Is diabetes mellitus a risk factor for pancreatic cancer?

Raffaele Pezzilli, Nico Pagano

Pezzilli R, Pagano N. Is diabetes mellitus a risk factor for pancreatic cancer? World J Gastroenterol 2013; 19(30): 4861-4866 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i30/4861.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i30.4861

INTRODUCTION

The relationship between diabetes mellitus and the risk of pancreatic cancer has been a matter of study for a long period of time. The importance of this topic is due to two main causes: the possible use of recent onset diabetes as a marker of the disease and, in particular, as a specific marker of pancreatic cancer, and the selection of a population at risk for pancreatic cancer. Thus, we decided to make an in-depth study of this topic; thus, we carried out an extensive literature search in order to re-assess the current knowledge on this topic. Even if diabetes is found a decade before the appearance of pancreatic cancer as reported in meta-analytic studies, we cannot select those patients already having non detectable pancreatic cancer, at least with the imaging and biological techniques available today. We believe that more studies are necessary in order to definitively identify diabetes mellitus as a risk factor for pancreatic cancer taking into consideration that approximately 10 years are needed to diagnose symptomatic pancreatic cancer. At present, the answer to the as to whether diabetes and pancreatic cancer comes first similar to the adage of the chicken and the egg is that diabetes is the egg.

Key words: Diabetes mellitus; Obesity; Pancreatic neoplasms; Risk factors; Clinical studies

Core tip: Even if diabetes is found a decade before the appearance of pancreatic cancer we cannot select those patients already having non detectable pancreatic cancer, at least with the imaging and biological techniques available today. We believe that more studies are necessary in order to definitively identify diabetes mellitus as a risk factor for pancreatic cancer taking into consideration that approximately 10 years are needed to diagnose symptomatic pancreatic cancer. At present, the answer to the as to whether diabetes and pancreatic cancer comes first similar to the adage of the chicken and the egg is that diabetes is the egg.

SEARCH STRATEGY

Taking into consideration diabetes mellitus irrespective of type, there is a lack of agreement regarding the data; thus, we decided to make an in-depth study of this topic. On July 24, 2012, we carried out a PubMed/Medline search using the following strategy: (“Diabetes Mellitus” [Mesh]...
or “Diabetes Mellitus, Type 2” [Mesh] or “Diabetes Mellitus, Type 1” [Mesh] and “Pancreatic Neoplasms” [Mesh] and (“humans” [MeSH Terms] and English [lang]); other papers were manually extracted from the references of the papers selected. From 1966, a total of 787 papers were found and, of these, we selected 74 papers[3-9] and nine meta-analyses[10-18].

### ANALYSIS OF LITERATURE AND CLINICAL CONSIDERATIONS

One of the first studies on the relationship between pancreatic cancer and diabetes is that of Maruchi et al[11] who found that there was an association between pancreatic carcinoma and diabetes from 1935 through 1974 only in cases of confirmed pancreatic carcinoma in residents of Olmsted County, Minnesota. In their series, 17% of the patients were diabetic (19/113) and nine cases (8%) of pancreatic cancer were found in patients who had had diabetes of ≥ 5 years 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.

Taking into account all findings in the literature, all the studies and the meta-analyses found an association between diabetes mellitus and pancreatic cancer at the time of diagnosis. However, little is known about glucose tolerance and insulin secretion in patients with this tumor. Gapstur et al[19] 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% CI) 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. 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. In addition, whereas postoperative diabetes was seen in all long-standing diabetic patients, and in some patients with intolerance fasting glucose and normal fasting glucose, the diabetes was resolved in more than 50% of patients with new-onset diabetes despite removal of half of the beta-cell mass[20]. Thus, it seems that diabetes is caused by pancreatic cancer. The answer to whether the diabetes is a specific marker of the disease comes from the study of Aggarwal et al[21]; these authors retrospectively reviewed the medical records of 500 consecutive patients with cancer (lung, breast, prostate, colorectal cancers and pancreatic cancer) and 100 non-cancer controls, and found that whereas the prevalence of diabetes mellitus in pancreatic cancer is high, diabetes mellitus prevalence in other common cancers is no different from that in non-cancer controls. Thus, diabetes mellitus is not useful as an early or specific marker of pancreatic cancer.

