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Metabolic syndrome and pancreatic cancer risk: a case-control study in Italy and meta-analysis

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ABSTRACT

We assessed the relation between metabolic syndrome (MetS), its components, and pancreatic cancer risk in an Italian case-control study and performed a meta-analysis of epidemiological studies published up to February 2011. The case-control study included 326 patients with incident pancreatic cancer and 652 controls admitted to the same hospitals for acute, non-neoplastic conditions. MetS was defined as having at least 3 conditions among diabetes, drug-treated hypertension, hyperlipidemia, and body mass index at least 25 kg/m^2 at age 30 years. We computed multivariate odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) from logistic regression models adjusted for tobacco smoking, education, and other sociodemographic variables. For the meta-analysis, we calculated summary relative risks (RRs) using random-effects models. The OR of pancreatic cancer in the case-control study was 2.36 (95% CI, 1.43-3.90) for diabetes, 0.77 (95% CI, 0.55-1.08) for hypertension, 1.38 (95% CI, 0.94-2.01) for hypercholesterolemia, and 1.27 (95% CI, 0.91-1.78) for being overweight at age 30 years. The risk was significantly increased for subjects with 3 or more MetS components (OR = 2.13, 95% CI 1.01-4.49) compared with subjects with no component, the estimates being consistent among strata of sex, age, and alcohol consumption. The meta-analysis included 3 cohort studies and our case-control study, and found a summary RR of 1.55 (95% CI, 1.19-2.01) for subjects with MetS. Metabolic syndrome is related to pancreatic cancer risk. Diabetes is the key component related to risk.

1. Introduction

Pancreatic cancer is the fifth cause of cancer deaths in Europe [1] and is characterized by late diagnosis, poor prognosis, and limited opportunities for prevention. Cigarette smoking, high alcohol drinking, diabetes, pancreatitis, and family history are established risk factors for pancreatic cancer [2]; but they explain only a small proportion of cases [3].

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The metabolic syndrome (MetS) is a complex of interrelated conditions including insulin resistance, dyslipidemia, hypertension, and central obesity [4]. Several studies have suggested that MetS may play a role in breast, endometrial [5,6], and colorectal [7] cancers.

Although several epidemiological studies considered the relation of pancreatic cancer with diabetes and other single MetS components [8], a few studies only evaluated the relation with combinations of MetS components. An Italian record-linkage study including 43 pancreatic cancer cases reported an overall standardized incidence ratio of 1.62 (95% confidence interval [CI], 1.17-2.18) for subjects with a combined therapy for antihypertensive, hypolipid, and hypoglycemic drugs [9]. A Japanese cohort study found a relative risk (RR) of pancreatic cancer of 1.80 (95% CI, 0.94-3.45) in 41 overweight female cases with at least 3 MetS components, but found no relation in men [10]. In another cohort of US men, the RR for pancreatic cancer mortality was 1.38 (95% CI, 0.76-2.49, based on 58 cases) for those with *MetS*, defined as having at least 3 conditions among abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, hypertension, hyperglycemia, or diabetes [11]. The Metabolic Syndrome and Cancer Project, based on 7 cohorts from Austria, Norway, and Sweden, found an RR of 1.58 (95% CI, 1.34-1.87) for a continuous MetS score based on body mass index (BMI), blood pressure, glucose, cholesterol, and triglyceride levels among 315 female cases, but found no relation in men [12].

We assessed whether diabetes and other components of MetS (ie, hypercholesterolemia, hypertension, and obesity) are associated with the risk of pancreatic cancer using data from a multicentric Italian study. Moreover, we combined all published data using a meta-analytic approach to provide an overall quantitative estimate of this association.

