INCREASING INCIDENCE AND DECLINING MORTALITY AFTER CANCER-ASSOCIATED VENOUS THROMBOEMBOLISM -- NATIONWIDE COHORT STUDY

Authors

Anne Gulbech Ording[a], Ph.D., a.ording@rn.dk

Flemming Skjøth[b,c], Ph.D., fls@rn.dk

Mette Søgaard[a,c], Ph.D., ms@rn.dk

Anette Arbjerg Højen[a], Ph.D., a.wind@rn.dk

Thure Filskov Overvad[a,d], MD, t.overvad@rn.dk

Simon Noble[e], MD, NobleSI1@cardiff.ac.uk

Samuel Zachary Goldhaber[f], MD, sgoldhaber@bwh.harvard.edu

Torben Bjerregaard Larsen[a,c], MD, tobl@rn.dk

Affiliations

[a]Unit for Thrombosis and Drug Research, Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark.

[b]Unit Clinical Biostatistics, Aalborg University Hospital, Aalborg, Denmark.

[c]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Faculty of Medicine, Aalborg University, Denmark

[d]Department of Oncology, Aalborg University Hospital, Aalborg, Denmark.

[e]Marie Curie Palliative Care Research Centre, Cardiff University, Cardiff, UK

[f]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Corresponding author: Anne Gulbech Ording, Unit for Thrombosis and Drug Research, Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark

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ABSTRACT

PURPOSE: The incidence of cancer-associated venous thrombosis has increased, but whether short-term mortality after cancer-associated thrombosis has changed remains uncertain. We investigated whether the increasing incidence of venous thromboembolism in cancer patients is associated with a change in mortality.

METHODS: We used administrative medical registries to identify a cohort of all Danish patients diagnosed with a first primary cancer from 2006 to 2017. We examined temporal changes in one-year risks of cancer-associated thrombosis and in mortality risks at 30 days and 1 year after cancer-associated thrombosis. Cox regression was used to assess changes in mortality rate ratios over time.

RESULTS: We included 350,272 cancer patients (median age 68 years, 49.1% female), of whom 8167 developed cancer-associated thrombosis within one year after cancer diagnosis. The cumulative 1-year risk of cancer-associated thrombosis was 1.8% in 2006-2008, increasing to 2.8% for patients diagnosed in 2015-2017. The 30-day mortality after cancer-associated thrombosis declined from 15.1% in 2006-2008 to 12.7% in 2015-2017, and the 1-year mortality decreased from 52.4% to 45.8%, equivalent to a hazard ratio=0.83 (95% CI: 0.75-0.90). This pattern of declining one-year mortality was consistent for patients with pulmonary embolism, hazard ratio=0.79 (95% CI: 0.69- 0.90) and deep venous thrombosis, hazard ratio=0.76 (95% CI: 0.67- 0.87). Lower mortality over time was evident across all strata of cancer stage, cancer type, and cancer treatment.

CONCLUSIONS: The 1-year risk of cancer-associated thrombosis after a first primary cancer diagnosis in Denmark increased during 2006-2017. This increase was accompanied by declining mortality.

INTRODUCTION

Venous thromboembolism is a frequent and serious complication of cancer, associated with frequent recurrence, premature mortality, poorer cancer prognosis and long-term patient distress [1–4]. The prothrombotic state of cancer is multifactorial but primarily driven by the direct release of tumour related procoagulants. The risk varies according to cancer primary and is further exacerbated by immobility, disease progression, surgery, venous catheters and systemic anti-cancer therapies [5,6].

The risk of cancer-associated thrombosis will vary according to disease status, treatments and other associated comorbidities which may or may not be cancer related [7–11]. The incidence of cancer-associated thrombosis has been increasing over time [12–14]. This is largely a reflection of the changing natural history of cancer following the progression of anticancer therapies, which has facilitated the treatment of patients longer through metastatic disease and progressive age. Other reasons for this increase may include patients living with an increasing burden of comorbidities, vascular effects of newer cancer-targeted therapies [15], suboptimal use of thromboprophylaxis [16], and improvement in cancer survival [16–18]. More frequent use of computed tomography chest scans may also increase the number of incidentally diagnosed pulmonary embolisms cases [12,19]. Hence, the characteristics of cancer patients presenting with venous thromboembolism are evolving, but whether this is accompanied by a change in mortality following cancer-associated venous thromboembolism remains uncertain.

