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Metabolic and inflammatory markers as risk factors for pancreatic cancer within the European Prospective Investigation into Cancer and Nutrition (EPIC)

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A nested case-control approach was used to investigate the associations of markers of insulin sensitivity and impaired glucose metabolism (C-peptide, adiponectin, HbA_{1c}, AGE) and of pro-inflammatory cytokines (CRP, IL-6, sTNF-R1, sTNF-R2) with risk of pancreatic cancer. These markers were selected based on characteristics of known modifiable risk factors of pancreatic cancer, namely diabetes, excess body weight, chronic pancreatitis, and smoking. The current project was embedded within a large European prospective cohort and baseline questionnaire data and blood specimens of 466 pancreatic cancer cases and 466 individually matched controls were available for laboratory and statistical analyses.

In this prospective nested case-control study, we observed an increase in pancreatic cancer risk with elevated pre-diagnostic HbA_{1c} levels, a borderline increase in risk with elevated sTNF-R2 levels, and a borderline decrease in risk with higher adiponectin and CML concentrations. Higher levels of C-peptide, sTNF-R1, CRP, IL-6, and esRAGE levels were not associated with risk of pancreatic cancer. Combining all biomarkers into a risk profile resulted in a decrease in risk for participants with a “favourable” metabolic profile (low levels of HbA_{1c}, C-peptide, CRP, and IL-6 and high levels of adiponectin, CML, and esRAGE) and a suggestive increase in risk for those with an “unfavourable” metabolic profile (high levels of HbA_{1c}, CRP, IL-6, and sTNF receptors).Subgroup results by established risk factors (diabetes, smoking, overweight) showed no coherent and general pattern in terms of a direct relationship between risk factors, suspected altered biomarkers, and subsequent risk of

pancreatic cancer. In addition, our analyses showed only little heterogeneity of the associations of metabolic and inflammatory markers with pancreatic cancer risk by length of lag-time till cancer diagnosis.

We suspect an underlying low-grade pancreatic inflammation and impaired β-cell response predisposing a pancreatic tumour and fuelling its development in a vicious cycle. We also speculate that individuals with known risk factors are at an even higher pancreatic cancer risk if they additionally have an unfavourably altered metabolic or inflammatory blood profile with levels that are higher than generally observed in these individuals. Finding risk factor independent associations of biomarkers with pancreatic cancer risk was achieved for HbA_{1c} but not for other biomarkers. For that reason and in addition, it might be more forward-looking to develop a more comprehensive risk profile with not only changed levels of certain biomarkers but also including medical conditions (such as diabetes or chronic pancreatitis) and lifestyle behaviours (such as smoking and excess body weight). This tool might be the more efficient aim to reduce the incidence of pancreatic cancer than single environmental changes.