Defining Determinants of Pancreatic Cancer Risk: Are We Making Progress?

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Pancreatic cancer is the fourth leading cause of cancer-related mortality in the United States, and 80%–85% of patients have incurable disease at the time of diagnosis. Furthermore, more than 95% of patients diagnosed with pancreatic cancer will ultimately die from the disease, highlighting the urgent need for novel insights into pancreatic tumorigenesis.

Why has progress been so slow in defining predisposing factors for pancreatic cancer? First, its incidence rate is relatively low, when compared with other leading causes of cancer-related death, such as colorectal or breast cancer, so that fewer cases are available for study. Second, case-control studies have proved difficult. The rapid and nearly universal demise of patients with pancreatic cancer increases the susceptibility of retrospective studies to recall bias, selection bias, and exposure misclassification, particularly when using proxy (i.e., next of kin) respondents to collect eligibility and exposure data. In addition, studies in which plasma samples are collected at the time of diagnosis are difficult to interpret, due to the large alterations in patient nutritional and functional status caused by this malignancy. Third, although studies of families with high rates of pancreatic cancer have identified several predisposing genetic variants, these variants are rare and contribute little to the overall population burden of pancreatic cancer. Fourth, no screening tests have been able to detect pancreatic cancer at an early, more treatable stage, leaving some to question whether risk factor identification will impact patient outcomes, in the absence of a clear commitment to risk factor modification or the development of novel screening modalities.

The best defined, modifiable risk factor for pancreatic cancer remains tobacco use, which increases risk by two- to three-fold and contributes to approximately 25% of pancreatic cancer cases in the United States (1). The other modifiable risk factors for which we have reasonable evidence are chronic alterations in energy balance: obesity, type 2 diabetes mellitus, and markers of insulin resistance are all associated with incident pancreatic cancer, separate from the insulin resistance caused by the disease and commonly observed in patients immediately before diagnosis.

The differences in rates of pancreatic cancer among countries, the changes in rates over time, and the increases among migrants moving from low-risk to high-risk areas suggest that other factors may also play an etiologic role. However, studies of diet and pancreatic cancer have generated mixed results. For example, both null and statistically significant associations have been observed for total meat, red meat, processed meat, total fat, saturated fat, or monounsaturated fat consumption in prospective studies (2–5), with risk ratios ranging from 1.3 to 1.6 for high intakes vs low intakes in several of these studies.

With this background, Thiébaut et al. have provided high-quality data from the prospective National Institutes of Health–formerly known as American Association of Retired Persons (NIH-AARP) Diet and Health Study (6). In the NIH-AARP cohort, this group previously demonstrated a modest association between total meat intake and pancreatic cancer risk (hazard ratio, 1.26) (7). In the current study (6), they work to extend this finding and demonstrate a modest increase in risk among those participants who consumed total fat, saturated fat, and monounsaturated fat in the highest vs the lowest quintile, with multivariable-adjusted hazard ratios between 1.2 and 1.4. Interestingly, only fatty acids from animal sources were statistically significantly associated with risk.

The study by Thiébaut et al. (6) has several notable and important strengths. The large base population leads to an impressively large number of pancreatic cancer cases available for analysis. The prospective design of the study without the need for proxy respondents increases the interpretability of the results, by limiting the potential for bias and misclassification. The data collected on dietary habits were sufficiently detailed to capture information on the diversity of food products, such as “low-fat” versions of foods, and nicely demonstrate the utility of well-designed food-frequency questionnaires in prospective studies of diet and cancer.

Overall, this well-performed prospective cohort study is a welcome addition to our understanding of a disease that is in great need of new insights. However, the available epidemiological and laboratory evidence are insufficient to confirm the importance of animal fats, per se, or even that meat is the important factor, as opposed to other dietary or lifestyle preferences associated with meat consumption. Nonetheless, sufficient evidence already suggests health benefits from limiting meat and saturated fat intake (8), and the current study provides additional support for these recommendations. Also, with further investigation, this work has the potential to provide interesting clues to the mechanisms underlying pancreatic tumorigenesis.

Although large prospective cohort studies with questionnaire-based analyses will continue to have much to offer in defining predisposing factors for difficult diseases, such as pancreatic cancer, how can we move beyond what has been done before? Two principles are worth mentioning: increased collaboration and greater use of participant-derived biological samples. Because of the relatively low incidence rate of pancreatic cancer, collaboration is vital to provide the critical mass of cases for meaningful analyses. Second, there is great potential for well-designed studies using banked plasma, germline DNA, and tumor tissue samples to advance our understanding of pancreatic cancer pathogenesis.
Evidence of this potential is clearly visible in studies of other malignancies, such as colon (9) and breast (10) cancer, and in the work linking prediagnostic insulin resistance with pancreatic cancer risk (11,12). In the realm of pancreatic cancer research, a laudable example of this approach is the Pancreatic Cancer Cohort Consortium, a collaborative effort of 12 prospective cohort studies working to identify novel risk markers for pancreatic cancer. The results of this collaboration and others similar to it are likely to push our research efforts in novel directions and provide hope for meaningful progress in this highly lethal disease.

References

Note
The authors report no conflicts of interest.