We performed a nationwide Danish cohort to examine time trends after 2006 in changes in 1-year incidence of cancer-associated thrombosis and changes in subsequent 30-day and 1-year mortality after cancer-associated thrombosis.

MATERIALS AND METHODS

We used a prospective nationwide cohort, design including all patients with a first-time, primary cancer in Denmark during 2006-2017. Through linkage of nationwide health registries, we collected individual-level information about cancer characteristics, anticancer treatments, diagnoses of venous thromboembolism, comorbidities, and vital status. This design allowed us to follow all Danish cancer patients for venous thromboembolism and subsequently to follow patients with cancer and venous thromboembolism to assess mortality.

Setting and data sources

The Danish National Health Service is tax-supported and provides health care to all residents free of additional charge [20]. Nationwide registries track vital status, hospital diagnoses, and procedures for the entire population, allowing for continuous population surveillance. Data can be linked accurately among the registries using the unique civil registration number assigned to all Danish residents at birth or upon immigration, which is recorded in the registries during each encounter. The Danish Cancer Registry maintains compulsory information on all incident cancers diagnosed in Denmark since 1943, including morphology and stage at diagnosis [21]. The Danish National Patient Registry has recorded all inpatient hospitalizations in Denmark since 1977 and all outpatient and emergency department visits since 1995 [22]. The Danish National Prescription Database contains information on utilization of reimbursed prescriptions from pharmacies since 1995 [23]. Migration and vital status are tracked by the Civil Registration System since 1968 [24].

Cancer cohort

We established a cancer cohort including all patients ≥18 years of age at date of first-time incident cancer diagnosis recorded in the Danish Cancer Registry during 2006-2017. Non-melanoma skin

cancer was not included. We excluded all patients diagnosed with a primary or secondary inpatient or outpatient diagnosis of pulmonary embolism or deep venous thrombosis, splanchnic thrombosis and cerebral venous thrombosis recorded in the Danish National Patient Registry within six months prior or on the same date as the cancer diagnosis.

We included information on patient birth year, sex, cancer diagnosis year, cancer type, stage, and comorbidity defined with the Charlson Comorbidity Index [25], and diagnoses of obesity and alcohol-related disorders. Cancer treatment recorded in the Danish National Patient Registry within four months after cancer diagnosis included surgery, chemotherapy, radiotherapy, endocrine therapy, immune-based, protein kinase inhibitors, and other targeted therapies.

Follow-up for cancer associated thrombosis

Follow-up began on the date of cancer diagnosis and continued for one year until the first diagnosis of venous thromboembolism, death, emigration, or censoring on December 31, 2018, whichever came first. Outcomes were cancer-associated venous thromboembolism, and deep venous thrombosis and pulmonary embolism as separate endpoints. Occurrence of cancer-associated thrombosis was defined by both primary and secondary inpatient or outpatient diagnoses. Emergency diagnoses were not considered due to a documented low positive predictive value of 31% [26]. If a patient had a diagnosis of both pulmonary embolism and deep venous thrombosis, preference was given to the pulmonary embolism diagnosis.

Cancer-associated thrombosis cohort and follow-up for mortality

Cancer patients who developed venous thromboembolism within one year after the cancer diagnosis were included in the cancer-associated thrombosis cohort. We collected information on any anticancer treatments received within 4 months before diagnosis of venous thromboembolism. Follow-up began on the date of diagnosis of the venous thromboembolic event, and the vital status

of all patients in the cancer-associated thrombosis cohort was followed until death, migration, or 31 December 2019, whichever came first.

Statistical analysis

We used summary statistics to describe baseline characteristics of the cancer cohort and the cancer-associated thrombosis cohort. Patient inclusion in each cohort was stratified in four periods (2006-2008, 2009-2011, 2012-2014, and 2015-2017), which were applied as study exposure. Discrete variables are expressed as proportions; continuous variables are expressed as medians and interquartile range for each study period.

