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Arterial Thromboembolism Risk Varies Across Cancer Types, Ages

Patrice Wendling

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Patients with cancer face an increased risk of arterial thromboembolic events, including myocardial infarction (MI) and stroke, and for some that risk appears substantial, according to a new population-based study.

For example, the 6-month incidence of arterial thromboembolism (ATE) was 4.09% among men older than age 75 with diabetes and a diagnosis of bladder cancer but only 0.12% among women younger than age 65 with no comorbidities and a diagnosis of breast cancer.

Further, ATE was tied to more than a threefold higher risk of all-cause mortality (hazard ratio [HR], 3.28; 95% CI, 3.18 - 3.38).

"This increased mortality risk underscores the importance of arterial thromboembolism in cancer patients," study author Frits I. Mulder, MD, University of Amsterdam, the Netherlands, said in an interview. "The risk is lower than for venous thrombosis, but the association with mortality is really high and could be due to the fact that MI and stroke is such a severe complication that it could interrupt cancer treatment or surgery."

Physicians are well aware of the relationship between cancer and venous thromboembolism, which develops in about 3% of patients with cancer, but less appreciated is the risk for ATE, he noted. Prior studies have reported an excess risk but were often restricted to specific types of cancer or ATE, provided only relative risks, or were limited in size.

Mulder and colleagues linked Danish registry-based health data for 458,462 patients (median age, 69 years; 51% women) with a first-time cancer diagnosis between 1997 and 2017 and 1.3 million matched individuals in the general population.

Among patients with solid cancer, cancer stage at diagnosis was localized in 34%, regional in 27%, distant metastasis in 22%, and unknown in 17%.

During the 6 months after a cancer diagnosis, the cumulative incidence of ATE, defined as the composite of myocardial infarction, ischemic and unspecified stroke, and peripheral arterial occlusion, was 1.50% in patients with cancer and 0.76% in control patients (HR, 2.36; 95% CI, 2.28 - 2.44).

The cumulative incidence was 2.11% and 1.48%, respectively, at 12 months (HR, 1.87; 95% CI, 1.82 - 1.92) and generally diminished thereafter, according to the study, published April 20 in *JACC CardioOncology*.

In contrast, a 2017 study reported a 6-month cumulative ATE incidence of 4.7% among Medicare beneficiaries, aged 66 or older, with cancer. The inclusion of younger patients in their cohort and missing risk factors in both cohorts, such as body weight and smoking status, could explain the difference in risk, Mulder suggested.

"The absolute risk is different but the relative risk between cancer patients and cancer-free individuals is more or less the same between both cohorts – the risk is between two- and threefold higher among cancer patients," he said.

In the Dutch cohort, cancer types with the highest 6-month incidence of ATE were bladder (2.49%), lung (2.08%), and colon (2.08%), all of which are associated with smoking, the authors noted. The risk was lowest with breast cancer (0.58%).

In adjusted analyses, age was a predictor of ATE in the cancer cohort. Compared with patients younger than 65 years, the 6-month risk was higher in those age 65 to 75 years (adjusted subdistribution HR, 1.53; 95% CI, 1.43 - 1.65) and in those older than 75 years (aSHR, 1.88; 95% CI, 1.75 - 2.02).

Other independent predictors were prior ATE (aSHR, 2.96); distant metastasis (aSHR, 1.21); chemotherapy (aSHR, 1.47); male sex (aSHR, 1.15); hypertension (aSHR, 1.29); and diabetes (aSHR, 1.20).

Mulder noted that the Khorana risk score was developed over a decade ago for venous thromboembolism in patients with cancer and is endorsed in the latest guideline updates of the American Society of Clinical Oncology and the National Comprehensive Cancer Network to select ambulatory patients with cancer for thromboprophylaxis. No such tool exists for ATE risk.

This study, he said, is "a call for further development of risk scores in this population and preventive measures in certain subgroups."

The findings are interesting and based on a large cohort of patients but "I'm not surprised to see this," Edward T.H. Yeh, MD, an expert in cardio-oncology and chair of internal medicine at University of Arkansas for Medical Sciences, Little Rock, told

theheart.org | *Medscape Cardiology*. "This is pretty well known and people certainly pay attention to this."

Multiple mechanisms could account for the increased thrombotic risk in patients with cancer, including the ability of tumors to secrete pro-coagulating factors such as tissue factor, mucin, and cysteine protease, he noted. But certain cancer therapies — such as thalidomide, cisplatin, and ponatinib — are also associated with thromboembolism. "So it's not a generic problem for all cancer patients," Yeh said.

Cardiologists can work with oncologists to modify cardiovascular risk factors for patients with cancer but there isn't a good score for predicting thrombotic events, said Yeh, who founded the cardiology department at University of Texas MD Anderson Cancer Center.

"There are better scores for predicting bleeding risk than predicting clotting," he observed. "So, I think we should look at the different drugs associated with cancer therapy. That should be one of the major factors that you need to consider."

In an accompanying editorial, Katherine S. Panageas, DrPH, and Lisa M. DeAngelis, MD, both at Memorial Sloan Kettering Cancer Center in New York City, point out that elevated levels of absolute neutrophil count and soluble P-selectin have been identified as potential biomarkers for cancer-associated ATE but have not been prospectively validated.

"However, well-known risk factors for ATE include age, hypertension, hypercholesteremia, smoking, obesity, diabetes, and distant metastases. These are easily identified at cancer diagnosis and should be addressed to try to reduce the heightened ATE risk," the editorialists write.

The present study may also "inform clinical trials for the evaluation of therapeutic strategies including antithrombotic and statin medications for ATE," Panageas and DeAngelis observe.

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Full Text, Editorial

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