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ORIGINAL ARTICLE

Risk factors for gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs): a three-centric case–control study

T. Feola[1,2] · G. Puliani[1,3] · F. Sesti[1] · R. Modica[4] · R. Centello[1] · R. Minotta[4] · G. Cannavale[4] · S. Di Meglio[4] · V. Di Vito[1] · R. Lauretta[3] · M. Appetecchia[3] · A. Colao[4] · A. Lenzi[1] · A. M. Isidori[1] · A. Faggiano[5] · E. Giannetta[1]

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Abstract

Purpose Risk factors for sporadic GEP-NENs are still not well defined. To identify the main clinical risk factors represents the aim of this study performed by three Italian referral centers for NENs.

Methods We performed a retrospective case–control study including 148 consecutive sporadic GEP-NENs and 210 age- and sex-matched controls. We collected data on clinical features, cancer family history and other potential risk factors.

Results Mean age was 58.3 ± 15.8 years; 50% males, primary site was pancreas (50.7%), followed by ileum (22.3%). The 62.8% and 29.1% of cases were G1 and G2, respectively; the 40% had locally advanced or metastatic disease at diagnosis. Independent risk factors for GEP-NENs were: family history of non-neuroendocrine GEP cancer (OR 2.16, 95% CI 1.31–3.55, $p = 0.003$), type 2 diabetes mellitus (T2DM) (OR 2.5, 95% CI 1.39–4.51, $p = 0.002$) and obesity (OR 1.88, 95% CI 1.18–2.99, $p = 0.007$). In the T2DM subjects, metformin use was a protective factor (OR 0.28, 95% CI 0.08–0.93, $p = 0.049$). T2DM was also associated with a more advanced (OR 2.39, 95% CI 1.05–5.46, $p = 0.035$) and progressive disease (OR 2.47, 95% CI 1.08–5.34, $p = 0.03$). Stratifying cases by primary site, independent risk factors for pancreatic NENs were T2DM (OR 2.57, 95% CI 1.28–5.15, $p = 0.008$) and obesity (OR 1.98, 95% CI 1.11–3.52, $p = 0.020$), while for intestinal NENs family history of non-neuroendocrine GEP cancer (OR 2.46, 95% CI 1.38–4.38, $p = 0.003$) and obesity (OR 1.90, 95% CI 1.08–3.33, $p = 0.026$).

Conclusion This study reinforces a role for family history of non-neuroendocrine GEP cancer, T2DM and obesity as independent risk factors for GEP-NENs and suggests a role of metformin as a protective factor in T2DM subjects. If confirmed, these findings could have a significant impact on prevention strategies for GEP-NENs.

Keywords Gastroenteropancreatic neuroendocrine neoplasms · GEP-NET · Diabetes mellitus · Obesity · Cancer family history · Metformin

T. Feola and G. Puliani contributed equally to this work.

✉ E. Giannetta
elisa.giannetta@uniroma1.it

1 Department of Experimental Medicine, "Sapienza" University of Rome, Viale Regina Elena, 324, 00161 Rome, Italy

2 Neuroendocrinology, Neuromed Institute, IRCCS, Pozzilli, Italy

3 Oncological Endocrinology Unit, Regina Elena National Cancer Institute, IRCCS, Rome, Italy

4 Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

5 Endocrinology Unit, Department of Clinical and Molecular Medicine, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy

Introduction

The gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are heterogeneous tumors, arising from the diffuse neuroendocrine system of the gastrointestinal tract and pancreas. According to the last World Health Organization (WHO) classification, GEP-NENs are classified into well-differentiated neoplasms, the neuroendocrine tumors (GEP-NETs), and poorly differentiated ones, the neuroendocrine carcinomas (GEP-NECs) [1]. The annual worldwide incidence of GEP-NENs has been steadily increasing over last decades, mainly reflecting the improvement in diagnostic procedures [2]. However, the increased incidence could be explained also by a rise of the exposure to risk factors for the occurrence of GEP-NENs.