For the cancer cohort, we then estimated the 1-year risks of cancer-associated thrombosis in each study period using the Aalen-Johansen estimator, assuming death as a competing risk.

Next, we assessed changes in 1-year mortality over time in the cancer-associated thrombosis cohort. We computed Kaplan-Meier curves for survival up to 1 year and calculated 30-day and 1-year mortality risks for venous thromboembolism, pulmonary embolism and deep venous thrombosis by study period. Cox proportional hazards regression was used to measure changes in 1-year hazard rate ratios for mortality over time using 2006-2008 as the reference period. Analyses were adjusted for age, sex, Charlson comorbidity index score, obesity, and alcohol-related comorbidities. Since changes in prognosis may differ according to cancer stage, type, and treatment, we repeated the analyses within strata of cancer type, cancer stage, and receipt of chemotherapy within four months before the diagnosis of cancer-associated thrombosis. To increase the positive predictive value of the diagnoses, we conducted sensitivity analyses restricted to patients with a chest computed tomography scan or ultrasound of the leg recorded within 2 weeks before or 10 days after cancer-associated thrombosis diagnosis.

Analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA) and Stata MP version 16 (StataCorp, College Station, TX, USA).

Ethics

The study was conducted in compliance with the General Data Protection Regulation Article 30, recorded at Aalborg University Hospital and Aalborg University (record no: 2017-509-00006). Danish law does not require ethical approval or informed consent from patients in studies based on routinely collected registry data. The analyzed data were provided by the Danish Health Data Authority.

RESULTS

We identified 355,756 patients with incident cancer during 2006-2017. After exclusion of patients aged <18 years (N=1814), and patients with record of venous thrombosis in the six months before or on cancer diagnosis (N=3670), the final cancer cohort included 350,272 cancer patients.

Trends in baseline characteristics of the cancer cohort

Table 1 summarizes the baseline characteristics of the cancer cohort across study periods. The median age increased from 67.0 years (IQR: 59.0, 76.0 years) in 2006-2008 to 69.0 years (IQR: 59.0, 76.0 years) in 2015-2017, mainly driven by an increase in patients aged 70-79 years, whereas the proportion of patients aged 80 years and older declined. The distribution of cancer types remained relatively stable over time, whereas the proportion with distant cancer at diagnosis decreased from 19.5% in 2006-2008 to 10.9% in 2015-2017. Concurrently, the proportion of patients receiving targeted therapy increased. The comorbidity burden as defined by the Charlson Comorbidity Index increased slightly over time; in 2006-2008, 62.7% had no recorded comorbidity versus 60.2% in 2015-2017.

Trends in incidence and characteristics of cancer-associated thrombosis

In total, 8167 patients were diagnosed with cancer-associated thrombosis (4191 with pulmonary embolism and 3976 with deep venous thrombosis, and 819 with both deep venous thrombosis and pulmonary embolism) during the first year after cancer diagnosis. Figure 1 displays the one-year cumulative incidence of cancer-associated thrombosis, pulmonary embolism, and deep venous thrombosis, by study period. As shown, the cumulative incidence was progressively higher in each successive study period; the 1-year cumulative risk of cancer-associated thromboembolism risk was 1.8% for patients with a cancer diagnosis in 2006-2008

versus 2.8% for those diagnosed in 2015—2017. This risk increase occurred predominantly for pulmonary embolism, which rose from 0.7% to 1.6%, while the one-year risk of deep venous thromboembolism over time was essentially unchanged (from 1.1% in 2006-2008 to 1.2% in 2015-2017) (Figure 1).

The characteristics of patients with cancer-associated thrombosis changed over time (Table 2). The median age at cancer-associated thrombosis diagnosis increased from 67 years in 2006-2008 to 70 years in 2015-2017, whereas the proportion of females declined from 48.1% to 45.5%. Concurrently, the proportion of patients with no comorbidities defined with the Charlson Comorbidity Index decreased from 58.5% to 53.2%.

