Endocrine (2020) 69:441–450
https://doi.org/10.1007/s12020-020-02331-3

ORIGINAL ARTICLE

Epidemiology of pancreatic neuroendocrine neoplasms: a gender perspective

Giovanna Muscogiuri[1] · Barbara Altieri[1,2] · Manuela Albertelli[3,4] · Andrea Dotto[5] · Roberta Modica[1] · Luigi Barrea[1] · Giuseppe Fanciulli[6] · Tiziana Feola[7] · Roberto Baldelli[8] · Rosaria Maddalena Ruggeri[9] · Marco Gallo[10] · Valentina Guarnotta[11] · Pasqualino Malandrino[12] · Erika Messina[13] · Mary Anna Venneri[7] · Elisa Giannetta[7] · Diego Ferone[3,4] · Annamaria Colao[1] · Antongiulio Faggiano[7] · on behalf of NIKE group

Received: 3 February 2020 / Accepted: 25 April 2020 / Published online: 28 May 2020

Abstract

Purpose Pancreatic neuroendocrine neoplasms (PNENs) are a group of clinically rare and heterogeneous tumors of the pancreas. Currently there are no studies investigating the gender difference in PNEN susceptibility. Thus, the purpose of this study was aimed at examining how gender shapes risk factors, clinicopathological features, and comorbidities in PNENs.

Methods The study design consisted of an Italian multicenter, retrospective study. The study included all consecutive patients with PNENs followed at the participating centers. Two hundred and twenty-nine patients (105 males,124 females, age 54 ± 0.98 years) with PNENs were enrolled at the participating centers. The clinicopathological features (age, gender, BMI, histology, tumor size, tumor grade, distant metastasis, hormonal function, and diagnostic circumstances), comorbidities (cardiovascular diseases (CVD), pancreatitis, type 2 diabetes (T2DM), and potential risk factors (smoking and drinking) were included in the analysis.

Results Females were slightly prevalent (54.15%). PNENs were diagnosed at younger age in females compared to males ($p = 0.04$). The prevalence of CVD was significantly higher in males than in females ($p = 0.006$). In the female group, the presence of T2DM was significantly associated with higher tumor grade ($p = 0.04$) and metastatic disease ($p = 0.02$). The proportion of smokers and alcohol drinkers was significantly higher in the male group ($p < 0.001$). No significant gender differences were detected regarding the other parameters included in the analysis.

Conclusions This study has identified gender differences of PNENs in terms of age at diagnosis, associated comorbidities, and potential risk factors. A *gender-tailored* approach could become a potential strategy to better understand the natural history of PNENs and improve the effectiveness of PNENs clinical management.

Keywords Pancreatic neuroendocrine neoplasms · Cardiovascular diseases · Sex · Gender · Epidemiology · Type 2 diabetes

Introduction

Gender medicine focuses on the impact of the gender on human physiology, pathophysiology, and clinical features of disease [1, 2]. It has been reported a sex difference in the incidence of different types of cancer, tumor aggressiveness, and disease prognosis [3], but little is known about the impact of sex on pancreatic neuroendocrine neoplasms (PNENs). PNENs are relatively rare cancers, representing less than 3% of all primary tumors of the pancreas [4]. However, together with an increased incidence all neuroendocrine neoplasms (NENs), a dramatic increase of PNENs has been reported in the last decades, resulting in an incidence of 0.8 per 100,000/year [5–7]. In different countries, including France, USA, and Norway, a male predominance for PNENs incidence has been highlighted, suggesting that a sex milieu could contribute to the pathogenesis of these neoplasms [5]. Most PNENs arise sporadically and occur between the fourth and the sixth decade, but approximately 5–7% are related to inherited syndromes, including multiple endocrine neoplasia type 1 (MEN1), Von-Hippel Lindau (VHL) syndrome, neurofibromatosis type 1, and tuberous sclerosis [8, 9]. In case of

These authors contributed equally: Giovanna Muscogiuri, Barbara Altieri

Members of the NIKE group are listed below Acknowledgements

✉ Giovanna Muscogiuri
giovanna.muscogiuri@gmail.com

Extended author information available on the last page of the article

inherited syndrome, PNENs usually arise at younger age and tend to be multiple and detected at earlier stage, showing a relatively indolent nature when compared to sporadic PNENs [10]. Personal history of type 2 diabetes mellitus is associated with an increased risk of sporadic PNENs, although smoking and previous history of chronic pancreatitis are also considered potential risk factors [11, 12]. Between 60% and 90% of PNENs are "non-functioning", and cause local symptoms due to mass effect or are incidentally diagnosed, whereas 30% of cases are "functioning" PNENs and symptoms are related to hormones and amine hypersecretion [9, 13].

