

Is Type 2 Diabetes a Risk Factor for Pancreatic Cancer?

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The relationship between diabetes mellitus and the risk of pancreatic cancer has been a matter of study for a long time. Taking into consideration diabetes mellitus irrespective of type, there is a lack of agreement regarding the data; in fact, some epidemiological studies have excluded this possibility whereas others have found a relationship between the presence of diabetes and the development of pancreatic cancer. On the other hand, a recent study has reported that metformin may have a protective effect on the development of pancreatic cancer [1]. Therefore, we would briefly revise the data both for and against the possibility that pancreatic cancer is a consequence of long-standing diabetes.

In 1994, our group performed a case-control study matching a large number of patients with and without pancreatic cancer [2]. The main findings were as follows: in the majority of cases, the diabetes was diagnosed at the same time as the cancer or within a few years prior to its identification, suggesting that it was the cancer which caused the diabetes; in fact, diabetes mellitus of long duration (>7 years) had essentially no association with pancreatic cancer whereas, in a small group of patients who had had diabetes of a 5-7 year duration when the cancer was diagnosed, the association was statistically significant. Finally, all the patients in whom the diagnosis of diabetes had been made prior to that of the tumor had non-insulin-dependent diabetes, and no association was found with the insulin-dependent form.

On the contrary, numerous epidemiological studies have reported a positive association between diabetes

mellitus and the risk of pancreatic cancer [3, 4, 5, 6, 7, 8]. However, the assessment of the relationship between diabetes and pancreatic cancer is further complicated by cases of self-reported diabetes which could result in misclassification. Moreover, heterogeneity among individuals with diabetes in terms of physiologic status, sequelae and treatment could also confuse this relationship. While the association between pancreatic cancer and recent onset diabetes is well recognized, little is known about glucose tolerance and insulin secretion in patients with this tumor. Gapstur *et al.* [9] prospectively studied the postload plasma glucose concentration in 84 patients with pancreatic cancer in order to determine the presence of an independent association between postload plasma glucose concentration and the risk of pancreatic cancer mortality among people without self-reported diabetes. Compared to a postload plasma glucose level of 119 mg/dL or less and, after adjusting for age, race, cigarette smoking and body mass index, the relative risks (95% confidence intervals) of pancreatic cancer mortality were 1.65 (1.05-2.60) for postload plasma glucose levels between 120 mg/dL and 159 mg/dL, 1.60 (0.95-2.70) for levels between 160 mg/dL and 199 mg/dL and 2.15 (1.22-3.80) for levels of 200 mg/dL or more; (P for trend=0.01). Such an association appeared to be stronger in men than in women. Estimates were only slightly lower after excluding 11 men and 2 women who died from pancreatic cancer during the first 5 years of follow-up. Elevated body mass index and serum uric acid concentration were also independently associated with an elevated risk of pancreatic cancer mortality in men only. This study provides evidence for a positive, dose-response relationship between postload glycemia and pancreatic cancer mortality. The possible mechanisms underlying the increased pancreatic cancer risk among patients with diabetes mellitus is the involvement of insulin resistance and hyperinsulinemia.

Thus, other complicating factors, such as the progression of type 2 diabetes and the use of diabetes medications can influence the extent of insulin resistance and hyperinsulinemia, sometimes in opposite