2. Materials and methods

2.1. Case-control study

We conducted a case-control study on pancreatic cancer between 1991 and 2008 in the provinces of Milan and Pordenone, Northern Italy [13]. Cases were 326 subjects (174 men and 152 women; median age, 63 years; range, 34-80 years) with incident pancreatic cancer, admitted to major teaching and general hospitals in the study areas, with no previous history of cancer. Controls were 652 subjects (348 men and 304 women; median age, 63 years; range, 34-80 years) selected among patients admitted to the same hospitals of cases for a wide spectrum of acute non-neoplastic conditions, frequency-matched to cases by age, sex, and study center. Thirty-one percent of controls were admitted for traumatic orthopedic disorders, 31% for other orthopedic disorders, 28% for acute surgical conditions, and 10% for miscellaneous other illnesses, including eye, nose, ear, skin, or dental disorders. Less than 5% of cases and controls approached refused to participate, and all patients gave informed consent.

Trained personnel interviewed cases and controls during their hospital stay using a structured questionnaire, including information on sociodemographic characteristics, anthropometric measures at various ages, lifestyle habits (eg, tobacco smoking, alcohol drinking, and dietary habits), personal history of selected medical conditions, and menstrual and reproductive factors for women. Information on clinical diagnosis of medical conditions, including diabetes, drug-treated hypertension, and hypercholesterolemia, were self-reported and included age at diagnosis. Diseases whose onset was less than 1 year before the interview were not considered. Height and weight were also self-reported, and BMI was computed according to the Quetelet index (weight/height^2, kilograms per square meter).

MetS was defined as the combined presence of at least 3 of the following factors: (1) diabetes, (2) drug-treated hypertension (as an indicator of elevated blood pressure), (3) clinical diagnosis of hypercholesterolemia, and (4) BMI at least 25 kg/m^2 at age 30 years (as a measure of central obesity). When the last information was missing (16 cases and 37 controls), subjects were excluded from the analyses on combined MetS components.

We estimated the odds ratios (ORs) and the corresponding 95% CIs by multiple logistic regression models [14], including terms for age (quinquennium), study center, year of interview (continuous), education (<7, 7-11, ≥12 years, categorically), and tobacco smoking (never, former, current smokers of <15 and ≥15 cigarettes per day, categorically). We built additional models to assess the potential modifying effect of selected covariates. All statistical analyses were performed with SAS 9.1 statistical software (SAS Institute, Cary, NC).

2.2. Meta-analysis

We performed a MEDLINE search in PubMed to identify all epidemiological studies on MetS and pancreatic cancer published up to February 2011 using the string '(pancreas OR pancreatic OR "digestive tract") AND (cancer OR neoplasm OR carcinoma) AND ("metabolic syndrome" OR "syndrome X" OR "metabolic factors")', limiting the search to English-language articles [15]. Two authors, VR and AT, independently selected articles reporting data on the association between MetS as a single entity and pancreatic cancer risk. They also searched in the reference lists of the articles retrieved to obtain other pertinent publications. Unpublished results were not included. No studies were excluded a priori for weakness of design or data quality.

For each study, we extracted data on study design, country, number of subjects (number of cases and non-cases or cohort size), definition of MetS, covariates included in the analysis, RR estimates, and the corresponding 95% CIs. Whenever available, we considered multivariate risk estimates adjusted for the largest number of potential confounding factors.

Summary RRs were calculated using random-effects models considering both within-study and between-study variations [16]. Study-specific and overall RRs were presented using forest plot. In forest plot, the area of the square is proportional to the inverse of the variance of the natural logarithm of the RR, thus giving a measure of the amount of information available from each estimate. A diamond was used to plot the summary RRs, the center of which represents the RR estimates and the extremes of which show the 95% CIs.

3. Results

3.1. Case-control study

Table 1 shows the distribution of pancreatic cancer cases and controls and corresponding ORs according to individual components of MetS and their combination. Compared with patients without the corresponding disorder, the OR of pancreatic cancer was 2.36 (95% CI, 1.43-3.90) for diabetes, 0.77 (95% CI, 0.55-1.08) for hypertension, 1.38 (95% CI, 0.94-2.01) for hypercholesterolemia, and 1.27 (95% CI, 0.91-1.78) for being overweight at 30 years. Compared with subjects with no MetS component, the OR was 2.13 (95% CI, 1.01-4.49) for those with at least 3 components, with a significant trend in risk. The OR was 1.20 (95% CI, 1.00-1.43) for an increase of 1 component. When we excluded diabetes from MetS, the OR of pancreatic cancer was 1.05 (95% CI, 0.75-1.47) for subjects with 1 component, 1.26 (95% CI, 0.79-1.99) for subject with 2 components, and 1.52 (95% CI, 0.52-4.46) for subjects with 3 components of MetS.