Controversies also exist between the association of long-standing diabetes mellitus and pancreatic cancer; some, epidemiological studies have exclude the possibility that long-standing diabetes mellitus is a risk factor for pancreatic cancer[22-26], whereas others (Table 1) have found a relation-
Pancreatic cancer and diabetes

It should be pointed out that, in papers showing an association between long standing diabetes and pancreatic cancer there are some biases due to self-reported diabetes which could result in misclassification, heterogeneity among individuals with diabetes in terms of physiologic status, sequelae and treatment which could also confuse this relationship. In addition, Yachida et al.\(^{[87]}\), sequencing the genomes of seven pancreatic cancer metastases to evaluate the clonal relationships among primary and metastatic cancers, found that clonal populations which give rise to distant metastases are represented within the primary carcinoma (but these clones are genetically evolved from the original parental, non-metastatic clone) and they performed a quantitative analysis of the timing of the genetic evolution of pancreatic cancer found at least a decade between the occurrence of the initiating mutation and the birth of the parental, non-metastatic founder cell. At least five more years are required for the acquisition of metastatic ability and patients usually die on an average of 2 years thereafter\(^{[86]}\).

Thus, even if diabetes is found a decade before the appearance of pancreatic cancer as reported in meta-analytic studies, we cannot select those patients already having non-detectable pancreatic cancer, at least with the imaging and biological techniques available today (Figure 1).

**CONCLUSION**

We believe that more studies are necessary in order to definitively identify diabetes mellitus as a risk factor for pancreatic cancer taking into consideration that approximately 10 years are needed to diagnose symptomatic pancreatic cancer. At present, the answer to the question posed by Magruder et al.\(^{[83]}\) as to whether diabetes and pancreatic cancer comes first similar to the adage of the chicken and the egg is that diabetes is the egg.

**REFERENCES**

1. Pezzilli R, Fabbri D, Imbrogno A. Pancreatic ductal adenocarcinoma screening: new perspectives. *World J Gastroenterol* 2012; 18: 4973-4977 [PMID: 23049204 DOI: 10.3748/wjg.v18.i36.4973]
2. Maruchi N, Brian D, Ludvig J, Elvebeck LR, Kurland LT. Cancer of the pancreas in Olmsted County, Minnesota, 1935-1974. *Mayo Clin Proc* 1979; 54: 245-249 [PMID: 423604]
3. Blot WJ, Fraumeni JF, Stone BJ. Geographic correlates of pancreatic cancer in the United States. *Cancer* 1978; 42: 373-380 [PMID: 667908]
4. Wynder EL. An epidemiological evaluation of the causes of cancer of the pancreas. *Cancer Res* 1975; 35: 2228-2233 [PMID: 1149034 DOI: 10.1002/1097-0142(197807)43:11<373::AID-CAN2803731>3.0.CO;2-Q]
5. Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K, Ohyanagi H, Fujiki T, Motojima K. A multi-institute case-control study on the risk factors of developing pancreatic cancer. *Ipn J Clin Oncol* 1992; 22: 286-291 [PMID: 1434027]
6. Bueno de Mesquita HB, Maisonneuve P, Poereman CJ, Walker AM. Aspects of medical history and exocrine carcinoma of the pancreas: a population-based case-control study in The Netherlands. *Int J Cancer* 1992; 52: 17-23 [PMID: 1500222 DOI: 10.1002/ijc.291052013]
7. Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. *Int J Cancer* 1989; 43: 415-421 [PMID: 2925272 DOI: 10.1002/ijc.291043013]
8. Norell S, Ahlbom A, Erwold R, Jacobson G, Lindberg-Navier I, Olins R, Wuchel KL. Diabetes, gall stone disease, and pancreatic cancer. *Br J Cancer* 1986; 54: 377-378 [PMID: 3741772 DOI: 10.1038/bjc.1986.185]
9. O’Mara BA, Byers T, Schoenfeld E. Diabetes mellitus and cancer risk: a multisite case-control study. *J Chronic Dis* 1985; 38: 435-441 [PMID: 3998058 DOI: 10.1016/0021-9681(85)90139-0]
10. Wynder EL, Mabuchi K, Maruchi N, Fortner JG. Epidemiology of cancer of the pancreas. *J Natl Cancer Inst* 1973; 50: 645-667 [PMID: 4350660]
11. Wynder EL, Mabuchi K, Maruchi N, Fortner JG. A case control study of cancer of the pancreas. *Cancer* 1973; 31: 641-648 [PMID: 4693593 DOI: 10.1002/1097-0142(197303)31<641::AID-CAN2803131>3.0.CO;2-3]
12. Levin DL, Connelly RR. Cancer of the pancreas. Available epidemiologic information and its implications. *Cancer* 1973; 31: 1231-1236 [PMID: 4705161]
13. Lowe WC, Palmer ED. Carcinoma of the pancreas. An analysis of 100 patients. *Am J Gastroenterol* 1967; 47: 412-420 [PMID: 5229081]
14. Karmody A, Kyle J. Diabetes mellitus and carcinoma of the pancreas. *Bull Soc Int Chir* 1968; 27: 119-124 [PMID: 5742753]
15. Karmody AJ, Kyle J. The association between carcinoma of the pancreas and diabetes mellitus. *Br J Surg* 1969; 56: 362-364 [PMID: 5781048 DOI: 10.1002/bjs.1800560512]
16. Morris DV, Nabarro JD. Pancreatic cancer and diabetes mellitus. *Diabet Med* 1984; 1: 119-121 [PMID: 6242787 DOI: 10.1111/j.1464-5491.1984.tb01941.x]
Andrén-Sandberg A, Hise I. Factors influencing survival after total pancreatectomy in patients with pancreatic cancer. *Ann Surg* 1983; 198: 605-610 [PMID: 6639161 DOI: 10.1097/00000658-198308000-00008].