Recent evidence has emphasized a gender difference of PNENs in terms of clinical behavior. Male patients with PNENs have a worse prognosis, a greater risk of disease recurrence after curative surgery, and a higher incidence of complications than females [14–16]. Conversely, female patients with PNENs have a longer survival and a better response to locoregional treatment of liver metastases than males [17, 18]. Despite these concerns, no "gender-driven" diagnostic or therapeutic approaches are currently available. With the underlying goal to delineate gender differences in terms of potential risk factors and clinical features of PNENs, we performed a nationwide multicenter retrospective study in the Italian population.

Materials and methods

Study population

We performed a retrospective study among nine Italian centers (University "Federico II" of Naples, University "La Sapienza" of Rome, University of Genoa, University of Sassari, "San Camillo-Forlanini" Hospital of Rome, University of Messina, University of Turin, University of Palermo, and University of Catania) including 229 patients with cytological or histological diagnosis of PNEN. The study was conducted in accordance with the Declaration of Helsinki and the subjects were enrolled after providing their informed consent.

Clinical and pathological data, including gender and age at diagnosis, tumor size and site, presence at types of metastases, were collected for all patients. All patients were screened for inherited syndromes associated to PNENs. PNENs were classified as functioning or non-functioning tumors according to hormonal or amine secretion and the presence of clinical syndromes. Symptoms at diagnosis were considered as hormonal- or tumor mass-related, whereas clinically asymptomatic tumors were diagnosed incidentally or after screening due to familial history of inherited syndromes. In case of multiple pancreatic nodules, tumor sizes and site were considered for the biggest lesion. PNENs were divided into well-differentiated or poorly differentiated neuroendocrine carcinomas (NECs) according to the WHO 2017 classification [19]. Patients with well-differentiated tumor were graded as G1 (ki67+ <3%, and mitotic count <2), G2 (ki67+ between 3% and 20%, and mitotic count between 2 and 20), or G3 (ki67+ >20%, and mitotic count >20%) [18]. We also looked at body mass index (BMI) and classified patients according to WHO's criteria as underweight (BMI < 18.0 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese (BMI ≥ 30.0 kg/m^2 [19, 20]. From the medical records were also collected the presence of comorbidities, including type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD; included hypertension), and pancreatitis, as well as history of other diseases, including hypercholesterolemia, thyroid disorders, osteoporosis, rheumatoid arthritis, chronic obstructive pulmonary diseases, asthma, diverticulitis, and prostatic hypertrophy (in men), and history of other benign and malignant tumors (only for sporadic cases of PNEN).

Smoking status was evaluated according to the Center for Disease Control and Prevention (CDC)—National Center for Health Statistics (NCHS) [21] and divided into the followed categories: "current smoker", when patient currently smokes cigarettes, "former smoker", when patient has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview, "never smoked", and "smoking status unknown". Drinking status was also defined according to the CDC-NCHS glossary [21] and categorized as: "lifetime abstainer/former infrequent drinker", when patient had fewer than 12 drinks in lifetime and no drinks in past year, "current light drinker", when patient has 3 drinks or fewer per week, and "current moderate/heavier drinker", if patient has more than 3 per week.

Statistical analysis

Continuous variables are reported as mean with standard deviation, whereas categorical variables are reported as numbers (percentages). Mann–Whitney *U* test or Student's *t*-test was used to assess differences between groups according to the distribution of variables. Categorical variables were compared using Chi square test as appropriate. All the comparisons were evaluated between the male and female groups. Odds ratio (OR) with 95% confidence interval (CI) between the two groups was also evaluated. A p value < 0.05 was considered statistically significant. Statistical analyses were made using GraphPad Prism (version 7.0, La Jolla, CA, USA) and SPSS Software (PASW Version 21.0, SPSS Inc., Chicago, IL, USA).

Results

Characteristics of patients

A total of 229 subjects affected by PNEN were enrolled. Females were slightly prevalent (54.15%). The main

characteristics of PNENs in the entire cohort and according to gender are presented in Table 1. The mean age at diagnosis of the entire population was 54.0 ± 0.98 years old. PNENs were diagnosed at younger age in females compared to males (mean age 51.99 vs 56.44 years; $p = 0.04$). The mean tumor size was 24.57 ± 1.41 mm, without significant differences between males and females. Considering only the biggest lesion in case of multiple pancreatic nodules, the majority of PNENs were located in the head and body of pancreas (31.4% and 38.1%, respectively), followed by tail (30.5%). No differences regarding tumor localization were detected between the two sexes (Table 1).

