

FIBRINOLYSIS

ELEVATED CIRCULATING TISSUE PLASMINOGEN ACTIVATOR LEVELS PREDICT GASTROINTESTINAL AND BREAST CANCER RISK: A PROSPECTIVE NESTED CASE-COHORT STUDY

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Introduction. Identifying predictive biomarkers in healthy populations is essential for early cancer interception. While tissue plasminogen activator (tPA) is a key regulator of fibrinolysis and tissue remodeling, prospective evidence linking it to cancer risk is extremely limited, with only one major study currently addressing this association.

Aim. This study aims to further evaluate the prospective association between baseline circulating tPA levels and the risk of incident cancer in an independent, large-scale cohort of healthy subjects.

Materials and Methods. This analysis was conducted within the HYPERCAN prospective cohort (ClinicalTrials.gov NCT02622815), including 10,294 blood donors (72% men; mean age 48 years) enrolled between 2012 and 2022. Participants were followed up every 6 months for cancer occurrence for at least 5 years. Plasma tPA levels were measured at baseline using a commercial ELISA kit. A nested case-cohort design was applied, excluding cancers diagnosed within 6 months from enrollment. Multivariable Cox regression models were adjusted for age, glycemia, smoking status, alcohol intake, and lipid profile, using SPSS 21.0.

Results. Over a median follow-up of 9 years (range 5-11),

265 incident cancer cases and 715 controls were included. Most cancers (91%) occurred within 5 years from enrollment. Prostate cancer was the most frequent malignancy in men, and breast cancer in women, followed by gastrointestinal cancers (GI). Cancer cases were older and more frequently active smokers and hypertriglyceridemic ($p < 0.05$). Median tPA levels were 4.4 ng/mL (IQR 1.4-7.9) and were significantly higher in men than in women (6.7 vs 3.4 ng/mL, $p < 0.05$). Elevated tPA independently predicted cancer risk (HR 1.04, 95% CI 1.01-1.07; $p = 0.003$). tPA levels above 7.85 ng/mL were associated with an increased risk of overall cancer (HR 1.78, 95% CI 1.39-2.29; $p < 0.001$) and GI cancer (HR 3.29, 95% CI 1.70-6.38; $p < 0.001$). Sex-specific thresholds showed a significant association with breast cancer risk in women (HR 2.21, 95% CI 1.09-4.47; $p = 0.017$), while no association was observed with prostate cancer in men.

Conclusions. Elevated circulating tPA levels serve as an independent predictor of future cancer risk, particularly for GI and breast malignancies. Our results support the potential utility of tPA as a novel biomarker for identifying high-risk individuals within the general population. □