Manousos O, Trichopoulos D, Koutselinis A, Papadimitrrou C, Polychronopoulos A, Zavitsanos X. Epidemiologic characteristic and traces elements in pancreatic cancer in Greece. *Cancer Detect Prev* 1981; 4: 439-442 [PMID: 7349806].

Chow WH, Gridley G, Nyrén O, Linet MS, Ekbom A, Fraumeni JF, Adami HO. Risk of pancreatic cancer following diabetes mellitus: a nationwide cohort study in Sweden. *J Natl Cancer Inst* 1995; 87: 930-931 [PMID: 7664683 DOI: 10.1093/jnci/87.12.930].

La Vecchia C, Negri E, Franceschi S, D’Avanzo B, Boyle P. A case-control study of diabetes mellitus and cancer risk. *Br J Cancer* 1994; 70: 950-953 [PMID: 7947103 DOI: 10.1038/bjc.1994.427].

Shibata A, Mack TM, Pagani-Hill A, Ross RK, Henderson BE. A prospective study of pancreatic cancer in the elderly. *Int J Cancer* 1994; 58: 46-49 [PMID: 8014014 DOI: 10.1002/ijc.2910580109].

Friedman GD, van den Eeden SK. Risk factors for pancreatic cancer: an exploratory study. *Int J Epidemiol* 1993; 22: 30-37 [PMID: 8449644 DOI: 10.1093/ije/22.1.30].

Balkau B, Eschenwe E, Richard J, Claude JR, Ducimetiere P. Diabetes and pancreatic carcinoma. *Diabetes* 1992; 41: 458-462 [PMID: 8056126].

Calle EE, Rodriguez C, Thun MJ, Henley SJ, Jemal A, Heath CW. Projecting cancer deaths in the US by major race/ethnicity, gender, and birth cohort groups. *Cancer* 2007; 109: 1827-1845 [PMID: 17215969 DOI: 10.1002/cncr.22682].