One-hundred and eighty-six (81.2%) cases of PNEN were sporadic while 43 (18.8%) were related to hereditary syndromes; no significant differences have been detected between genders (Fig. 1a). The majority of PNENs (50%) were

Table 1 Clinicopathological characteristics of the entire cohort and according to gender

Parameter	All patients	Males	Females	*p* value	Chi squared
Number of patients	229 (100)	105 (45.85)	124 (54.15)	–	–
Age at diagnosis, years ± SD	54.0 ± 0.98	56.44 ± 1.33	51.99 ± 1.40	**0.045**	–
Tumor size, mm ± SD	24.57 ± 1.41	2818 ± 1.62	24.9 ± 2.19	0.48	–
Tumor site, *n* available	226	104	122	0.90	0.22
Head	71 (31.4)	34 (32.7)	37 (30.3)		
Body	86 (38.1)	38 (36.5)	48 (39.4)		
Tail	69 (30.5)	32 (30.8)	37 (30.3)		
Type of PNEN					
Sporadic	186 (81.2)	91 (86.7)	95 (76.6)	0.052	3.77
Inhered syndromes	43 (18.8)	14 (13.3)	29 (23.4)		
Modality of diagnosis, *n* available	220	102	118	0.13	3.54
Incidentaloma	110 (50.0)	55 (53.9)	55 (46.6)		
Familial screening	29 (13.2)	11 (10.8)	18 (15.3)		
Hormone hypersecretion	27 (12.3)	9 (8.8)	18 (15.3)		
Tumor mass	54 (24.5)	27 (26.5)	27 (22.9)		
Hormonal status, *n* available:	227	104	123	0.52	0.42
Functioning	48 (21.1)	20 (19.2)	28 (22.8)		
Non-functioning	179 (78.9)	84 (80.8)	95 (77.2)		
Functioning only				0.63	3.43
Insulin	27 (56.3)	9 (45.0)	18 (64.3)		
Gastrin	12 (25.0)	6 (30.0)	6 (21.4)		
Calcitonin	3 (6.3)	2 (10.0)	1 (3.6)		
Glucagon	2 (4.2)	1 (5.0)	1 (3.6)		
Carcinoid syndrome	3 (6.3)	1 (5.0)	2 (7.1)		
Pancreatic polypeptide	1 (2.1)	1 (5.0)	0		
Tumor grade, *n* available	176	79	97	0.36	3.20
G1	90 (51.1)	36 (45.6)	54 (55.7)		
G2	75 (42.6)	39 (49.4)	36 (37.1)		
G3	7 (4.0)	2 (2.5)	5 (5.2)		
NEC	4 (2.3)	2 (2.5)	2 (2.1)		
BMI, *n* available (kg/m^2)	196	87	109	0.17	5.04
<18	6 (3.1)	1 (1.1)	5 (4.6)		
18–25	69 (35.2)	27 (31.0)	42 (38.5)		
25–30	84 (42.9)	44 (50.6)	40 (36.7)		
>30	37 (18.9)	15 (17.2)	22 (20.2)		

Continuous variables are reported as mean with standard deviation, whereas categorical variables are reported as numbers (percentages). Statistical analysis for the comparison of the evaluated variables between the male and female groups was performed by Mann–Whitney *U* test or Chi square test as appropriate, and only in the available cases for each category. A *p* value in bold denoted a statistically significant difference. *BMI* body mass index, *G* grading, *n* number of patients, *NEC* neuroendocrine carcinoma, *PNEN* pancreatic neuroendocrine neoplasm, *SD* standard deviation

