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by Bengt Zöller

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Trends in mortality rate after cancer-related thrombosis give hope for the future

Bengt Zöller

Center for Primary Health Care Research, Lund University/Region Skåne, Malmö, Sweden.

Correspondence: Bengt Zöller, Center for Primary Health Care Research
CRC, Building 28, Floor 11

Jan Waldenströms gata 35 Skåne University Hospital S-205 02 Malmö, Sweden

Tel: +46 40-391954; Fax: +46 40 391370

bengt.zoller@med.lu.se

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Cancer-associated thrombosis is the second leading cause of mortality in patients with cancer after disease progression and is a major problem in oncology.[1] Moreover, it is estimated that ~20% to 30% of all first events of venous thromboembolism (VTE) are cancer- associated.[2] Despite this, there is no recommendation for general screening in VTE patients more than limited screening among those with unprovoked VTE, recurrent VTE, or VTE at unusual locations.[3] The incidence of cancer-related thrombosis has been reported to increase.[4] Previous studies have shown an especially high mortality rate in cancer-associated VTE.[4] Moreover, in a nationwide study it has been reported that cancer explains more than 80% of short-term mortality after the first event of VTE.[5] However, it is unclear whether the improved diagnostic and therapeutic strategies for cancer and VTE have led to improved prognosis and decreased mortality after cancer-related VTE.

In this issue of *Haematologica*, Eide and colleagues provide a new piece of the puzzle.[4] They report the mortality risk after cancer-related VTE over the last three decades in a high-quality Norwegian population-based cohort.[4] A total of 111,119 study participants from Tromsø (1994-2016) and HUNT (1995-2008) surveys were followed until 2019, and all first-lifetime cancer and VTE events were recorded.[4] They found that the one-year cumulative mortality after cancer-related VTE decreased from 61.8% in 1994-2002 to 55.6% in 2003-2011, and 45.5% in 2012-2019. This was reflected by a decreased age- and sex-adjusted hazard ratio (HR) for mortality after cancer-related VTE versus disease-free group decreased from 25.3 in 1994-2002 to 22.6 in 2003-2011, and 16.9 in 2012-2019. The study by Eide and colleagues provides hope for patients and healthcare providers by indicating that high cancer-related VTE mortality is possible to fight. The decreased mortality trend is presumably the result of substantial advances in cancer and VTE management.[4]

The reported results by Eide and colleagues raise several points of interest.[4] First is the question of generalizability. Norway is one of the wealthiest countries in the world with high-quality and egalitarian healthcare for all citizens and permanent residents of the country.[6] The health expenditure per head is higher in Norway than in most countries.[6] It will be of importance to perform similar studies in other countries with different levels of health expenditures and different healthcare organizations.

Another limitation of the study is the lack of information on treatment precluded the assessment of novel cancer- and VTE treatments as potential explanations for the decreased mortality in cancer-related VTE.[4] However, one possible bias could be excluded, i.e. incidental VTE. Incidental VTEs were not included in the present analysis by Eide and colleagues, and therefore an increase in incidental VTE detection cannot explain the finding of a declining mortality rate in cancer-related VTE.[4] The decline in mortality over time was only observed among those with non-metastatic cancer-related VTE, which may be due to the detection of cancer at increasingly early stages, facilitating earlier and more radical treatment with subsequently improved life expectancy.[4]

Clinical factors such as the delay or interruption of cancer therapy in patients who develop VTE along with complications associated with VTE treatment, including bleeding, may have a detrimental consequence on mortality in cancer-related VTE.[4] Prevention of VTE patients with cancer therefore remains an important research issue with development of a better risk algorithm for VTE risk stratification and prevention. The risk of VTE depends on cancer types and stages, treatment measures, and patient-related factors (Figure).[2] Patient-related factors

are older age, prolonged immobility, ethnicity, previous VTE, comorbidities, and thrombophilia (Figure).[2] Patients with black ethnicity have increased risk, whereas patients with Asian ethnicity have decreased risk of VTE compared with whites.[2] It is noteworthy that classic thrombophilia, i.e. factor V Leiden (rs6025) and prothrombin G20210A (rs1799963), are risk factors for cancer-related VTE.[7,8] However, these variants are not screened for in patients with cancer. Genetically determined classical thrombophilia is present in up to 15% of the middle-aged and older population and is associated with the risk of VTE, also at this age, in the general population.[9] Related to risk stratification for VTE in patients with cancer is the lack of a safe strategy for prophylactic treatment. For instance, Apixaban therapy results in a significantly lower rate of VTE compared with placebo among intermediate-to-high-risk ambulatory patients with cancer who were starting chemotherapy.[10] However, Apixaban also results in a higher rate of major bleeding episodes than with placebo.[10]

The substantial risk of death in cancer-related VTE still represents a burden for the affected individuals, their families, and the healthcare systems.[4] Future research should seek a deeper understanding of factors that contribute to maintaining high mortality rates in cancer-related VTE as well as strategies to alleviate them. However, the study by Eide and colleagues[4] is a step forward because it gives hope for the future that it is possible to decrease the high mortality rate in cancer-related VTE.

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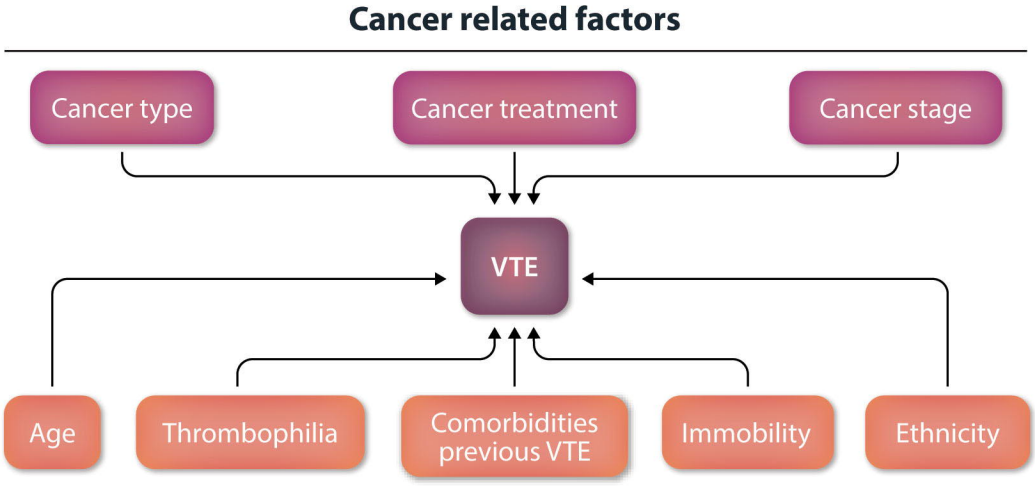
Figure legend

The thrombotic potential in cancer patients depends on cancer types and stages, treatment measures, and patient-related factors.[2] Patient-related factors are older age, prolonged immobility, ethnicity, previous venous thromboembolism (VTE), comorbidities, and thrombophilia.[2]


Cancer related factors
Cancer type
Cancer treatment
Cancer stage
VTE
Age
Thrombophilia
Comorbidities previous VTE
Immobility
Ethnicity
Patient related factors