In few conditions, the risk factors for GEP-NEN development are well known. In the inherited syndromes, such as Multiple Neuroendocrine Neoplasia type 1 (MEN1), the *MEN1* gene mutation is the main contributor. The achlorhydria of the atrophic gastritis has been demonstrated as a clear predisposing condition of type I gastric NENs [2]. However, in the majority of sporadic GEP-NENs the risk factors are still not well defined.

In the last 30 years, some heterogeneous, although well described, case–control studies investigated potential clinical risk factors for GEP-NENs: family history of cancer, smoking habit, alcohol consumption, high body mass index (BMI), previous cholecystectomy, chronic diseases such as diabetes mellitus (DM), inflammatory bowel disease, and some medical treatments [3–15]. These studies present often conflicting results; therefore, some meta-analyses were performed. The main results were that, according to the primary site, a first degree family history of cancer and DM would be relevant risk factors for GEP-NENs [16], cigarette smoking and alcohol consumption were associated with a high risk of pancreatic NENs (pNENs), while smoking was a risk factor for small intestinal NENs [17]. However, the published meta-analyses are limited by the heterogeneity across the studies relative to the population sample (small series), the different definitions used to identify and categorize the risk factors, and the study design (prospective, retrospective, registry data), making it difficult to draw definitive conclusions. Moreover, only two studies investigated the prognostic role of the risk factors, analyzing their distribution according to NEN stage and grading, showing that DM, particularly in case of non-recently-onset, is associated to a more advanced and aggressive disease [4, 12]. A recent interesting study showed that also metabolic syndrome is more frequent in GEP-NETs and associated with more aggressive clinical-pathological features [18].

This case–control study, although limited to three Italian centers with a small number of patients and controls enrolled, aims at identifying the main clinical, metabolic, lifestyle habits risk factors in patients with sporadic GEP-NENs.

Materials and methods

Study design and participants

Study design was retrospective, three-center case–control. The study population included 148 patients affected by sporadic GEP-NEN and 210 age- and sex-matched controls, affected by benign thyroid disease. Controls came from the same area of residence, thus from the same socio-cultural background, of GEP-NEN patients. Cases were selected in three different Italian centers: Sapienza Endocrinology Department (Rome), Regina Elena National Cancer Institute IRCCS (Rome), Federico II Hospital (Naples). Inclusion criteria were: (1) age higher than 18 years; (2) confirmed histological or cytological diagnosis of sporadic GEP-NEN. Exclusion criteria were: (1) genetic form of GEP-NENs, (2) primary site other than entero-pancreatic. The decision to not include gastric NENs is related to the high prevalence of the type 1 gastric carcinoid, that recognizes atrophic gastritis as a yet demonstrated predisposing condition. For the control group, exclusion criteria were: (1) diagnosis of any malignancies; (2) genetic predisposition for any type of tumors.

All patients provided written informed consent to data collection. The study was approved by the local review board at Regina Elena National Cancer Institute of Rome IRCCS (Reference number 1370/20) and conducted in accordance with the Declaration of Helsinki.

Data collection

For all subjects, we collected the following information: age at diagnosis, sex, BMI, family history including family history for any cancer and for GEP cancer other than NEN, alcohol use (defined as more than 7 unit of alcohol per week), smoking habits (never smoker defined as less than 100 cigarettes smoked during lifetime, according to national cancer institute thesaurus), comorbidities such as type 2 DM (T2DM), arisen at least 1-year prior to the NEN diagnosis, obesity (defined as BMI higher than 30 kg/m^2), hypertriglyceridemia, hypercholesterolemia, low HDL cholesterol, inflammatory bowel diseases, celiac disease, and pancreatitis. Patients were defined as affected by T2DM and dyslipidemia based on personal anamnesis, laboratory tests or medical treatment, but only data on diabetes medications were collected. For NEN group, we collected also: tumor site, staging, grading, and disease status (cured, stable, progressive, died).

Statistical analysis

The categorical variables of interest were expressed as frequencies and percentage values. Difference between the binomial proportions between cases and controls on a dichotomous variable has been assessed by chi-square test for homogeneity. Odds Ratios (ORs) and the 95% Confidence Intervals (CI) for the association between selected variables and the risk of GEP-NENs were analyzed by simple logistic regression analysis. A multiple logistic regression analysis was performed with an Enter model. In the multivariate analysis, we included only the variables with $p < 0.05$ at univariate analysis.