The OR was similar in younger (<60 years) and older (≥60 years) subjects and in men and women, but somewhat stronger in abstainers/low alcohol drinkers (<7 drinks per week) than in moderate/heavy drinkers (≥7 drinks per week) (Table 2). However, no significant heterogeneity emerged across strata of the covariates considered.

Table 3 shows the combined effect of MetS and smoking on the risk of pancreatic cancer. Compared with never smokers with no component of MetS, the OR reached 2.62 (95% CI, 0.93-7.38) in ever smokers with at least 3 components of MetS.

Table 1 – Distribution of 326 cases of pancreatic cancer and 652 controls, and odds ratios (OR) with corresponding 95% confidence intervals (CI), according to individual components of metabolic syndrome (MetS) (Italy, 1991-2008)

Components	Cases	Controls	OR (95% CI) [a]
	n (%)	n (%)	
Diabetes			
No	279 (85.6)	615 (94.3)	1 [b]
Yes	47 (14.4)	37 (5.7)	2.36 (1.43-3.90)
Drug-treated hypertension			
No	239 (73.3)	474 (72.7)	1 [b]
Yes	87 (26.7)	178 (27.3)	0.77 (0.55-1.08)
Hypercholesterolemia			
No	259 (79.4)	555 (85.1)	1 [b]
Yes	67 (20.6)	97 (14.9)	1.38 (0.94-2.01)
BMI ≥25 kg/m^2 at age 30 y [c]			
No	214 (69.0)	460 (74.8)	1 [b]
Yes	96 (31.0)	155 (25.2)	1.27 (0.91-1.78)
No. of MetS components [c]			
None	122 (39.4)	289 (47.0)	1 [b]
1	107 (34.5)	226 (36.7)	1.03 (0.73-1.46)
2	60 (19.4)	84 (13.7)	1.34 (0.86-2.09)
≥3	21 (6.8)	16 (2.6)	2.13 (1.01-4.49)
P for trend			.048
Increment of 1 component of MetS			1.20 (1.00-1.43)

[a] Estimates from logistic regression models adjusted for sex, age, study center, year of interview, education, and tobacco smoking.
[b] Reference category.
[c] The sum does not add up to the total because of some missing values.

Table 2 – Odds ratios (OR) and corresponding 95% confidence intervals (CI) according to number of metabolic syndrome (MetS) components in strata of selected covariates (Italy, 1991-2008)

Covariates	No. of MetS components, OR (95% CI) [a]			
	0	1	2	≥3
Age (y)				
<60	1 [b]	1.12 (0.62-2.00)	1.66 (0.70-3.93)	1.87 (0.46-7.63)
≥60	1 [b]	1.01 (0.65-1.57)	1.27 (0.75-2.15)	1.88 (0.77-4.59)
Sex				
Men	1 [b]	0.88 (0.54-1.42)	1.29 (0.73-2.28)	2.07 (0.87-4.94)
Women	1 [b]	1.36 (0.80-2.33)	1.50 (0.71-3.16)	2.10 (0.47-9.34)
Alcohol consumption (drinks/wk)				
<7	1 [b]	1.12 (0.58-2.15)	1.29 (0.56-2.99)	3.45 (0.64-18.7)
≥7	1 [b]	1.01 (0.66-1.55)	1.44 (0.85-2.46)	1.96 (0.84-4.59)

[a] Estimates from logistic regression models adjusted for sex, age, study center, year of interview, education, and smoking habit.
[b] Reference category.

3.2. Meta-analysis

Besides the present case-control study, we identified 4 cohort studies [9-12] considering the association between MetS and pancreatic cancer risk. The main characteristics of these studies are summarized in Table 4. The studies were conducted in Italy [9], Japan [10], United States [11], and northern Europe (Austria, Norway, Sweden) [12]. All studies showed estimates by sex, except 1 study that included men only [11]. In our study, we calculated the OR for subjects with at least 3 MetS components compared with 2 or less for consistency with other studies. One study with 862 subjects with pancreatic cancer [12] was excluded because of reporting a continuous MetS score, calculated by summarizing 5 (BMI, mid-blood pressure, glucose, cholesterol, and triglycerides) individual standardized scores. Thus, there were 4 studies for a total of 490 cancers of the pancreas (278 men and 212 women).