Trends in mortality after cancer-associated thrombosis

The overall mortality risk after cancer associated thrombosis was 13.6% at 30 days and 48.3% at one year. For those with pulmonary embolism the corresponding risks were 16.8% and 52.2%, respectively, and 10.4% and 44.2% for deep venous thrombosis. Both 30-day and 1-year mortality declined over time. For patients with cancer-associated thrombosis, the 30-day mortality declined from 15.1% in 2006-2008 to 12.7% in 2015-2017, whereas 1-year mortality declined from 52.4% to 45.8%. Similar patterns of declining mortality risks were observed for pulmonary embolism and deep venous thrombosis separately (Figure 2). The hazard ratios for 1-year mortality comparing the years 2015-2017 with 2006-2008 after adjustment for sex, age, and comorbidity were 0.83 (95% CI: 0.75- 0.90) after cancer-associated thrombosis, 0.79 (95% CI: 0.69- 0.90) after pulmonary embolism, and 0.76 (95% CI: 0.67- 0.87) after deep venous thrombosis. The adjusted hazard ratios for 1-year mortality declined over time across all strata of cancer stage, cancer type, and cancer treatment when compared with 2006-2008 (Figure 3).

Sensitivity analyses

The cumulative incidence of cancer-associated thrombosis was lower when restricting to imaging confirmed cases; the incidence increased from 1.2% in 2006-2006 to 1.9% in 2015- 2017 (from 0.4% to 1.2% for pulmonary embolism, and 0.8% to 0.7% for deep venous thrombosis) (Supplementary Figure 1). The number of patients with an imaging examination nearly doubled from 942 patients in 2006-2008 to 1748 in 2005-2018, but descriptive characteristics were similar for the patients with imaging verified cancer-associated thromboembolism (data not shown). The subsequent 30-day mortality was 13.2% in 2006-2008 and 13.5% in 2015-2017, whereas 1-year mortality declined from 53.1% in 2006-2008 to 49.4% in 2016-2018, hazard ratio=0.92 (95% CI: 0.82- 1.03) (Supplemental Figure 2 and 3). For imaging-verified pulmonary embolism, 1-year mortality declined from 59.0% to 53.8%, hazard ratio= 0.87 (05% CI: 0.74- 1.04); for deep venous thrombosis mortality declined from 50.4% to 42.0%, hazard ratio= 0.79 (95% CI: 0.67- 0.93).

DISCUSSION

Cancer-associated thrombosis is a serious complication among cancer patients and often considered the harbinger of poor prognosis. This nationwide cohort study provided insights into temporal changes in cancer-associated venous thrombosis in Denmark. The 1-year risk of cancer-associated thrombosis after first primary cancer diagnosis increased during 2006-2017. This increase was predominantly driven by increasing risks of pulmonary embolism over time, whereas risks of deep venous thrombosis remained relatively stable. At the same time, the 30-day and 1-year mortality after cancer-associated thrombosis declined over time. These improvements in prognosis were observed for both pulmonary embolism and deep venous thrombosis, and across cancer types, cancer stages, and cancer treatments.

Previous studies have established a trend toward higher incidence of venous thromboembolism in both the general population [27,28], and among cancer patients [12–14]. Our results extend these observations by showing a simultaneous decline in mortality following cancer-associated thrombosis. These findings may have several explanations. Similar to previous studies [12], we demonstrated the largest incidence increase for pulmonary embolism. Increasing use of imaging procedures for monitoring response to cancer treatment is likely to partially explain the observed time-trends in incidence of venous thromboembolism [29]. Indeed, we mainly observed a rise in incidence of pulmonary embolism and not deep vein thrombosis. If a 'true' rise in incidence of venous thrombosis had emerged over time, we would expect this to be reflected in a rise in incidence of both pulmonary embolism and deep vein thrombosis. Hence, our observations may merely reflect a time-trend in *diagnosed* venous thrombotic events and not necessarily a trend in actual incidence. Nonetheless, increasing use of more targeted cancer-therapies may have contributed to more incident venous thrombotic events [30].

Incidental pulmonary embolism without accompanying symptoms has been associated with much low 30-day mortality (3%). In contrast, the mortality rate was much higher among patient diagnosed due to symptoms (21% mortality) and among patients with incidental pulmonary embolism who in retrospect reported symptoms (20% mortality) [31].

