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REVIEW

Is diabetes mellitus a risk factor for pancreatic cancer?

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Abstract

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.

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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[1].

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]

Table 1 Diabetes as a risk factor for pancreatic cancer according to diabetes duration

Meta-analysis	Studies evaluated (*n*)		Diabetes duration (yr)	Risk	95%CI
Everhart *et al*[76]	20	All studies evaluated	> 1	RR = 2.1	1.6-2.8
	11	All case-control studies	> 1	RR = 1.8	1.1-2.7
	9	All cohort studies	> 1	RR = 2.6	1.6-4.1
	11	All studies	> 5	RR = 2.0	1.2-3.2
	6	All case-control studies	> 5	RR = 1.8	0.86-3.8
	6	All cohort studies	> 5	RR = 2.4	0.85-7.0
Li *et al*[64]	3		≤ 2	OR = 2.9	2.1-3.9
	3		3-5	OR = 1.9	1.3-2.6
	3		6-10	OR = 1.6	1.2-2.3
			11-15	OR = 1.3	0.9.2.0
			> 15	OR = 1.4	1.0-2.0
Huxley *et al*[80]	9		1-4	RR = 2.05	1.87-2.25
	9		5-9	RR = 1.54	1.31-1.81
	7		≥ 10	RR = 1.51	1.16-1.96
Ben *et al*[84]	3		< 1	RR = 5.38	3.49-8.30
	5		1-4	RR = 1.95	1.65-2.31
	4		5-9	RR = 1.49	1.05-2.12
	4		≥ 10	RR = 1.47	0.94-2.31

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[2-75] and nine meta-analyses[76-84].

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*[2] 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 diabetes had appeared at least 2 years before the diagnosis of pancreatic cancer. Twenty years later, our group carried out a case-control study matching a large number of patients with and without pancreatic cancer[24]. 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 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*[85] 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[52]. 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*[86]; 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 excluded the possibility that long-standing diabetes mellitus is a risk factor for pancreatic cancer[2,6,24,32,36,41,44,45,51,52,54,59,60,64,70] whereas others (Table 1) have found a relation-

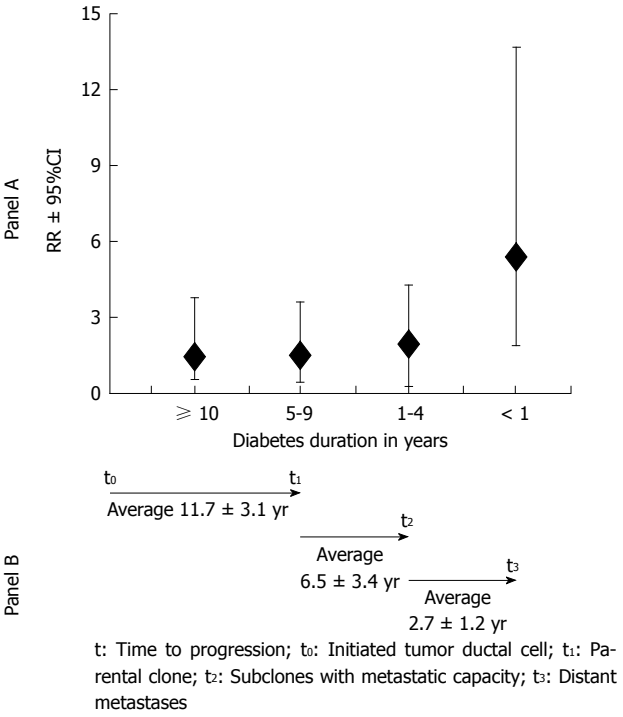

Figure 1 Relative risks and quantitative analysis. Panel A: Relative risks (RR) for the association between diabetes and pancreatic cancer according to the duration of the diabetes (originated from[63]). The risk disappears after 10 years; Panel B: Quantitative analysis of the timing of the genetic evolution of pancreatic cancer indicates that at least a decade is necessary between the occurrence of the initiating mutation and the birth of the parental, non-metastatic founder cell, that at least five more years are required for the acquisition of metastatic ability and patients usually die on an average of 2 years thereafter (originated from[87]).

ship[3-5,7-31,33,35,37-40,42,43,46-49,53,55-58,61,63,65-69,71-75]. 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 die an average of 2 years thereafter[87]. 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.

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