Lee CT, Chang FY, Lee SD. Risk factors for pancreatic cancer: an exploratory study. *Int J Cancer* 1981; 27: 143-149 [PMID: 17401636 DOI: 10.1007/s10552-007-9002-z].
Pezzili R et al. Is diabetes mellitus a risk factor for pancreatic cancer?

49 Hassan MM, Bondy ML, Wolf RA, Abbruzzese JL, Vauthey JN, Pisetsky EW, Evans DB, Khan R, Chou TH, Lenz R, Jiao L, Li D. Risk factors for pancreatic cancer: case-control study. Ann J Gastroenterol 2007; 102: 2696-2707 [PMID: 17764494 DOI: 10.1111/j.1572-0241.2007.01510.x]

50 Fyzenek JP, Garabrant DH, Schenk M, Kinnard M, Greenhorn JK, Sarkar FH. The association between selected risk factors for pancreatic cancer and the expression of p53 and K-ras codon 12 mutations. Int J Gastrointest Cancer 2006; 37: 139-145 [PMID: 18049799]

51 Chari ST, Leibson CL, Rabe KG, Timmons LJ, Ransom J, de Andrade M, Petersen GM. Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. Gastroenterology 2008; 134: 95-101 [PMID: 18061176 DOI: 10.1053/j.gastro.2007.10.040]

52 Pannala R, Leirness JB, Bamlot WR, Basu A, Petersen GM, Chari ST. Prevalence and clinical profile of cancer-associated diabetes mellitus. Gastroenterology 2008; 134: 981-987 [PMID: 18395079 DOI: 10.1053/j.gastro.2008.01.039]

53 Betty GD, Kivimaki M, Morrison D, Huxley R, Smith GD, Clarke R, Marmot MG, Shipley MJ. Risk factors for pancreatic cancer mortality: extended follow-up of the original Whitehall Study. Cancer Epidemiol Biomarkers Prev 2009; 18: 673-675 [PMID: 19190162 DOI: 10.1185/1055-9965.16881032]

54 Kuang TT, Jin da Y, Wang DS, Xu XF, Ni XL, Wu WC, Lou WH. Clinical epidemiological analysis of the relationship between pancreatic cancer and diabetes mellitus: data from a single institution in China. J Dig Dis 2009; 10: 26-29 [PMID: 19236544 DOI: 10.1111/j.1751-2980.2008.00359.x]

55 Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009; 137: 482-488 [PMID: 19375425 DOI: 10.1053/j.gastro.2009.04.013]

56 Ogunleye AA, Ogston SA, Morris AD, Evans JM. A cohort study of the risk of cancer associated with type 2 diabetes. Br J Cancer 2009; 101: 1199-1201 [PMID: 19690547 DOI: 10.1038/sj.bjc.6605240]

57 Chu CK, Mazo AE, Goodman M, Egnatashvili V, Sarmiento DA. Preoperative diabetes mellitus and long-term survival after resection of pancreatic adenocarcinoma. J Am Coll Surg 2009; 10: 502-513 [PMID: 19885697 DOI: 10.1245/s10434-009-0789-6]

58 Jamal MM, Yoon EJ, Vega KJ, Hashemzadeh M, Chang KJ. Diabetes mellitus as a risk factor for gastrointestinal cancer among American veterans. World J Gastroenterol 2009; 15: 5274-5278 [PMID: 19908334 DOI: 10.3748/wjg.v15.i52.5274]

59 Maisonneuve P, Lowenfels AB, Bueno-de-Mesquita HB, Ghadirian P, Baghurst PA, Zatonski WA, Miller AB, Duell EJ, Boffetta P, Boyle P. Past medical history and pancreatic cancer risk: Results from a multicenter case-control study. Ann Epidemiol 2010; 20: 92-98 [PMID: 21231596 DOI: 10.1016/j.annepidem.2009.11.010]

60 Olson SH, Chou JF, Ludwig E, O’Reilly E, Allen PJ, Jarnagin WR, Bayuga S, Simon J, Gonen M, Reisacher WR, Kurtz RC. Allergies, obesity, other risk factors and survival from pancreatic cancer. Int J Cancer 2010; 127: 2412-2419 [PMID: 20433955 DOI: 10.1002/ijc.25240]