The intensification of cancer therapy, new drugs, dosages, and routes of administration has changed over the years. Some new cancer chemotherapy drugs have thrombogenic effects on the hemostatic system [15] but improve cancer survival. Oral anticoagulation as primary venous thromboembolism prevention has been suggested in Danish guidelines since 2017 and is rarely used [16].

We demonstrated a reduction in mortality during the study period for all patient subgroups, including those who received chemotherapy up to four months prior to the diagnosis of venous thrombosis and those with metastatic cancer. These findings may reflect improvements in overall

supportive care for cancer patients. Nonetheless, mortality after cancer-associated venous thromboembolism remains high. It is the second leading cause of death after the cancer itself [32,33].

Strengths and limitations

Our study has several strengths. We used nationwide administrative and medical registries covering the entire Danish population. Data in the Danish Cancer Registry are nearly complete and valid due to compulsory reporting of malignancies except for non-melanoma skin cancer. Most tumors are histologically confirmed since 2009 [21]. All Danish hospitals and hospital clinics report data on diagnoses including venous thromboembolism the Danish National Patient Registry [22]. The positive predictive value of venous thromboembolism in the Danish National Patient Registry overall has been shown to be more than 90% in conjunction with an imaging procedure [26,34]. Follow-up of all study participants was virtually complete, as patients were identified using comprehensive hospital-based registries in a healthcare system providing free access to health care, and patients could be tracked easily through the Civil Registration System [22,24].

Our study also has limitations. We were unable to control for several risk factors such as body mass index, lifestyle factors, and use of central venous catheters. Autopsy studies have indicated that clinicians may underdiagnose pulmonary embolism as a cause of death [35,36]. Deaths due to undiagnosed cancer-associated thrombosis may have led to underestimating the incidence of cancer-associated thrombosis and associated mortality. Our results may not be generalizable to other countries with different health care systems. Direct oral anticoagulants are increasingly used as first line treatment for cancer-associated thrombosis and this may also impact survival.

Conclusion

This nationwide study provides an overview of the temporal changes in the incidence and prognosis of cancer-associated venous thrombosis. We found an increasing incidence of cancer-associated

thrombosis, especially pulmonary embolism, in Denmark from 2006 through 2017. Concurrently, mortality after incident cancer-associated venous thrombosis remains high but has declined over time, across venous thrombosis subtypes, cancer type, stage, and treatment modalities. Most importantly for clinicians, cancer associated thrombosis is a problem that is not going away, but rather is on the increase. These data support the assertion that the prevention, early detection and timely treatment of cancer associated thrombosis remains a clinical priority for those involved in cancer or thrombosis care.

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Declaration of interest:

All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest. Prof Larsen has served as an investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim and received speaking fees from Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, MSD, and AstraZeneca. Prof Noble has received speakers bureau for Leo Pharma, Pfizer, Bristol Myers Squib and advisory board for Daichi Sankyo, Bristol Myers Squib. Dr Skjøth and Dr. Søgaard has received consulting fees from Bayer. The other authors declare no conflicts of interest.

Author contribution:

Anne Ording: Conceptualization, Methodology, Investigation, Writing- Original draft preparation, Writing – Review & Editing, Project Administration.

Flemming Skjøth: Methodology, Investigation, Data Curation, Resources, Formal analysis, Software, Validation, Visualization, Writing- Original draft preparation, Writing – Review & Editing.

Mette Søgaard: Conceptualization, Methodology, Investigation, Writing- Original draft preparation, Writing – Review & Editing.

Anette Højen: Conceptualization, Writing – Review & Editing.

Thure Overvad: Conceptualization, Investigation, Writing- Original draft preparation, Writing – Review & Editing.

Simon Noble: Conceptualization, Writing – Review & Editing.

Samuel Goldhaber: Conceptualization, Writing – Review & Editing.

Torben Bjerregaard Larsen: Conceptualization, Methodology, Investigation, Supervision, Funding acquisition, Resources, Writing- Original draft preparation, Writing – Review & Editing.

