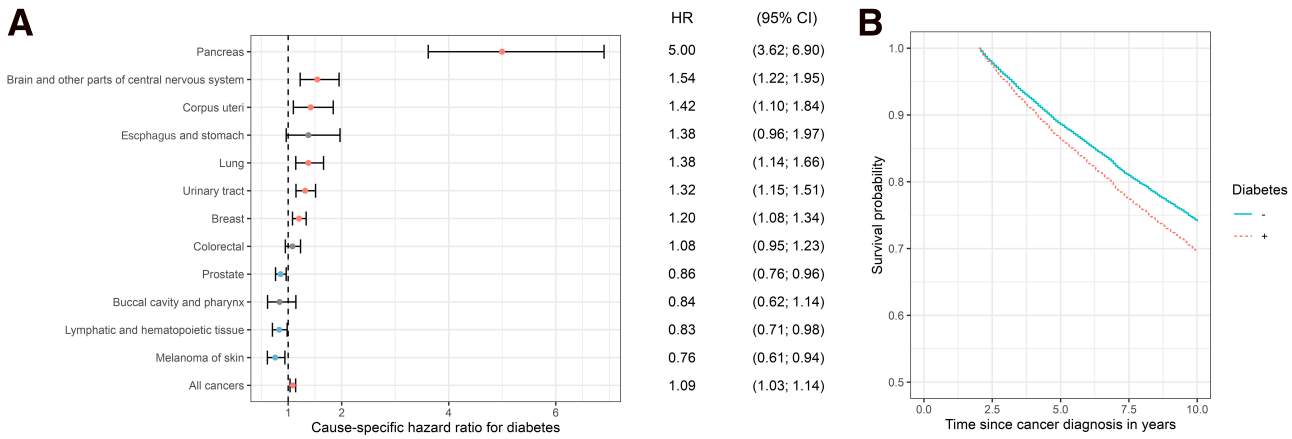

Figure 1–*A*: Cause-specific HRs for incident type 2 diabetes for cancer case subjects vs. control subjects by type of cancer and all cancers, with adjustment for age (penalized spline) and, when applicable, sex (strata). Error bars indicate 95% CIs. Red, gray, and blue denote HR significantly increased (>1), unchanged, and reduced (<1), respectively. The assumption of proportional hazards was not reasonable for lung cancer; hence, the HR should be thought of as a weighted average of a time-varying effect. *B*: Survival probability in all patients with cancer with or without type 2 diabetes was calculated based on the landmark Cox proportional hazards model. The predictions were made for 65-year-old women with a Charlson comorbidity index of 0 with or without diabetes.

underlying mechanisms still remain to be defined but could include common risk factors, tumor-secreted factors, or effects of treatment (4,5).

In this large Danish cohort, cancer increased the hazard of subsequent new-onset type 2 diabetes, which in turn was associated with increased overall mortality. Our data illustrate the need for increased focus on the development of type 2 diabetes in cancer survivors.

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References

1. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–1638
2. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 2008;300:2754–2764
3. Hwangbo Y, Kang D, Kang M, et al. Incidence of diabetes after cancer development: a Korean nat-ional cohort study. JAMA Oncol 2018;4:1099–1105
4. Fearon KCH, Glass DJ, Guttridge DC. Cancer cachexia: mediators, signaling, and metabolic pathways. Cell Metab 2012;16:153–166
5. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. Nat Rev Cancer 2015;15:484–498