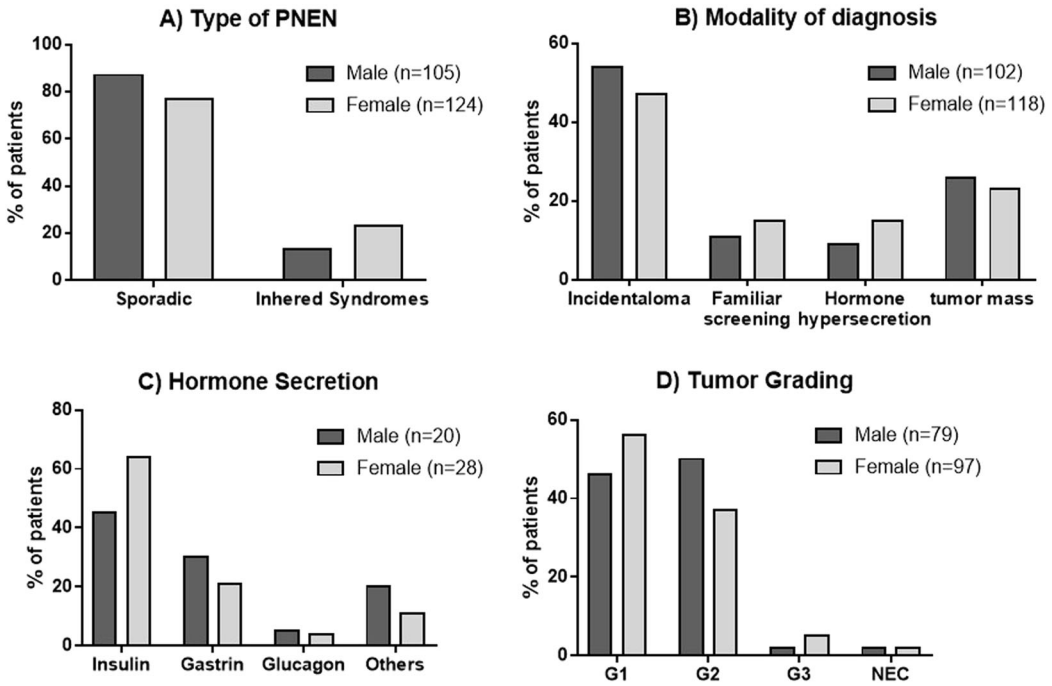

Fig. 1 Characteristics of pancreatic neuroendocrine neoplasms according to gender. Observed difference between males and females according to **a** sporadic or inhered syndrome, **b** modality of diagnosis, **c** hormone hypersecretion, **d** tumor grading. G grading; NEC neuroendocrine carcinoma; PNEN pancreatic neuroendocrine neoplasm

diagnosed as incidentaloma, followed by a 24.5% of cases which presented tumor mass-related symptoms. A rate of 13.2% of PNENs were diagnosed after familiar screening (13.2%), while hormonal hypersecretion-related symptoms were the diagnostic circumstance in only 12.3% (Table 1). No significant differences in terms of clinical presentation were observed between the two groups (Fig. 1b).

Among the 229 PNENs, 179 (78.2%) had a non-functioning tumor. Of the 48 functioning PNENs, the majority ($n = 27$, 56.3%) had an insulinoma, 12 (25%) cases had a gastrinoma, 2 (4.2%) a glucagonoma, and 7 (14.9%) other functioning tumors (Table 1). The proportion of subjects with non-functioning and functioning tumors were similar between males and females (OR 1.13, 95% CI 0.78–1.63 for non-functioning PNEN in man; chi square = 0.42, $p = 0.52$); considering only the functioning tumors, female sex had a trend toward a higher prevalence of insulinoma compared to male sex (64.3% vs 45.0%, OR 1.40, 95% CI 0.83–2.36), although these data did not reach statistical significance (chi square = 1.76, $p = 0.18$) (Fig. 1c). On the other side, males presented a trend to higher prevalence of Zollinger–Ellison syndrome (ZES) due to gastrinoma compared to females (30.0% vs 21.4%, OR 1.29, 95% CI 0.64–2.58), without statistical significance (chi square = 0.45, $p = 0.50$).

Tumor grading and tumor metastases

Among 176 cases with available data on tumor grading, well-differentiated low-grade G1 ($n = 90$, 51.1%) and G2 ($n = 75$, 42.6%) PNENs were more prevalent than well-differentiated high-grade G3 NECs ($n = 7$, 4.0%) and poorly differentiated NECs ($n = 4$, 2.3%) (Table 1). No difference in terms of G1 PNENs have been found between females and males (Fig. 1d). Similarly, male patients had similar prevalence of G2 PNEN, G3 PNEN, and NECs compared to female patients (Fig. 1d).

Distant metastases at diagnosis or during follow-up were found in 35.8% of total cases, without differences between gender (39% of males and 33% of females, chi square = 0.88, $p = 0.35$) (Table 2). The majority of patients ($n = 63$, 27.5%) reported liver metastases alone (50.8%) or in combination with metastases to other tissues (41.9%). Lymph node metastases were found in 48 cases (21% of the entire cohort), among which only 37.5% of cases were reported as single lymph node metastases. Bone metastases were described in a small number of patients ($n = 10$, 4.4% of the entire cohort) and were all associated to metastases to other tissues, including liver metastases in 90% of cases. No gender differences were found considering liver, lymph nodes, or bone metastases (Table 2).

