Plasma Adiponectin: A Possible Link Between Fat Metabolism and Pancreatic Cancer Risk

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Body fat may not just make you less attractive but may also increase your odds of developing pancreatic cancer, according to Bao et al., whose findings are published in this issue of the Journal (1). They report that a fat-derived hormone adiponectin in the circulation is inversely associated with pancreatic cancer risk. Likewise, the adiponectin-tumor risk association is independent of sex, age, smoking status, and other potential risk factors.

Risk Factors of Pancreatic Cancer

Population and animal studies suggest that obesity and metabolic diseases, similar to well-accepted risk factors such as heritable mutations and tobacco smoking, are associated with the development of pancreatic cancer (2, 3). These studies support the role of abnormal glucose and/or fat metabolism contributing to neoplastic growth of pancreatic tissues. Adiponectin, an adipocytokine, is exclusively produced and secreted by mature adipocytes or fat cells. Low levels of plasma adiponectin are associated with risk of diabetes in individuals with insulin resistance (4). Furthermore, adiponectin concentrations are inversely linked to risk of cancers such as multiple myeloma and breast cancer among obese individuals (5, 6). However, conflicting studies show that the median levels of adiponectin in patients with pancreatic cancer can be lower (7, 8) or higher (9) than those in control subjects. Small sample size (9) and other factors such as tobacco smoking (7) may contribute to the conflicting outcomes.

Bao et al. (1) report a long-term follow-up study on a relatively large population (N = 468) of pancreatic cancer patients. Their conclusion of the inverse association between plasma adiponectin levels and pancreatic cancer risk is supported by carefully designed methods and encouraging results. First, sampling protocols were well conceived. For instance, patients diagnosed within 1 year from the date of blood draw were excluded from the analysis to minimize the effects of reverse causation. Control subjects were matched to case patients by conditions such as smoking status and age. Sample adiponectin levels were assessed in a single batch, which minimizes the effects of the experimental variant on the assessments. Second, the inverse association between adiponectin levels and pancreatic cancer was consistently observed across all studied cohorts. Finally, the association was independent of other factors such as sex, age, smoking status, body mass index, and physical activity.

Nevertheless, despite the findings of the current study, the pathophysiologial role of plasma adiponectin in obesity/diabetes-associated pancreatic tumorigenesis is unclear. Adiponectin is released by fat cells to signal the use of fat for food as well as readiness to receive fat for storage. In response, eating is promoted, and energy expenditure/physical activity is suppressed. This can lead to fat storage and obesity in mice (10). However, adiponectin level declines have been observed under the condition of obesity and insulin resistance/diabetes in mice (11) and in humans (12). The molecular mechanism underlying the contradictory outcomes remains to be determined. However, the distribution of fat may affect pancreatic cancer risk since overexpression of adiponectin in leptin-deficient mice promotes fat storage under the skin instead of within organs and prevents diabetes (10). Accumulation of fat cells in the pancreas of adiponectin-deficient individuals may create a protumor microenvironment such as inflammation, thus increasing cancer risk. Owing to lack of fat distribution data in the Bao et al. study, the present report does not answer whether a fat-associated procancer microenvironment promotes a higher risk of cancer in people with lower adiponectin levels.

Total vs High/Low-Molecular-Weight Adiponectin

Although Bao et al. measured total adiponectin, the effects of total plasma adiponectin on the development of pancreatic cancer may be different from that of high- or low-molecular-weight adiponectin. After monomer adiponectin is released by adipocytes into the bloodstream, it combines with other monomers to form a homotrimer. Further self-association leads to high-molecular-weight polymers. High-molecular-weight adiponectin has been shown to be more bioactive and associated with diabetes and insulin sensitivity (13). In addition, high-molecular-weight but not low-molecular-weight adiponectin is positively associated with heart disease (14). Interpretation of the data of Bao et al. may warrant the consideration that the levels of high/low-molecular-weight adiponectin, compared to total adiponectin, might be better associated with pancreatic cancer risk.

Adiponectin Benefits

The relationship between elevated plasma adiponectin and the low risk of pancreatic cancer may be explained by inhibition of neoplasm growth. First, elevated adiponectin levels may promote fat storage under the skin but not within the pancreas. This may avoid forming a procancer microenvironment around pancreatic cells. Moreover, higher levels of plasma adiponectin may block or
eliminate abnormal growth in the pancreas because adiponectin has been reported to inhibit tumor cell growth and induce apoptosis (15).

The finding by Bao et al. of an association between adiponec-tin and pancreatic cancer has both mechanistic and translational potential. Firmly establishing a link between adiponectin levels and pancreatic cancer risk will suggest that glucose/fat metabolism contributes to the pathophysiology of pancreatic cancer. Future studies in this direction are expected to help us better understand the molecular events that are responsible for pancreatic cancer tumorigenesis. Further studies on issues such as the dynamic changes of high/low-molecular-weight adiponectin levels during the development of pancreatic cancer can yield key information to determine whether plasma adiponectin levels could be used as a predictive biomarker. Currently, most cases of pancreatic cancer are diagnosed at a late stage, contributing to high mortality rates. Adiponectin assessment may be used to prescreen patients with metabolic disorders such as diabetes for the detection of pancreatic cancer at an early stage. Early detection by the assessment of adiponectin has the potential to improve the survival rates of pancreatic tumor patients. It is also inviting to speculate that therapeutic interventions to increase the levels of circulating adiponectin may prevent the development of pancreatic cancer and/or improve the survival of patients with malignancy.

References

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Treatment for Breast Cancer: Is Time Really of the Essence?

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It is accepted for breast cancer that early detection and prompt treatment lead to better outcome. In this issue of the Journal, Vandergrift et al. (1) evaluate the time interval between breast cancer diagnosis and initiation of adjuvant chemotherapy after definitive surgery to identify patient demographic and clinical features that might be actionable variables to decrease treatment delays. Using the National Comprehensive Cancer Network (NCCN) outcomes database, mean time to chemotherapy for 6622 patients diagnosed with stage I to stage III breast cancer between 2003 and 2009 and treated at nine participating NCCN cancer centers was 12 weeks and increased monotonically from 10.8 weeks in 2003 to 13.3 weeks in 2009. Increased utilization of diagnostic testing such as the 21-gene reverse transcription polymerase chain reaction assay and breast magnetic resonance imaging (MRI) appeared to strongly contribute to this increase. Not surprisingly, multiple surgical excisions and postmastectomy reconstruction also delayed adjuvant chemotherapy. Finally, increasing age and comorbidities, lower socioeconomic status, and transfer of care to an NCCN cancer center after diagnosis, particularly for black women with Medicaid insurance, were associated with increased time to chemotherapy.