Inflammatory potential of diet and pancreatic cancer risk: interaction and mediation analysis in two prospective cohorts

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Background: Inflammation plays a pivotal role in pancreatic cancer etiology and can be modulated by diet. We aimed to examine the association between inflammatory potential of diet, assessed with the Dietary Inflammatory Index (DII\textsuperscript{TM}), and pancreatic cancer risk in two prospective cohorts, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the National Institutes of Health American Association of Retired Persons (NIH-AARP) Diet and Health Study. We explored effect modification by important inflammation-related lifestyle factors, and investigated whether type-2 diabetes mediated the association in a pooled analysis of both studies. Methods: A total of 101,449 and 533,286 participants aged between 50 to 78 years at baseline were included in the analytical cohort of PLCO and NIH-AARP, respectively. Energy-adjusted DII (E-DII) scores were computed based on food and supplement intake. Multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for pancreatic cancer by E-DII quintiles with participants in the lowest E-DII quintile (most anti-inflammatory scores) as the referent. We estimated natural direct effect, natural indirect effect, and marginal total effect of both categorical and continuous E-DII scores on pancreatic cancer with type-2 diabetes as a mediator using causal mediation approach. Results: A total of 328 and 3,338 pancreatic cancer cases were identified in the PLCO and NIH-AARP, respectively. There was no significant association between dietary inflammatory potential and pancreatic cancer risk in either the PLCO or NIH-AARP. However, time significantly modified the association in PLCO (P-interaction=0.02). An inverse association in the first four years of follow up was observed (HR\textsubscript{Q5 vs Q1}=0.55; 95% CI=0.32-0.95; P-trend=0.15), while there was a positive trend among those with ≥4 years of follow-up (HR\textsubscript{Q5 vs Q1}=1.36; 95% CI=0.85-2.17; P-trend=0.03). Type-2 diabetes significantly mediated the E-DII and pancreatic cancer association (P<0.05). Conclusion: Findings from these two large prospective cohorts did not support the association between inflammatory potential of diet and pancreatic cancer risk. Reverse causality owing to undetected disease may account for the inverse association observed in the first four years of follow-up in the PLCO. Type-2 diabetes explained an underlying mechanism through dietary inflammatory potential to pancreatic cancer development.