

## **DARWIN EU® - Incidence rates of venous thromboembolic events in individuals with selected cancers**

**Melissa Leung<sup>1</sup>, Anton Barchuk<sup>1</sup>, Cesar Barboza<sup>1</sup>, Ioanna Nika<sup>1</sup>, Ger Inberg<sup>1</sup>, Maarten van Kessel<sup>1</sup>, Adam Black<sup>1</sup>, Berta Raventós<sup>1</sup>, Julieta Politi<sup>1</sup>, Natasha Yefimenko<sup>1</sup>, Gargi Jadhav<sup>2</sup>, Isabella Kacmarczyk<sup>2</sup>, Akram Mendez<sup>2</sup>, Dina Vojinovic<sup>3</sup>, Elvira Bräuner<sup>4</sup>, Susanne Bruun<sup>4</sup>, Marek Oja<sup>5</sup>, Raivo Kolde<sup>5</sup>, Ami Sild<sup>5</sup>, Laura Salonen<sup>6</sup>, Anna Palomar-Cros<sup>7</sup>, Irene López-Sánchez<sup>7</sup>, Agustina Giuliadori<sup>7</sup>, Antonella Delmestri<sup>8</sup>, Ross Williams<sup>1</sup>, Katia Verhamme<sup>1</sup>, Talita Duarte-Salles<sup>1,7</sup>**

<sup>1</sup>*Erasmus Medical Center, The Netherlands*

<sup>2</sup>*IQVIA, IQVIA, London, UK*

<sup>3</sup>*IQVIA, Real World Solutions, Amsterdam, The Netherlands*

<sup>4</sup>*Danish Medicines Agency, Denmark*

<sup>5</sup>*University of Tartu, Estonia*

<sup>6</sup>*Data and Analytics, Finnish Institute for Health and Welfare (THL), Finland*

<sup>7</sup>*IDIAPJGol, Spain*

<sup>8</sup>*University of Oxford, United Kingdom*

### **Background**

Individuals with cancer have a higher risk of venous thromboembolism (VTE) than those without.<sup>1</sup> VTE remains a major cause of mortality among individuals with cancer,<sup>2</sup> and approximately 20% to 30% of all primary VTE are cancer-associated.<sup>3</sup> The reported incidence rates (IRs) vary across populations and cancer types and are influenced by patient characteristics, treatments, and the stage of cancer at diagnosis.<sup>3</sup> When evaluating a potential safety signal associated with a novel cancer treatment, reliable, up-to-date information on background VTE rates in individuals with cancer is crucial. This multicentre study aimed to estimate the IRs of VTE among adults with newly diagnosed cancers.

### **Methods**

We conducted a cohort study of individuals aged ≥18 years with a primary diagnosis of one of the following selected cancers between 2016 and 2022: bone, brain, breast, colorectal, corpus uteri, kidney, leukaemia and lymphoma, liver, lung, melanoma, oesophageal, ovary, pancreas, prostate, and stomach, as defined by SNOMED and ICD-O-3 codes. Only individuals with a first cancer diagnosis were included.

The VTE outcomes of interest were: deep vein thrombosis (DVT), pulmonary embolism (PE), composite DVT and PE, pelvic venous thrombosis (PVT), splanchnic vein thrombosis (SVT), retinal vein thrombosis (RVT), and disseminated intravascular coagulation (DIC).

Data were drawn from nine European databases from Belgium (IQVIA LPD), Denmark (DK-DHR), Estonia (EBB), Finland (FinOMOP-THL), Germany (IQVIA DA), the Netherlands (IPCI), Spain (SIDIAP) and the UK (CPRD GOLD & UK Biobank).

Crude IRs per 100,000 person-years (PY) with 95% confidence intervals (CIs) for thromboembolic events were estimated at one and two years after cancer diagnosis. Follow-up started on the date of cancer diagnosis and ended at the first occurrence of the outcome, the end of the prespecified follow-up period (one or two years), loss to follow-up, the end of data availability, or the date of death, whichever came first. Each cancer type and outcome was analysed separately. Random-effects meta-analysis was then applied to the overall crude IRs to obtain pooled estimates, with 95% CIs calculated using the Knapp-Hartung method. Results were additionally stratified by age, sex and period.

