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Stolzenberg-Solomon et al. Respond to "What Do We Know about Pancreas Cancer?" by Potter

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In his commentary (1) on our study (2), Dr. John Potter summarizes current knowledge regarding risk factors for pancreatic cancer and makes several points relevant to not only our study but nutritional epidemiologic studies generally. Dr. Potter is astute in his assertion that examining nutritional and other modulators of pancreatic cancer risk within a relatively homogeneous population of smokers might be appropriate or even advantageous (1), and our previous findings of associations between pancreatic cancer and dietary folate (3), serum folate and vitamin B_6 (4), and *Helicobacter pylori* (5) provide evidence in support of this. Somewhat analogous are experimental studies in which all animals are exposed to (pancreatic) carcinogens and dietary constituents are tested for their ability to modulate tumorigenesis. By contrast, epidemiologic studies that use questionnaire data rely on self-reported exposure information, which may inherently be prone to measurement error that can influence risk estimates. The validity and reliability of such data are derived from the quality of the dietary assessment instrument used and the consistency and veracity of the subjects' responses. We believe that residual confounding by smoking is unlikely in our study of long-term smokers, given that self-reported current smoking is highly accurate in adults (6–8), our smoking variables were not confounders (2), and restriction of our analysis to only those men who reported smoking *exactly* 20 cigarettes daily (n = 44 cases) yielded similar associations for intakes of total fat and carbohydrate (highest tertile vs. lowest: adjusted for age and years of smoking, hazard ratio (HR) = 1.87 (95 percent confidence interval (CI): 0.91, 3.86; p-trend = 0.07) for total fat and HR = 0.50 (95 percent CI: 0.24, 1.05; p-trend = 0.06) for carbohydrate. Residual confounding is more likely to have originated from our simple assessment of physical activity. This could possibly explain the inverse associations we observed for both energy and carbohydrate (2). The complex intercorrelations between nutrients in foods and health behaviors (e.g., physical activity) often cannot be easily separated, and it may be beneficial to understand the relation of eating and health-behavior patterns to disease risk.

Dr. Potter expresses concern about the validity of our carbohydrate data, with starch accounting for only 50 percent of total carbohydrate and with starch and starch food sources such as rye and wheat products, potatoes, legumes, and root vegetables not being consistent with the carbohydrate association (2). One of our study's strengths was the high quality of the dietary data: The questionnaire was developed specifically for the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study population, and food composition data and nutrient analyses were based on Finnish foods. The instrument had good reliability and validity; intraclass and Pearson's correlation coefficients for carbohydrate were 0.70 and 0.55–0.75, respectively (9). Carbohydrate food sources include all foods except meat and pure fat, and carbohydrate is composed of starch, fiber, and mono- and disaccharides. Dr. Potter seems to have overlooked the fact that dairy products and fruit are important sources of carbohydrate (e.g., lactose, fructose, and glucose) in our population's diet. Historically, Finland has had a lower rate of colorectal cancer than other countries (10), which may be explained by high intakes of calcium and fiber from dairy products and rye bread, respectively (11). Additional analysis of our data shows inverse associations between pancreatic cancer and mono- and disaccharides combined (fructose, glucose, lactose, and maltose) and sucrose (fifth quintile vs. first: adjusted for age, years of smoking, and energy-adjusted saturated fat, HR = 0.68 (95 percent CI: 0.40, 1.15; p-trend = 0.16) for combined saccharides and HR = 0.59 (95 percent CI: 0.36, 0.96; p-trend = 0.10) for sucrose). In addition, the median total carbohydrate intake (296 g) approximates the sum of its components in the cohort (i.e., sucrose, 57 g; other free sugars, 63 g; starch, 143 g; and fiber, 24 g). Potentially relevant to pancreatic carcinogenesis is the fact that, unlike starch, the simple sugars do not require pancreatic enzymes for digestion, instead using enzymes in the intestinal brush border (12), and they may impose a lower stimulatory "load" on the exocrine pancreas for enzyme secretion and hence less pancreatic glandular proliferation than, for example, dietary fat, which in our investigation and other studies (animal experiments and epidemiologic studies) is positively associated with pancreatic cancer risk (13–17).

Our study is among the first to have prospectively examined associations between nutrients and pancreatic cancer.

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Abbreviations: CI, confidence interval; HR, hazard ratio.

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As other cohorts mature, identification of similar risk factors in both smoking and nonsmoking populations may provide etiologic clues that can be applied to the prevention of this highly fatal disease.

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