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directions. This has recently been studied by Li *et al.* [1]. These authors investigated the effect of antidiabetic therapies on the risk of pancreatic cancer. A hospital-based case-control study was conducted from 2004 to 2008 involving 973 patients with pancreatic adenocarcinoma, including 259 diabetic patients and 863 controls, 109 of whom were diabetics. Information on diabetes history and other risk factors was collected by personal interview. The frequencies of the use of insulin, insulin secretagogues, metformin and other antidiabetic medications among the diabetic patients were compared between cases and controls. Diabetic patients who had taken metformin had a significantly lower risk of pancreatic cancer as compared to those who had not taken metformin ($P=0.001$), with adjustments for potential confounders. This difference remained statistically significant when the analysis was restricted to patients with a duration of diabetes >2 years or those who never used insulin. In contrast, diabetic patients who had taken insulin or insulin secretagogues had a significantly higher risk of pancreatic cancer as compared to diabetic patients who had not taken these drugs. The author concluded that the use of metformin was associated with a reduced risk of pancreatic cancer in diabetic patients while the use of insulin or insulin secretagogues was associated with an increased risk. In our opinion, some points of this study should be discussed. The authors pointed out that theirs was a hospital-based case-control study, but there was a difference in the number of subjects studied (973 cases and 863 controls); regarding the characteristics of the participants, black subjects ($P=0.007$) and individual over 70 years of age ($P=0.002$) were significantly underrepresented in the control group; finally, there was a significantly higher number of overweight and obese subjects ($P<0.001$) as compared to the controls and the authors did not include BMI in their analysis model due to a problem of colinearity. The data reported in this study have a major drawback; since obesity might be the “true” risk factor for pancreatic cancer, the role of obesity as a confounding factor should be better evaluated. In fact, overweight and obesity have well-established public health implications as having an increased risk for various diseases, such as cardiovascular disease and diabetes, and also play a role in an increased risk for multiple types of cancer [10], including pancreatic cancer [11]. It has recently been reported that pancreatic duct cell replication is increased in humans in response to both obesity and type 2 diabetes [12]. Finally, metformin, given to treat patients with diabetes associated with obesity and those subjects with non-alcoholic steatohepatitis [13], is a potent inhibitor of cell proliferation and this effect is partially mediated through AMPK activation and the subsequent inhibition of the mTOR pathway [14].

In conclusion, we believe that more studies are necessary in order to definitively identify type 2 diabetes mellitus as a risk factor for pancreatic cancer.

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References

1. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009; 137:482-8. [PMID 19375425]
2. Gullo L, Pezzilli R, Morselli-Labate AM; Italian Pancreatic Cancer Study Group. Diabetes and the risk of pancreatic cancer. *N Engl J Med* 1994; 331:81-4. [PMID 8208269]
3. Wideroff L, Gridley G, Møller-Jensen L, Chow WH, Linet M, Keehn S, et al. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J Natl Cancer Inst* 1997; 89:1360-5. [PMID 9308706]
4. Chow WH, Gridley G, Nyrén O, Linet MS, Ekblom A, Fraumeni JF Jr, Adami HO. Risk of pancreatic cancer following diabetes mellitus: a nationwide cohort study in Sweden. *J Natl Cancer Inst* 1995; 87:931-2. [PMID 7666483]
5. Calle EE, Murphy TK, Rodriguez C, Thun MJ, Heath CW Jr. Diabetes mellitus and pancreatic cancer mortality in a prospective cohort of United States adults. *Cancer Causes Control* 1998; 9:403-10. [PMID 9794172]
6. Smith GD, Egger M, Shipley MJ, Marmot MG. Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. *Am J Epidemiol* 1992; 136:1110-4. [PMID 1462971]
7. Silverman DT. Risk factors for pancreatic cancer: a case-control study based on direct interviews. *Teratog Carcinog Mutagen* 2001; 21:7-25. [PMID 11135318]
8. Bonelli L, Aste H, Bovo P, Cavallini G, Felder M, Gusmaroli R, et al. Exocrine pancreatic cancer, cigarette smoking, and diabetes mellitus: a case-control study in Northern Italy. *Pancreas* 2003; 27:143-9. [PMID 12883263]
9. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA* 2000; 283:2552-8. [PMID 10815119]
10. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med* 2003; 348:1625-38. [PMID 12711737]
11. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS. Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA* 2001; 286:921-9. [PMID 11509056]
12. Butler AE, Galasso R, Matveyenko A, Rizza RA, Dry S, Butler PC. Pancreatic duct replication is increased with obesity and type 2 diabetes in humans. *Diabetologia* 2009 Oct 21. [PMID 19844672]
13. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchionda N. Metformin in non-alcoholic steatohepatitis. *Lancet* 2001; 358:893-4. [PMID 11567710]
14. Cantrell LA, Zhou C, Mendivil A, Malloy KM, Gehrig PA, Bae-Jump VL. Metformin is a potent inhibitor of endometrial cancer cell proliferation-implications for a novel treatment strategy. *Gynecol Oncol* 2009 Oct 10. [PMID 19822355]