61 Hemminki K, Li X, Sundquist J, Sundquist K. Risk of cancer following hospitalization for type 2 diabetes. Oncologist 2010; 15: 548-555 [PMID: 20497276 DOI: 10.1634/theoncologist.2009-0500]

62 Price S, Cole D, Alcaldo JC. Diabetes due to exocrine pancreatic disease—a review of patients attending a hospital-based diabetes clinic. QJM 2010; 103: 759-763 [PMID: 20650969 DOI: 10.1093/qjmed/hcq127]

63 Ben Q, Cai Q, Li Z, Yuan Y, Ning X, Deng S, Wang K. The relationship between new-onset diabetes mellitus and pancreatic cancer risk: a case-control study. Eur J Cancer 2011; 47: 248-254 [PMID: 20709528 DOI: 10.1016/j.ejca.2011.03.003]
C-peptide levels in relation to pancreatic cancer risk: a study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Diabetologia* 2011; **54**: 3037-3046 [PMID: 21953276 DOI: 10.1007/s00125-011-2316-0]

**75** Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of antidiabetic agents and the risk of pancreatic cancer: a case-control analysis. *Am J Gastroenterol* 2012; **107**: 620-626 [PMID: 22290402 DOI: 10.1038/ajg.2011.483]

**76** Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. *JAMA* 1995; **273**: 1605-1609 [PMID: 7745774 DOI: 10.1001/jama.1995.03520440059037]

**77** Noy A, Bilezikian JP. Clinical review 63: Diabetes and pancreatic cancer: clues to the early diagnosis of pancreatic malignancy. *J Clin Endocrinol Metab* 1994; **79**: 1223-1231 [PMID: 7962312 DOI: 10.1210/jc.79.5.1223]

**78** Fisher WE. Diabetes: risk factor for the development of pancreatic cancer or manifestation of the disease? *World J Surg* 2001; **25**: 503-508 [PMID: 11396427 DOI: 10.1007/s002680020344]

**79** Berrington de Gonzalez A, Sweetland S, Spencer E. A meta-analysis of obesity and the risk of pancreatic cancer. *Br J Cancer* 2003; **89**: 519-523 [PMID: 12888824 DOI: 10.1038/sj.bjc.6601140]

**80** Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005; **92**: 2076-2083 [PMID: 15886696 DOI: 10.1038/sj.bjc.6602619]

**81** Ansary-Moghaddam A, Huxley R, Barzi F, Lawes C, O’ku-bo T, Fang X, Jee SH, Woodward M. The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 2435-2440 [PMID: 17164367 DOI: 10.1158/1055-9965.EPI-06-0368]

**82** Stevens RJ, Roddam AW, Beral V. Pancreatic cancer in type 1 and young-onset diabetes: systematic review and meta-analysis. *Br J Cancer* 2007; **96**: 507-509 [PMID: 17224924 DOI: 10.1038/sj.bjc.6603571]

**83** Magruder JT, Elahi D, Andersen DK. Diabetes and pancreatic cancer: chicken or egg? *Pancreas* 2011; **40**: 339-351 [PMID: 21412116 DOI: 10.1097/MPA.0b013e318209e05d]

**84** Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, Zhang H, Li Z. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. *Eur J Cancer* 2011; **47**: 1928-1937 [PMID: 21458985]

**85** Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A. Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA* 2000; **283**: 2552-2558 [PMID: 10815119 DOI: 10.1001/jama.283.19.2552]

**86** Aggarwal G, Kamada P, Chari ST. Prevalence of diabetes mellitus in pancreatic cancer compared to common cancers. *Pancreas* 2013; **42**: 198-201 [PMID: 23000893]

**87** Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, Kamiyama M, Hruban RH, Eshleman JR, Nowak MA, Velculescu VE, Kinzler KW, Vogelstein B, Iacobuzio-Donahue CA. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature* 2010; **467**: 1114-1117 [PMID: 20981102 DOI: 10.1038/nature09515]

**P- Reviewers** Chiaro MD, Pastromas S, Tarantino G
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