A p value of less than 0.05 was considered significant. All statistical analyses were performed using SPSS for Windows, version 20.0 (SPSS, Inc.).

Results

Patient characteristics

Patients' characteristics are summarized in Table 1. In the GEP-NEN group, the mean age was 58.3 ± 15.8 years old, 50% males ($n = 74$ patients). The most common tumor primary sites were: pancreas (50.7%; $n = 75$), ileum (22.3%; $n = 33$), and large intestine and rectum (11.5%; $n = 17$). Most patients were metastatic at diagnosis (66.9% $n = 99$). Most GEP-NENs were G1 and G2 NETs (62.8% and 29.1%, respectively). No statistically significant difference in age and sex was found between patients and controls.

Risk factors for GEP-NENs

The proportion of subjects who had family history of non-neuroendocrine GEP cancer was significantly higher in cases than in controls (37.8% vs. 21.4%, $p = 0.001$), while family history of any malignancies was not different between cases and controls. Simple regression analysis confirmed that family history of non-neuroendocrine GEP cancer was associated with double risk of GEP-NEN development (multivariate OR 2.16, 95% CI 1.31–3.55).

The proportion of patients affected by T2DM was higher in the group of cases than in the group of controls (23.3% vs. 11.9%, $p = 0.004$), the multivariate OR was 2.50 (95% CI 1.39–4.51), $p = 0.002$. In the subgroup analysis of subjects affected by T2DM, the percentage of individuals assuming metformin was lower in GEP-NEN patients compared with controls (47.1% *vs.* 76.1%, $p = 0.049$, OR 0.28, 95% CI 0.08–0.93).

The overall prevalence of obesity was higher in patients than in controls (44.1% vs. 28.1%, $p = 0.002$), the multivariate OR was 1.88 (95% CI 1.18–2.99).

The prevalence of hypertriglyceridemia was higher in GEP-NEN patients (24.3% vs. 13.8%, $p = 0.011$) even if multiple hierarchical logistic regression analysis did not confirm the role of hypertriglyceridemia as an independent risk factor.

No difference in hypercholesterolemia, low levels of HDL cholesterol, smoking status, and alcohol consumption was found between cases and controls.

Table 2 reports frequency comparisons and relative ORs for all the factors analyzed.

Table 1 Baseline characteristics of NENs patients

	GEP-NENs (148)
Age (years)	58.3 ± 15.8
Sex (M/F, *n*)	74/74
Site	
Pancreas *n*/tot (%)	75/148 (50.7%)
Ileum	33/148 (22.3%)
Large intestine	17/148 (11.5%)
Appendix	14/148 (9.5%)
Duodenum	9/148 (6.1%)
Grade	
G1	93/148 (62.8%)
G2	43/148 (29.1%)
G3	8/148 (5.4%)
NA	4/148 (2.7%)
Stage	
Localized (TNM stage 1, 2)	68/148 (46.0%)
Locally advanced or metastatic (TNM stage 3, 4)	60/148 (40.6%)
NA	20/148 (13.4%)
Disease status	
Stable disease	90/148 (60.8%)
Progressive disease	40/148 (27.0%)
NA	18/148 (12.2%)

GEP-NENs gastro-entero-pancreatic neuroendocrine neoplasms, *M* males, *F* females, *NA* not available

Risk factors according to primary tumor site

We subsequently divided cases according to primary tumor site into two groups: pNENs (75 patients) and intestinal NENs, which included tumors arising from ileum, large intestine and rectum, appendix, and duodenum (73 patients). No difference in age and sex was found between controls and each case group.

Comparing pNENs and controls, we found a statistically significant difference in the proportion of family history of non-neuroendocrine GEP cancer (34.6% vs. 21.4%, $p = 0.023$), T2DM (25.7% vs. 11.9%, $p = 0.005$), obesity (44.4% vs. 28.1%, $p = 0.010$), hypertriglyceridemia (28.0% vs. 13.8%, $p = 0.006$), and a borderline significance for pancreatitis (4% vs. 0.5% $p = 0.057$). However, only T2DM and obesity has been confirmed as risk factors, with a multivariate OR of 2.57 (95% CI 1.28–5.15, $p = 0.008$) and 1.98 (95% CI 1.11–3.52, $p = 0.020$), respectively.