Table 3 – Distribution of 326 cases of pancreatic cancer and 652 controls, odds ratios (OR) with corresponding 95% confidence intervals (CI), according to number of metabolic syndrome (MetS) components and smoking habit (Italy, 1991-2008)

No. of MetS components	Smoking habit			
	Never smoker		Ever smoker	
	Ca:Co [a]	OR (95% CI) [b]	Ca:Co [a]	OR (95% CI) [b]
None	49:137	1 [c]	72:150	1.37 (0.84-2.22)
1	47:123	0.97 (0.58-1.61)	60:101	1.40 (0.84-2.33)
2	22:36	1.21 (0.61-2.40)	38:48	1.98 (1.08-3.65)
≥3	9:8	2.17 (0.73-6.45)	12:8	2.62 (0.93-7.38)

Ca:Co indicates number of cases:controls.
[a] The sum does not add up to the total because of missing values.
[b] Estimates from logistic regression models adjusted for sex, age, study center, year of interview, and education.
[c] Reference category.

Table 4 – Main characteristics of the studies on metabolic syndrome (MetS) and pancreatic cancer risk

Study [reference]	Country	No. of cases (sex)	Size of cohort/ no. of controls	Definition of the MetS	MetS, highest vs lowest category	Adjustment factors
Cohort studies						
Russo et al [9]	Italy	24 (M) 19 (W)	16 677	Combined therapy for antihypertensive, hypolipid, and hypoglycemic drugs	SIRs for subjects with ≥3 components compared with cancer registry	
Inoue et al [10]	Japan	24 (M) 41 (W)	9 548 (M) 18 176 (W)	At least 3 of the following: (a) high glucose, (b) high blood pressure, (c) high triglycerides, (d) low HDL cholesterol, and (e) overweight	≥3 vs ≤2 components	Age, study area, smoking status, weekly ethanol intake, and total serum cholesterol
Matthews et al [11]	United States	56 (M) deaths	33 230 (M)	At least 3 of the following: (a) high glucose, (b) high blood pressure, (c) high triglycerides, (d) low HDL cholesterol, and (e) abdominal obesity	≥3 vs ≤2 components	Age, examination year, height, current smoking, alcohol intake, family history of cancer, and treadmill test duration
Johansen et al [12]	Austria, Norway, Sweden	547 (M) 315 (W)	288 976 (M) 288 339 (W)	Z score of the following components: (a) glucose, (b) mid-blood pressure, (c) cholesterol, (d) triglycerides, and (e) overweight	Continuous	Age and smoking status
Case-control study						
Rosato et al, 2011 [present study]	Italy	174 (M) 152 (W)	348 (M) 304 (W)	At least 3 of the following self-reported components: (a) diabetes, (b) drug-treated hypertension, (c) clinical diagnosis of hypercholesterolemia, and (d) overweight at age 30 y	≥3 vs ≤2 components	Age, study center, year of interview, education, and smoking habit

M indicates men; W, women; SIR, standardized incidence ratio.

Fig. 1 shows the risk estimates of pancreatic cancer for subjects with MetS in each study. The pooled RR was 1.46 (95% CI, 1.04-2.04) for cohort studies and 1.55 (1.19-2.01) for all studies combined, with no significant heterogeneity between studies (P for heterogeneity = .338). The RR estimates were above unity for all studies, except for men in the Japanese cohort (RR = 0.28) [10]. In analysis stratified by sex, a somewhat stronger association was observed in women (RR = 1.57; 95% CI, 1.08-2.28; P for heterogeneity = .867; I^2 = 0.0%) than in men (RR = 1.40; 95% CI, 0.83-2.37; P for heterogeneity = .088; I^2 = 54.1%), although the 2 estimates were not significantly heterogeneous (P = .727). When we excluded the study considering cancer mortality [11], the RR for MetS was 1.57 (95% CI, 1.13-2.17). When we included the study reporting the risk estimate as a continuous score, the RR was 1.37 (95% CI, 1.07-1.76) for cohort studies and 1.41 (95% CI, 1.12-1.78) overall.