### **Results**

A total of 975,962 adults with primary cancer were included. Overall, 47,076 thromboembolic events occurred within one year of cancer diagnosis, and 58,979 within two years. The highest IRs of thromboembolic events were consistently observed in pancreatic, oesophageal, liver, stomach, lung, brain, and ovarian cancers, whereas the lowest were observed in melanoma, breast, and prostate cancers.

Composite VTE was the most common event across all selected cancers, except for liver cancer, with combined IRs [95% CI] per 100,000 PY ranging from 597 [491–726] in melanoma to 11,607 [7,574–17,787] in pancreatic cancer (Figure 1). PE was generally the second most frequent event across all selected cancer types, with IRs ranging from 389 [297–511] in melanoma to 8,671 [5,578–13,479] in pancreatic cancer, followed by DVT. Other outcomes (SVT, RVT, PVT, and DIC) were rare across most cancers, with the exception of SVT, which was the most common thromboembolic outcome in liver cancer, with a combined IR of 7,448 [1,858–13,039] per 100,000 PY. IRs estimated after two years of follow-up showed the same pattern but were lower than those observed after one year.

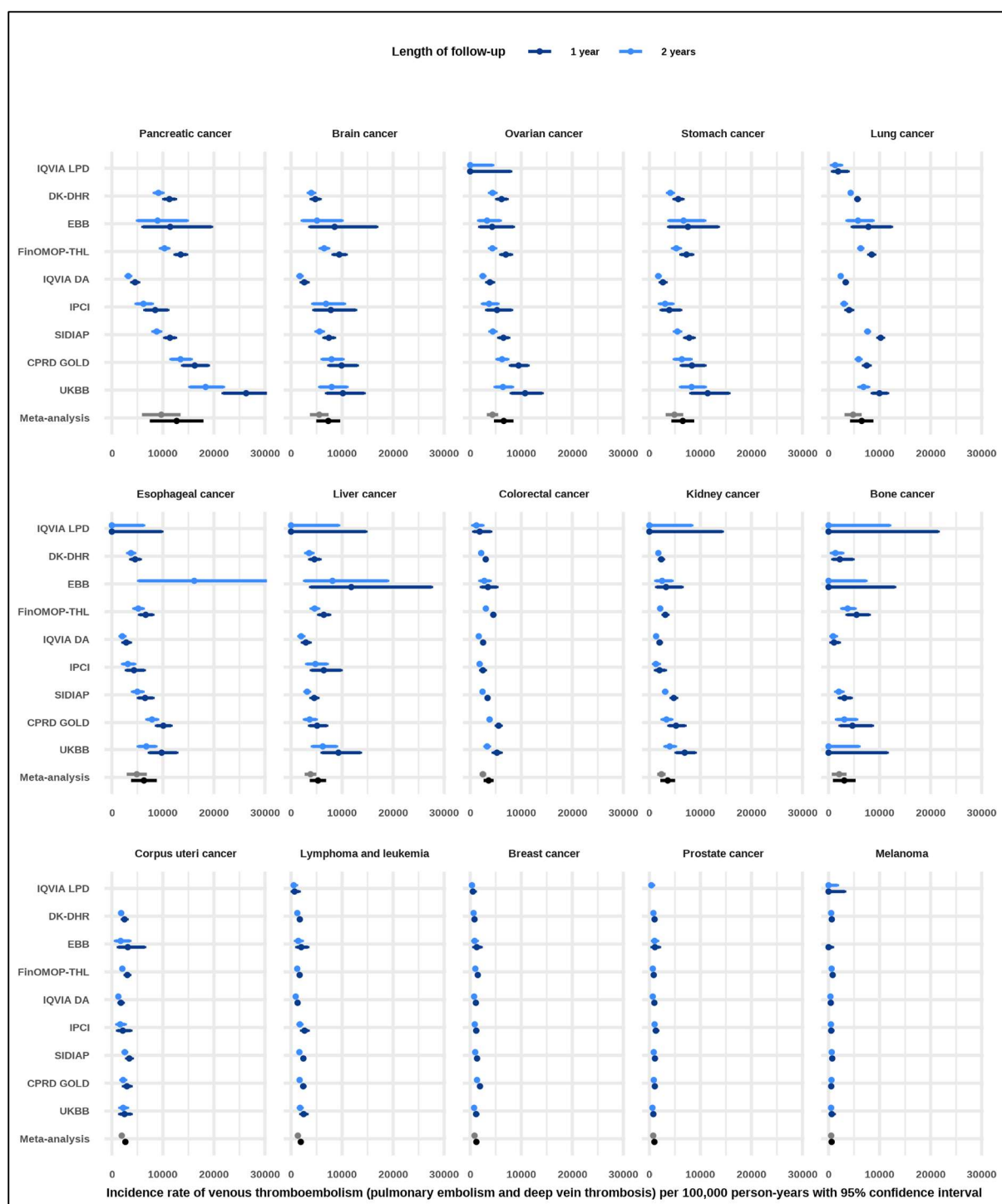


**Figure 1.** Meta-analysis of IRs with 95% CI of VTE (composite of PE and DVT) per 100,000 PY one year and two years after cancer diagnosis.

Stratification of IRs by age group, sex, and study period was limited by low event counts in some subgroups, and comparisons were inconsistent across data sources. Nevertheless, despite overlapping 95% CIs, point estimates differed across multiple data sources. Firstly, when stratified by age, the IRs of VTE in ovarian cancer increased with age. Secondly, when stratified by sex, IRs were lower among females than males for: DVT in brain cancer, VTE in brain cancer and melanoma, PE in melanoma and brain cancer, and SVT in liver cancer and colorectal cancer. In contrast, IRs were higher among females than males for: PE in stomach cancer and for DVT, PE, and VTE in liver cancer. Thirdly, when stratified

