**Increased skin autofluorescence predicts future cancer development**

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**Abstract**

Tissue glycation, measured as skin autofluorescence (SAF) with an AGE reader, is associated with type 2 diabetes (T2D) and cardiovascular disease (CVD), as well as mortality from both CVD and cancer. Recently, it has also been suggested that higher SAF is associated with higher cancer incidence.

We aimed to evaluate the relationship between SAF and time to new cancer diagnosis in the population-based Lifelines Cohort Study of adult inhabitants of the Northern Netherlands in participants with and without T2D. Initial participant screening, including SAF measurement, was performed from 2006 to 2013. Detailed pathology diagnoses were obtained from the Dutch Nationwide Pathology Databank (Palga) and linked to Lifelines data up to March 2023. Cox proportional hazard analyses were performed to evaluate the association between SAF and total cancer incidence, adjusted for confounders.

A total of 77,961 participants (75,678 without T2D; 42% males; mean age 43±12 yrs and 2,283 with T2D; 53% males; mean age 56±12 yrs) who were free of cancer at baseline were followed for a median of 11.5 years. The cumulative incidence of cancer was 10.7% in males and 12.5% in females without diabetes and 23.6 and 20.2% in males and females with T2D, respectively. In the group

without T2D, SAF was significantly associated with an increased overall cancer incidence when assessed as a single predictor (HR 2.33, 95%CI 2.23-2.43, p<0.001). This association was significantly stronger in males (HR 3.15, 95%CI 2.95-3.6, P<0.001) than in females (HR 1.95, 95%CI 1.85-2.07, p<0.001). After adjustment for age, sex, BMI, waist circumference and pack-years of smoking, the association between SAF and incident cancer remained significant (HR 1.11, 95%CI 1.05-1.18, p<0.001). Sensitivity analyses for incident cancers diagnosed over 2 years after baseline Lifelines screening and incident cancer after skin cancer exclusion yielded similar results. Several cancer types were associated with increased age-corrected SAF levels, among these were lung, oesophagus and urinary tract cancer (all p<0.001, Bonferroni correction) and ovarian, female genital and liver cancer (p<0.05). Similarly, higher SAF was associated with increased cancer risk in individuals with T2D (HR 1.76, 95%CI 1.50-2.06, p<0.001). This association was no longer statistically significant when adjusted for age and sex (HR 1.07, 95%CI 0.89-1.290, p=0.74) or age, sex, BMI and waist (HR 1.07, 95% CI 0.86-1.33, p=0.488).

In addition to its earlier demonstrated use for risk assessment of future diabetes, CVD and cause-specific mortality, in people without T2D, higher SAF is associated with slightly higher cancer incidence.