4. Discussion

In our case-control study, subjects with MetS had a more than 2-fold increased risk of developing pancreatic cancer. Diabetes is the single risk factor explaining most of the excess risk.

Information on history of the selected components of MetS was obtained through a questionnaire including history of clinical diagnosis of diabetes, drug-treated hypertension, and hypercholesterolemia, rather than obtaining direct values of fasting serum glucose levels, blood pressure, fasting serum triglycerides, and high-density lipoprotein cholesterol. This may lead to an underreporting of the real prevalence of such conditions, with a selection of subjects with more severe diseases. The information on medical conditions has been shown to be satisfactory in our questionnaire [17]; and hospital controls are more comparable to cases than population controls, as they are similarly sensitized toward recalling history of diseases and medical treatments [14]. Moreover, the comparable catchment areas and the high participation of cases and controls should have reduced any possible selection bias.

Diabetes is a recognized risk factor for pancreatic cancer [18-21]. However, it is debated whether diabetes is a causal risk factor or, on the opposite, pancreatic cancer causes diabetes. We considered only diagnosis of diabetes, as well as of other medical conditions, occurring at least 1 year before diagnosis of pancreatic cancer for cases or interview for controls to limit the potential for recognition of diabetes during the process of pancreatic cancer diagnosis (surveillance bias). We found a 2-fold increase in pancreatic cancer risk in diabetics, in agree-