Comparing intestinal NENs and controls, we found a statistically significant difference in the proportion of familial history of non-neuroendocrine GEP cancer (41.1% vs. 21.4%, $p = 0.001$), obesity (43.8% vs. 28.1%, $p = 0.013$), and inflammatory bowel disease (5.5% vs. 0.5%, $p = 0.017$). The first two risk factors were confirmed by simple regression, with a multivariate OR of 2.46 (95% CI 1.38–4.38, $p = 0.003$) and 1.90 (95% CI 1.08–3.33, $p = 0.026$), respectively.

Table 2 Risk factors investigated for the occurrence of GEP-NENs (overall population)

Variables	Overall					
	Controls *n*/tot (%)	Cases *n* (%)	*p* value	OR (95% CI)	Multivariate OR (95% CI)[a]	*p* value
Familial history of cancers (any)			0.639	1.11 (0.72–1.73)	–	
No	76/210 (36.2%)	50/148 (33.8%)				
Yes	134/210 (63.8%)	98/148 (66.2%)				
Familial history of non-neuroendocrine GEP cancers			0.001*	2.23 (1.39–3.56)	2.16 (1.31–3.55)	0.003*
No	165/210 (78.6%)	92/148 (62.2%)				
Yes	45/210 (21.4%)	56/148 (37.8%)				
T2DM			0.004*	2.25 (1.27–3.96)	2.50 (1.39–4.51)	0.002*
No	185/210 (88.1%)	112/146 (76.7%)				
Yes	25/210 (11.9%)	34/146 (23.3%)				
Obesity			0.002*	2.02 (1.30–3.16)	1.88 (1.18–2.99)	0.007*
Normal weight/overweight	151/210 (71.9%)	81/145 (55.9%)				
Obese	59/210 (28.1%)	64/145 (44.1%)				
Hypertriglyceridemia			0.011*	2.01 (1.17–3.45)	1.55 (0.86–2.78)	0.142
No	181/210 (86.2%)	112/148 (75.7%)				
Yes	29/210 (13.8%)	36/148 (24.3%)				
Hypercholesterolemia			0.292	0.79 (0.51–1.23)	–	–
No	132/210 (62.9%)	101/148 (68.2%)				
Yes	78/210 (37.1%)	47/148 (31.8%)				
Low HDL			0.050	1.89 (0.99–3.06)	–	–
No	186/207 (89.9%)	103/125 (82.4%)				
Yes	21/207 (10.1%)	22/125 (17.6%)				
Smoking			0.309	0.80 (0.53–1.23)	–	–
No	110/210 (52.4%)	85/147 (57.8%)				
Ex/Yes	100/210 (47.6%)	62/147 (42.2%)				
Alcohol			0.500	0.4 (0.16-1.03)	–	–
No	190/210 (90.5%)	142/148 (95.9%)				
Yes	20/210 (9.5%)	6/148 (4.01%)				

OR odds ratio, *n* number, *tot* total, *BMI* body mass index

*Statistically significant

[a]Logistic regression analysis

Tables 3 and 4 report frequency comparisons of all the factors analyzed according to the primary site and the relative ORs between patients and controls.

Risk factors for the advanced stages and prognosis of GEP-NENs

In the group of NEN patients, we evaluated if the above-mentioned risk factors could play a role also in disease staging and prognosis. The frequency of T2DM was higher in patients with locally advanced or metastatic disease than in patients with localized disease (33.9% vs. 17.6%, $p=0.035$, OR 2.39, 95% CI 1.05–5.46) and in patients who experienced at least one progression (during treatment) than in patients with stable disease (62.5% vs. 20.2%, $p=0.030$, OR 2.47, 95% CI 1.08–5.34). No difference in the proportion of family history of non-neuroendocrine GEP cancer, obesity, and hypertriglyceridemia was found (data not shown). Moreover, the number of patients assuming metformin was not different according to stage and progression.

