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A U-shaped relationship between plasma folate and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition

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ABSTRACT

Folate intake has shown an inverse association with pancreatic cancer; nevertheless, results from plasma measurements were inconsistent. The aim of this study is to examine the association between plasma total homocysteine, methionine, folate, cobalamin, pyridoxal 5′-phosphate, riboflavin, flavin mononucleotide and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). We conducted a nested case–control study in the EPIC cohort, which has an average of 9.6 years of follow-up (1992–2006), using 463 incident pancreatic cancer cases. Controls were matched to each case by center, sex, age (±1 year), date (±1 year) and time (±3 h) at blood collection and fasting status. Conditional logistic regression was used to calculate the odds ratios (OR) and 95% confidence intervals (CI), adjusting for education, smoking status, plasma cotinine concentration, alcohol drinking, body mass index and diabetes status. We observed a U-shaped association between plasma folate and pancreatic cancer risk. The ORs for plasma folate ⩽5, 5–10, 10–15 (reference), 15–20, and >20 nmol/L were 1.58 (95% CI = 0.72–3.46), 1.39 (0.93–2.08), 1.0 (reference), 0.79 (0.52–1.21), and 1.34 (0.89–2.02), respectively. Methionine was associated with an increased risk in men (per quintile increment: OR = 1.17, 95% CI = 1.00–1.38) but not in women (OR = 0.91, 95% CI = 0.78–1.07; p for heterogeneity <0.01). Our results suggest a U-shaped association between plasma folate and pancreatic cancer risk in both men and women. The positive association that we observed between methionine and pancreatic cancer may be sex dependent and may differ by time of follow-up. However, the mechanisms behind the observed associations warrant further investigation.

1. Introduction

Pancreatic cancer is the 5th most common cause of death from cancer in Europe in 2008 (95,200 deaths, representing 5.5% total cancer deaths).[1] There is no effective screening test for the malignancy; it is often diagnosed at an advanced stage, which leads to a 5-year survival rate as low as 6% in Europe.[2] Few risk factors for pancreatic cancer have been consistently identified. Cigarette smoking,[3] obesity,[4] diabetes mellitus[5] and chronic pancreatitis[6] increase the risk of pancreatic cancer.

Evidence has been mounting for folate being a potentially important micronutrient in the prevention of cancer. Prospective studies in Finland[7] and Sweden[8] showed an inverse

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