

New-onset Diabetes: A Clue to the Early Diagnosis of Pancreatic Cancer

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Pancreatic cancer is the tenth most common cancer diagnosis; however, it is the fourth most common cause of death due to cancer. Recent estimates suggest that by 2020 pancreatic cancer will become the second most common cause of cancer death in the US. The five year survival rate in all patients is only ~5% and has not changed significantly over the past five decades. Though the relationship between diabetes mellitus and pancreatic cancer has been known for over 125 years, it still remains to be fully understood. The complex relationship between the two diseases has been the subject of numerous clinical, epidemiological, laboratory and experimental studies. Epidemiologic studies suggest that long-standing type 2 diabetes is a modest risk factor for the development of pancreatic cancer. Meta-analysis of multiple cohort and case-control studies show that the risk of pancreatic cancer in those with diabetes for >5 years is 1.5 to 2.0 fold higher. This is not fully explained by shared risk factors between the two diseases such as obesity. There is also strong clinical, epidemiological and experimental evidence to show that pancreatic cancer causes diabetes. Hyperglycemia and diabetes mellitus occur in ~85% of pancreatic cancer subjects, with diabetes being present in 45% to 67% of pancreatic cancer patients depending on how diabetes is ascertained. Majority (~75%) of diabetes in pancreatic cancer is new-onset, i.e., less than 3 years in duration. The new-onset diabetes often resolves with resection of cancer. The notion that new-onset diabetes in pancreatic cancer is a paraneoplastic phenomenon caused by tumor secreted products was strengthened by a recent study that proposed adrenomedullin, a 52 amino-acid polypeptide, as a strong candidate for mediator of diabetes in pancreatic cancer. In previous studies adrenomedullin has been shown not only to promote pancreatic cancer aggressiveness, but also inhibits insulin exocytosis from beta cells. In the aforementioned study pancreatic cancer cell lines overexpressing adrenomedullin were shown to inhibit insulin secretion, an effect that was reversed by silencing adrenomedullin. Adrenomedullin was also shown to be overexpressed in human pancreatic cancer and plasma levels of adrenomedullin were also increased in pancreatic cancer patients, especially those with diabetes. New-onset diabetes appears to be the only clue to the presence of asymptomatic sporadic pancreatic cancer. Nearly 25% of patients with pancreatic cancer are diagnosed with diabetes 6 months to 36 months before the diagnosis of pancreatic cancer. Conversely, subjects with new-onset diabetes over age 50 years have an 8-fold higher risk for having pancreatic cancer. Thus new-onset diabetes may be a clue to the early diagnosis of the cancer. However, the success of the strategy to use new-onset diabetes as a marker of pancreatic cancer will depend on our ability to distinguish pancreatic cancer-associated diabetes from the more common type 2 diabetes. This strategy provides for diagnosis of early, asymptomatic pancreatic cancer.