Discussion

The current three-center case–control study showed that the family history of non-neuroendocrine GEP cancer, T2DM, and obesity are independent risk factors for sporadic GEP-NEN occurrence and in the T2DM subjects metformin use seems to be a protective factor. T2DM is also more frequent with a more advanced (TNM stage 3 or 4) and progressive

Table 3 Risk factors investigated for the occurrence of pancreatic NENs

Variables	Pancreatic NENs					
	Controls *n*/tot (%)	Cases *n* (%)	*p* value	OR (95% CI)	Multivariate OR (95% CI)[a]	*p* value
Familial history of cancers (any)			0.388	1.28 (0.73–2.26)	-	
No	76/210 (36.2%)	23/75 (30.7%)				
Yes	134/210 (63.8%)	52/75 (69.3%)				
Familial history of non-neuroendocrine GEP cancers			0.023*	1.95 (1.09–3.47)	1.73 (0.95–3.31)	0.073
No	165/210 (78.6%)	49/75 (65.3%)				
Yes	45/210 (21.4%)	26/75 (34.6%)				
T2DM			0.005*	2.56 (1.31–4.99)	2.57 (1.28–5.15)	0.008*
No	185/210 (88.1%)	55/74 (74.3%)				
Yes	25/210 (11.9%)	19/74 (25.7%)				
Obesity			0.010*	2.04 (1.18–3.56)	1.98 (1.11–3.52)	0.020*
Normal weight/overweight	151/210 (71.9%)	40/72 (55.6%)				
Obese	59/210 (28.1%)	32/73 (44.4%)				
Hypertriglyceridemia			0.006*	2.43 (1.28–4.60)	1.94 (0.97–3.90)	0.061
No	181/210 (86.2%)	54/75 (72.0%)				
Yes	29/210 (13.8%)	21/75 (28.0%)				
Hypercholesterolemia			0.977	1.01 (0.54–1.74)	–	
No	132/210 (62.9%)	47/75 (62.7%)				
Yes	78/210 (37.1%)	28/75 (37.3%)				
Low HDL			0.105	1.91 (0.87–4.22)	–	
No	186/207 (89.9%)	51/62 (82.3%)				
Yes	21/207 (10.1%)	11/62 (17.7%)				
Smoking			0.309	0.98 (0.36–1.09)	–	
No	110/210 (52.4%)	47/74 (63.5%)				
Ex/Yes	100/210 (47.6%)	27/74 (36.5%)				
Alcohol			0.193	0.44 (0.13–1.55)	–	
No	190/210 (90.5%)	72/75 (96.0%)				
Yes	20/210 (9.5%)	3/75 (4.0%)				
Personal history of pancreatitis			0.057	–[b]	–	
No	209/210 (99.5%)	72/75 (96%)				
Yes	1/209 (0.5%)	3/75 (4%)				

OR odds ratio, *n* number, *tot* total, *BMI* body mass index

*Statistically significant

[a]Logistic regression analysis

[b]Not performed due to the low number of cases

disease, suggesting a prognostic role of this risk factor. According to the primary tumor site, T2DM and obesity were confirmed as independent risk factors associated with pNENs, while family history of non-neuroendocrine GEP cancer and obesity for intestinal NENs.

We identified a family history of non-neuroendocrine GEP cancer as an independent risk factor for the sporadic GEP-NEN occurrence, highlighting the importance of the cancer site in the oncological family history, and showing that the family history of any cancer, independently of the site, could play a role in the pathogenesis of both pancreatic [5, 16] and intestinal NENs [17]. These findings corroborate existing evidence. Our results regarding specific cancer sites are in line with Capurso et al. that reported a first-degree family history of pancreatic adenocarcinoma and hepatobiliary tumor as more frequent in pNET patients than in controls (data not confirmed at multivariate analysis) [4]. Other studies showed an increased risk of pNETs for subjects with a familial gastro-intestinal cancer history: esophageal cancer [7], stomach and gallbladder cancers [6]. Moreover, sarcoma, ovary or lung cancer have also been associated with an increased risk of pNETs [5, 6]. Regarding small-intestinal

Table 4 Risk factors investigated for the occurrence of intestinal NENs (Ileum, duodenum, large Intestine, appendix)