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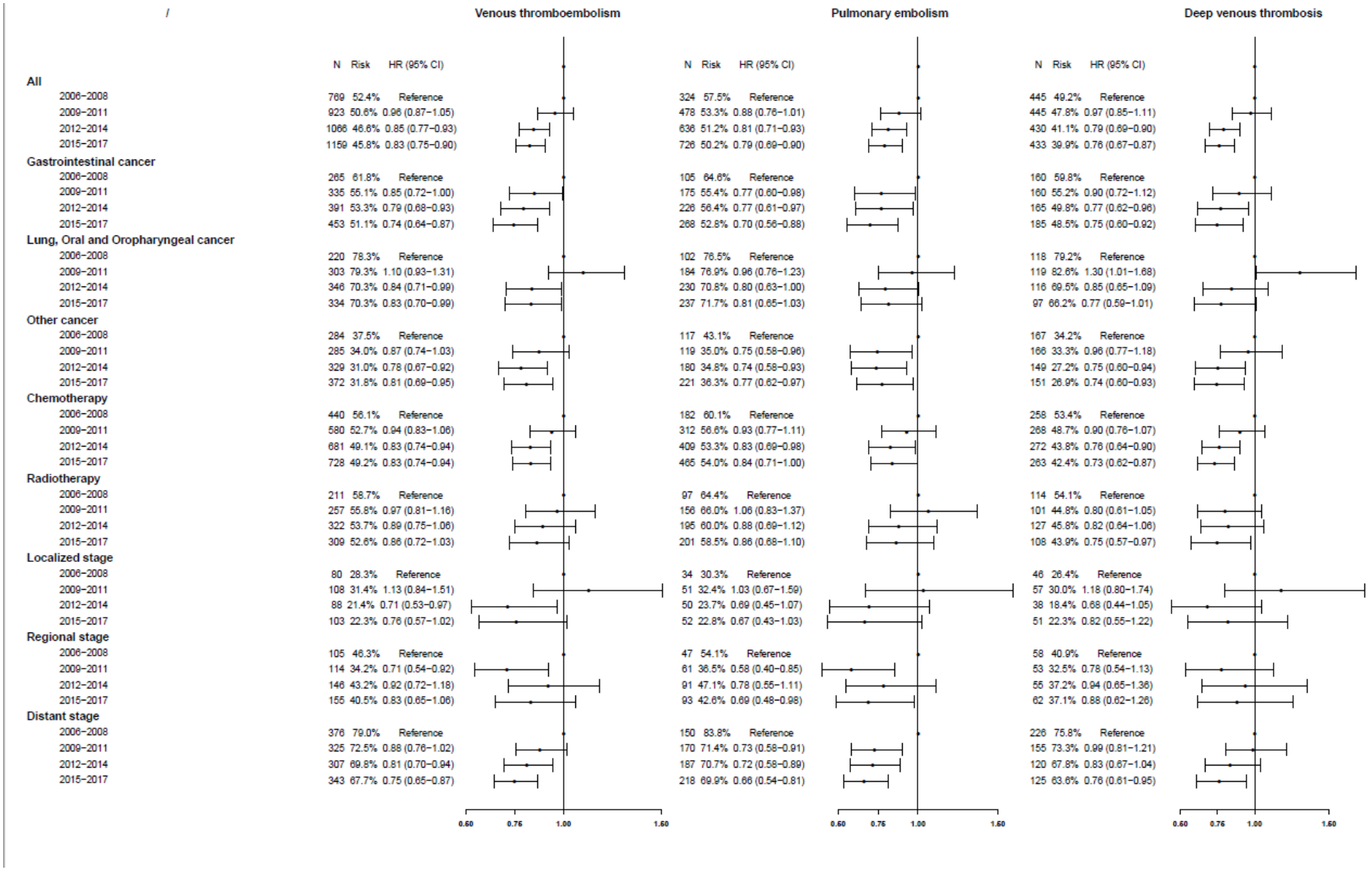

Figure 3. Temporal changes in 1-year mortality after cancer-associated thromboembolism, pulmonary embolism and deep venous thromboembolism.

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