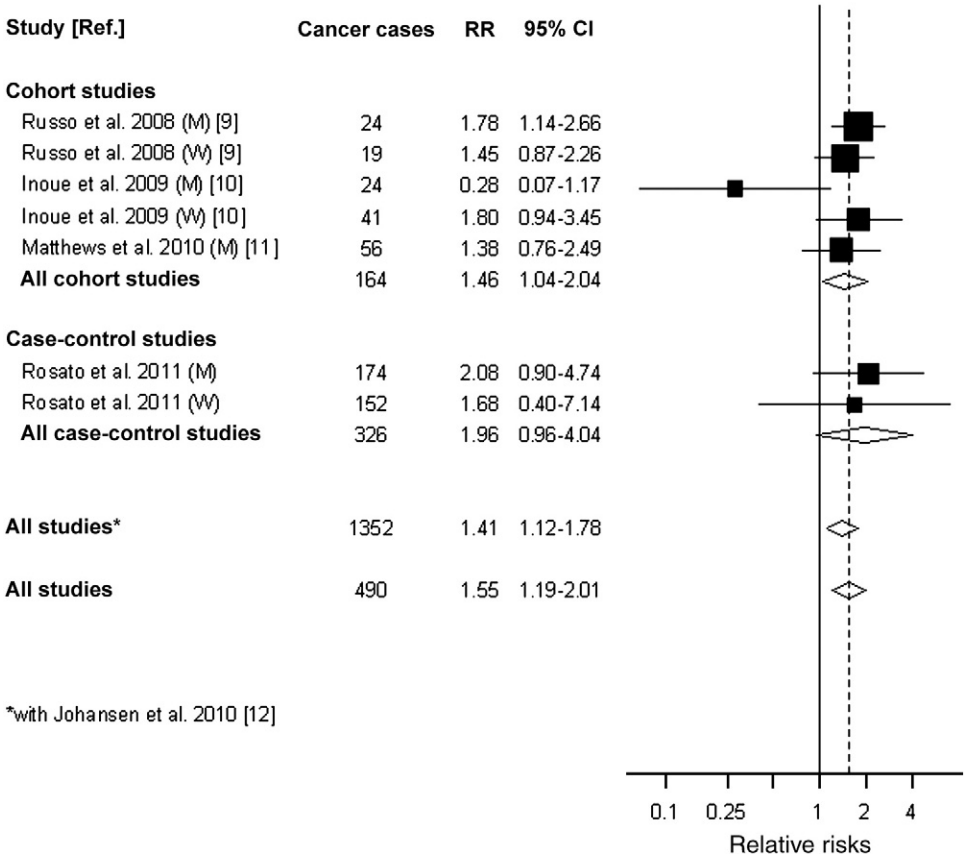

Fig. 1 – Meta-analysis of studies of the relation between metabolic syndrome and pancreatic cancer risk. Black squares indicate the relative risk (RR) in each study, with the square size proportional to the weight of the study in the meta-analysis and the horizontal lines represent 95% confidence intervals (CI). Random-effects model. M indicates men; W, women.

ment with a meta-analysis published in 2005 giving an RR of 1.82 (95% CI, 1.66-1.89) in patients with type 2 diabetes [19]. The combined analysis of the present study and another Italian case-control study, including overall 688 pancreatic cancer cases and 2204 controls, found an OR of pancreatic cancer of 2.74 (95% CI, 2.04-3.67), with a stronger association for a more recent diagnosis of diabetes; but the association persisted for at least 10 years before pancreatic cancer diagnosis [18].

Pancreatic cancer risk has been associated with overweight and obesity [22]. However, given the weight loss resulting from the disease [23], case-control studies are inadequate to assess the role of recent BMI [24]. To avoid such a bias, we used BMI at 30 years rather than recent BMI or waist circumference, as a body weight measurement.

With reference to the other factors in MetS, that is hypercholesterolemia and hypertension, we found no significant relations, consistently with the overall epidemiological evidence [25-27].

Our findings are in agreement with those of other studies considering the relation of pancreatic cancer with both MetS and its single components. Inoue et al [10] found a 2-fold borderline significant increased risk of pancreatic cancer for MetS, but no relation with each single component, in women, whereas there was no relation in men. Johansen et al [12] found a quantitatively similar increased risk for MetS, high glucose levels, and hypertension in women, and a significantly increased risk for high glucose levels, in the absence of a relation for MetS, in men.

Our meta-analysis summarized the studies evaluating the association between MetS as a single entity and pancreatic cancer risk [9-11] and found a significant increase in pancreatic cancer risk in subjects with MetS. This was consistent between prospective studies and our case-control study, and slightly stronger association in women (RR = 1.57) than in men (RR = 1.40). The inclusion of the Metabolic Syndrome and Cancer Project study defining MetS as a continuous score rather than a categorical variable (number of MetS components) did not materially change the results. The small number of studies did not allow further stratified analysis.

Possible mechanisms to explain such an association include hyperinsulinemia that may promote cell proliferation in pancreatic cancer cells through its mitogenic activity and by increasing the synthesis of insulin-like growth factor–I (IGF-I) [28]. Adipocytes and hyperglycemia induce elevation of insulin and IGF-I [29], which in turn stimulate cell proliferation, again pointing to diabetes as the key component of MetS in pancreatic cancer risk. Another possible mechanism include the effect of adiponectin, a protein secreted by adipocytes. Adiponectin levels are lower in diabetics and are negatively related with plasma glucose and insulin concentration, although it is not clear whether this is a cause or a consequence of insulin resistance [30]. Moreover, hypoadiponectinemia may be considered an independent risk factor for hypertension and has also been

associated with an atherosclerotic lipid profile, as it is an independent predictor of high-density-lipoproteins, low-density-lipoproteins, and very low-density-lipoproteins [30,31]. Thus, low adiponectin levels are a common characteristic of MetS components. Moreover, adiponectin levels have been shown to inhibit endothelial cell proliferation and migration [32] and have been implicated in the etiology of several cancers [33,34], particularly pancreatic cancer [35]. Furthermore, pancreatic cancer tumor tissue had positive expression of the adiponectin receptor AdipoR1 and AdipoR2. However, the results of studies relating adiponectin tissue levels with pancreatic cancer are inconsistent [35].

In conclusion, our study shows a significant trend between number of MetS components and pancreatic cancer risk. The key component of MetS in pancreatic carcinogenesis appears to be diabetes. These findings further indicate the importance of controlling overweight and related medical conditions.

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