Variables	Intestinal NENS					
	Controls *n*/tot %	Cases *n* %	*p* value	OR (95% CI)	Multivariate OR (95% CI)[a]	*p* value
Familial history of cancers (any)			0.903	0.97 (0.56–1.68)	–	
No	76/210 (36.2%)	46/73 (63.0%)				
Yes	134/210 (63.8%)	27/73 (37.0%)				
Familial history of non-neuroendocrine GEP cancers			0.001*	2.56 (1.45–4.53)	2.46 (1.38–4.38)	0.003*
No	165/210 (78.6%)	43/73 (58.9%)				
Yes	45/210 (21.4%)	30/73 (41.1%)				
T2DM			0.061	1.49 (0.96–3.94)	–	
No	185/210 (88.1%)	57/72 (79.2%)				
Yes	25/210 (11.9%)	15/72 (20.8%)				
Obesity			0.013*	2.00 (1.15–3.47)	1.90 (1.08–3.33)	0.026*
Normal weight/overweight	151/210(71.9%)	41/73 (56.2%)				
Obese	59/210 (28.1%)	32/73 (43.8%)				
Hypertriglyceridemia			0.171	1.61 (0.81–3.22)	–	
No	181/210 (86.2%)	58/73 (79.5%)				
Yes	29/210 (13.8%)	15/73 (20.5%)				
Hypercholesterolemia			0.085	0.60 (0.33–1.07)	–	
No	132/210 (62.9%)	54/73 (74.0%)				
Yes	78/210 (37.1%)	19/73 (26.0%)				
Low HDL			0.116	1.89 (0.85–4.14)	–	
No	186/207 (89.9%)	52/63 (82.5%)				
Yes	21/207 (10.1%)	11/63 (17.5%)				
Smoking			0.962	1.01 (0.60–1.73)	–	
No	110/210 (52.4%)	38/73 (52.1%)				
Ex/Yes	100/210 (47.6%)	35/73 (47.9%)				
Alcohol			0.094	0.3 (0.07–1.33)	–	
No	190/210 (90.5%)	71/73 (97.3%)				
Yes	20/210 (9.5%)	2/73 (2.7%)				
Personal history of IBD			0.017*	–[b]	–	
No	209/210 (99.5%)	69/73 (94.5%)				
Yes	1/210 (0.5%)	4/73 (5.5%)				

OR odds ratio, *n* number, *tot* total, *BMI* body mass index. *IBD* inflammatory bowel disease

*Statistically significant

[a]Logistic regression analysis

[b]Not performed due to the low number of cases

NETs a family history of colorectal cancer and breast cancer were found as independent risk factors [11]. The role of family history suggests that GEP-NENs and other cancers likely share both genetic and environmental pathogenic factors. A high prevalence of secondary primary malignancies was also found in NEN patients [19], suggesting a possible neoplastic susceptibility that could regard NEN patients and their families. In the inherited syndromes, such MEN1, MEN4, von Hippel-Lindau, the neurofibromatosis type 1, the genetic pathogenesis is well known, but also in sporadic NENs germline gene aberrations have been found [20, 21]. To remove confounding factors, familial GEP-NENs were excluded from the current series. In the literature, environmental (smoking and alcohol) and metabolic factors (DM and obesity) are associated to GEP cancer both of neuroendocrine and epithelial origin, these factors could be shared in the same family, giving another possible explanation of the role of family history of non-neuroendocrine GEP cancer as a predisposing factor for GEP-NENs.

Our findings confirmed the role of metabolic factors, such as T2DM and obesity in the occurrence of GEP-NENs. Summarizing data from the literature, personal history of DM is

