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Increased risk of active tuberculosis after cancer diagnosis

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Summary *Background:* Cancer may increase risk of active tuberculosis but evidence is sparse. We therefore examined tuberculosis risk in patients with incident cancer using Danish nationwide medical databases.
Methods: We conducted a matched follow-up study comparing risk of active tuberculosis in cancer-exposed individuals to that in a general population comparison cohort, matched on gender, age, and country of origin, in different follow-up intervals using Cox regression.
Findings: We identified 290,944 patients with incident cancer and 871,147 matched comparison cohort members during 1 January, 2004–30 November, 2013. After adjusting for comorbidities, the overall adjusted hazard ratio (aHR) for tuberculosis among cancer patients was 2.48 (95% confidence interval [CI]: 1.99–3.10). The highest tuberculosis risks were observed following cancers of the aerodigestive tract (aHR = 8.12; 95% CI: 4.33–15.22), tobacco-related cancers (aHR = 5.01; 95% CI: 3.37–7.44), and hematological cancers (aHR = 4.88; 95% CI: 2.27–10.48). Tuberculosis risk was highly elevated within the first year after cancer diagnosis (aHR = 4.14; 95% CI: 2.88–5.96), with a 6.78-fold increased aHR for cancer patients receiving cytostatics or radiotherapy. Beyond five years of observation, the overall aHR for tuberculosis remained at 2.66 (95% CI: 1.22–5.81).
Interpretation: Cancer is a clinical predictor for increased risk of active tuberculosis, probably related to decreased infection barriers, immunosuppression, and shared risk factors.

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Introduction

Cancer and tuberculosis are major public health problems. With 8.2 million cancer-related deaths and 1.5 million tuberculosis (TB)-related deaths worldwide in 2012, the two diseases contribute considerably to mortality on a global scale.[1,2] Many aspects of the association between cancer and TB are poorly understood.

Malignancy may be connected to TB risk in two ways. First, cancer and its treatment may diminish infection barriers proximal to the neoplasm and/or lead to generalized immunosuppression, rendering a patient susceptible to a new or reactivated TB infection.[3] Second, some risk factors for TB and cancer are shared, such as smoking, alcoholism, chronic obstructive pulmonary disease and immunosuppression (including human immunodeficiency virus infection).[4–6] A few studies reported an increased risk of TB following diagnosis of hematological and solid organ cancers, particularly those of the aerodigestive tract.[7–9] The aerodigestive tract, consisting of the upper/lower respiratory tract and the oropharynx/esophagus, is the most common entry portal and the most frequent anatomical location for TB infections.[10,11] While hematological cancers are likely to increase risk of active TB through generalized immunosuppression, it seems plausible that cancers of the aerodigestive tract may promote TB by weakening local barriers to infection.[12,13]

Most studies of cancer and TB were performed at referral centers, leaving unanswered questions about the general validity of the findings. Data are sparse on TB risk in cancer patients according to follow-up time, cancer site, and antineoplastic treatment. Such data are needed to understand—and potentially prevent—post-cancer death. We therefore used nationwide population-based data to examine the risk of TB after a site-specific diagnosis of cancer, controlling for major comorbidities.

Study population and methods

The Danish health care system provides tax-supported health care services to all residents, guaranteeing free access to hospitals and primary medical care. The civil registration number, a unique identifier assigned to every Danish citizen at birth or upon immigration, allowed for accurate linkage among the Danish databases used in this study.[14]

Identification of patients with cancer

We obtained information on all cancer diagnoses, including the date of first incident cancer with look-back (cancer diagnosis date), from the Danish Cancer Registry for the period 1 January, 2004 to 30 November, 2013. The Danish Cancer Registry contains nationwide data on cancer incidence in Denmark since 1943 and is 95%–98% complete and valid.[15]

We grouped all cancers according to anatomical sites (see diagnosis codes in Online Appendix). Non-melanoma skin cancer was excluded.

We then created larger cancer groupings based on possible mechanisms of action underlying the association between cancer and TB, as follows:

(1) **Locally decreased infection barriers:**[12] *Cancers of the aerodigestive tract* (oral cavity and pharynx, nasal cavity, middle ear and sinuses, larynx, esophagus, lung, bronchi, and trachea).
(2) **Generalized immunosuppression:**[6,13,16,17] *Hematological cancers* (see Online Appendix for list); and *cancers associated with immunosuppression* (liver, cervix, malignant melanoma, Kaposi sarcoma, and non-Hodgkin's lymphoma).[18]
(3) **Shared lifestyle risk factors:**[6] *Tobacco-related* cancers[19]; and *alcohol-related cancers*[19] (see all diagnosis codes in Online Appendix).

For all cancer patients, we obtained information on radiotherapy and cytostatic therapy given in the time interval four months prior to four months after the cancer diagnosis date.

Identification of the general population comparison cohort

For each cancer patient, we selected three comparisons from the general Danish population on the cancer diagnosis/index date. Comparison cohort members were matched to the cancer patients on gender, year of birth, and immigrant status/country of origin (using WHO regions, looking at Somalia isolated, being highly TB-endemic and a dominant country of origin among Danish immigrants), using matching with replacement (*i.e.*, one comparison cohort member could be paired with more than one cancer patient). Comparison cohort members who developed cancer were censored at this time and changed cohort contributing with follow-up time in the cancer-exposed cohort.

Identification of patients with tuberculosis

We used the Danish National Patient Registry (DNPR), which has recorded all hospitalizations in Danish hospitals since 1977 and all hospital outpatient clinic and emergency department visits since 1995,[20] to identify all patients who had a hospital contact yielding a primary diagnosis of active TB during 2004–2013 (see Online Appendix for diagnosis codes). We excluded cancer patients and comparison cohort members with a previous TB diagnosis from 1977 up to the cancer diagnosis/index date for our main analysis, but kept individuals with TB diagnoses within three months prior to that date for a sensitivity analysis.

Data on TB risk factors

To adjust for confounding comorbid conditions, we computed Charlson Comorbidity Index (CCI) scores based on each subject's medical history within five years before the cancer diagnosis/index date in the DNPR[21] (see Online Appendix). Cancer was excluded from the computation of scores, as it was the disease under study. Three comorbidity levels were defined: low (CCI score of 0), medium (CCI scores of 1–2), and high (CCI score $\geq$3). We also collected DNPR data on previous alcoholism-related disorders within five years prior to cancer diagnosis/index date (yes/no) not included in the CCI. The Danish National Database of