by calendar period, IRs were slightly lower in 2016–2019 than in 2020–2022 for DVT in brain cancer, PE in prostate cancer, and SVT in pancreatic cancer, while the IRs were higher for DVT in oesophageal cancer in 2016–2019 than in 2020–2022.

## **Conclusion**

PE and DVT, and their composite outcome, were the most frequently observed thromboembolic events among individuals with selected cancers. The highest IRs of thromboembolic events were observed in individuals with gastrointestinal cancers, particularly pancreatic, oesophageal, and gastric cancers. Relatively high IRs were also observed in lung, brain, and ovarian cancers, whereas the lowest IRs were observed in melanoma, prostate cancer, and breast cancer. The variation in VTE IRs across cancer types highlights the importance of considering cancer-specific and patient-level characteristics when contextualising the risk of VTE.

## **References**

1. Blom JW, Doggen CJM, Osanto S, Rosendaal FR. Malignancies, Prothrombotic Mutations, and the Risk of Venous Thrombosis. *JAMA*. 2005 Feb 9;293(6):715–22.
2. Wang T, Li A, Garcia D. Managing thrombosis in cancer patients. *Research and Practice in Thrombosis and Haemostasis*. 2018 July 1;2(3):429–38.
3. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood*. 2013 Sept 5;122(10):1712–23.

## **Disclaimer**

This study was funded by European Medicines Agency (EMA) and performed via DARWIN EU® (EUPAS1000000440). The study funder was involved in revising the study protocol and the objectives and reviewing the study report including the results. Data partners do not have an investigator role. They execute code at their data source, review, and approve their results. This communication represents the views of the DARWIN EU® Coordination Centre only and cannot be interpreted as reflecting those of the EMA or the European Medicines Regulatory Network.