associated with an increased risk of pNENs in a wide meta-analysis [16] and in a recent Italian multicenter study [5]. Moreover, DM and high BMI were confirmed to be relevant risk factors for both gastrointestinal and respiratory NENs in another meta-analysis [17]. Non-recently-onset DM as well as obesity are well-known risk factors for the development of pancreatic ductal adenocarcinomas [22]. Whether DM is truly a risk factor for the occurrence of pNENs, or whether this association is a secondary effect related to the pancreatic neoplasm, is still a debated topic [16]. However, the literature data seem to confirm that a non-recently-history of DM and obesity could be a predisposing factor for GEP-NENs, mainly because these conditions are both associated with insulin resistance and compensatory hyperinsulinemia that contribute to tumor growth [12, 23]. Our data referred to T2DM arisen at least 1-year prior to the NEN diagnosis, so the potential influence of the tumor or its therapy in DM development is excluded. Considering only subjects with T2DM, in our cohort, differently from Valente et al. [12], metformin users have been demonstrated more frequent in controls than in GEP-NEN patients, suggesting that it could be a protective factor for the occurrence of GEP-NENs. There are several evidence supporting the antitumor activity of metformin through two main mechanisms: by reducing circulating insulin and insulin-growth-factor levels and by inhibiting of mitochondrial oxidation, adenosine monophosphate-activated kinase (AMPK) activation, and mTOR signaling [24, 25]. However, the protective effect of metformin should be confirmed in future prospective trials with adequate follow-up times and powered to assess it, helping to select patients that would benefit from metformin for GEP-NEN prevention.

Regarding environmental factors, our data did not support the role of smoking and alcohol as risk factors for GEP-NENs. These factors are also debated and inconstantly reported in the literature. A meta-analysis showed that cigarette smoking and alcohol consumption are risk factors only for some anatomical sites including pancreas (both alcohol and cigarette smoking) and small intestine (smoking only) [17]. These conflicting data could be explained by the fact that these habits are self-reported by the patients and different definitions have been used by the authors, causing bias which may vary among the different case–control studies.

Among the other risk factors, it is interesting to observe that pancreatitis is more frequent in the pNEN subgroup, whereas inflammatory bowel disease in the midgut NEN subgroup. Our data are in accordance with the literature, even if the number of events is low, and therefore not statistically significant. In this view, the chronic inflammation and the pro-inflammatory cytokines production seem to play a role in the pathogenesis of GEP-NENs, stimulating the neuroendocrine cells to proliferate and leading to neoplastic transformation [26].

The history of DM was already associated with a more advanced disease stage at diagnosis [4], particularly, the prevalence of non-recently-onset DM was higher both in cases with metastatic disease or advanced grade at the time of diagnosis [12]. Moreover, an Italian retrospective study focused on gender differences in pNENs, showed that in the female group, the pre-existence of T2DM was significantly associated with higher tumor grade and metastatic disease [27]. Our findings are in line with these previous studies demonstrating that T2DM is also associated with a more advanced (TNM stage 3 or 4) and progressive disease.

The major strengths of the present study are the homogeneity of the series according to the most recent WHO classification of GEP-NENs and the lack of ethnic and sociocultural differences, as all patients were Caucasian and born in Italy. However, some limitations should be considered: the retrospective nature of the study; the low number of the involved centers (only three) with a small sample of patients and controls enrolled; the choice of no healthy donors as control group; the quality of data collected (i.e., family history of any cancer needs to be specifically asked for in the control group); the paucity of the data regarding the onset of DM; the lack of data on other components of the metabolic syndrome, such as hypertension and waist circumference, and their medications.

Conclusions

This three-center retrospective case–control study reinforces the role of the family history, in particular of non-neuroendocrine GEP cancer, as a predisposing factor for GEP-NENs, suggesting that GEP neoplasms share common pathogenic mechanisms. Moreover, T2DM and obesity have been confirmed as independent risk factors for GEP-NENs, and T2DM is associated with a more advanced disease and a poorer prognosis. Finally, this study, unlike previous works, investigated the role of metformin in the occurrence of GEP-NENs in patients with T2DM, suggesting a protective effect, that need to be confirmed in the future.

These findings could have a significant impact on the early screening and prevention strategies for GEP-NENs. However, further prospective studies, involving larger number of centers, are needed to confirm our results and to clarify the role of the metabolic syndrome and the medical treatment of its components in GEP-NENs development and prognosis.

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Availability of data and material The datasets generated during end/or analyzed during the current study are available from the corresponding author on reasonable requests.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval The study was approved by the local review board at Regina Elena National Cancer Institute of Rome (Reference number 1370/20).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publication Not applicable.

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