Body mass index

Data on BMI were available in 196 patients (87 males and 109 females) (Table 1). Most part of patients had normal weight (35.2%) or overweight (42.9%) without significant difference between gender, even though the overall prevalence of underweight/normal weight subjects was more

Table 2 Site of distant metastases in the entire cohort and according to gender

Parameter	All patients	Males	Females	*p* value	Chi squared	[a]OR (95% CI)
Disease status						
Localized disease	147 (64.2)	64 (61.0)	83 (66.9)	0.35	0.88	1.55 (0.86–1.53)
Metastatic disease	82 (35.8)	41 (93.0)	41 (33.1)			
Liver metastases						
Yes	63 (27.5)	32 (30.5)	31 (25.0)	0.35	0.85	1.15 (0.86–1.55)
No	166 (72.5)	73 (69.5)	93 (75.0)			
Lymph node metastases						
Yes	48 (21.0)	23 (21.9)	25 (20.2)	0.74	0.10	1.06 (0.76–1.48)
No	181 (79.0)	82 (78.1)	99 (79.8)			
Bone metastases						
Yes	10 (4.4)	5 (4.8)	5 (4.0)	0.79	0.07	1.09 (0.58–2.07)
No	219 (95.6)	100 (95.2)	119 (96.0)			

[a]The reported odds ratio (OR), together with the 95% confidence interval (CI), is referred to male in comparison to female patients. Variables are reported as numbers (percentages). Statistical analysis for the comparison of the evaluated variables between the male and female groups was performed by Chi square test

frequent in females (43.1% vs 32.2%), and the overall prevalence of overweight/obesity subjects was more frequent in males (67.8% vs 56.9 %) but without reaching statistical significance. A BMI ≥ 25 kg/m^2 was not associated with more aggressive tumors by grading and presence of metastasis in both genders.

Comorbidities

History of T2DM, CVD, and pancreatitis was reported in 26%, 51.9%, and 6.6% of cases, respectively. The prevalence of CVD was significantly higher in males than in females (62% vs 43.1%, OR 1.51, 95% CI 1.20–2.05, $p = 0.006$); no difference was observed between genders regarding T2DM (31.7% vs 21.2%, OR 1.32, 95% CI 0.98–1.76, $p = 0.08$) and pancreatitis (9.1% vs 4.1%, OR 1.41, 95% CI 0.93–2.15, $p = 0.17$) (Table 3). On the contrary, other diseases, including hypercholesterolemia and thyroid disorders, were slightly more frequent in females compare to males (31.5% vs 20%, OR 1.29, 95% CI 1.02–1.64, $p = 0.05$), although this difference was not statistically significant (Table 3).

In the female group, the presence of T2DM was significantly associated with higher tumor grade (G2–G3 and NECs, OR 2.29, 95% CI 1.00–8.14, chi square = 4.04, $p = 0.04$) and metastatic disease (OR 2.19, 95% CI 1.11–4.31, chi square = 5.11, $p = 0.02$). In males no association of T2DM with tumor grade and/or the risk of metastasis was observed. The presence of the other comorbidities was not associated with more aggressive tumors.

Secondary tumors

In a subgroup of 117 patients with sporadic PNENs, the diagnosis of secondary benign and malignant tumors was recorded. Among these patients, 33.3% reported a history of malignant tumors, without significant difference between genders (Table 3). Seven patients had a history of more than one malignant tumor. The most frequent reported malignant tumor was thyroid cancer (14.9%), followed by colon and prostate cancer (both in 12.8% of cases), and by skin (excluded melanoma) and urothelial bladder cancer (both in 10.6% of cases) (Fig. 2a). Other NENs were reported only in two cases (4.2%), including one medullary thyroid cancer and one NEN of the appendix. With the exception of sex-related tumors, including breast, endometrial, and prostate cancer, all cases of colon cancer ($n = 6$) were reported in males, as well as males had a higher frequency of urothelial bladder cancer compared to females (80% vs. 20%: $p < 0.05$) (Fig. 2b). Skin cancers (excluded melanoma) was more frequent in females than in males (80% vs. 20%: $p < 0.05$) (Fig. 2b).

Alcohol intake and smoking

The prevalence of current and former smoker in the entire cohort of patients with available data was 23.5% and 19.9%, respectively (Table 3). Males presented a significantly higher proportion of current smoker or former smoker compared to females (30.3% vs. 17.8% for current smoker and 31.5% vs 10.3% for former smoker; chi square = 24, $p < 0.001$). Considering current and former smoker as one group, males presented a significantly increased risk for smoke exposure compared to females (OR 2.11, 95% CI 1.53–2.91, chi square = 22.5, $p < 0.001$).

PNEN patients presented a prevalence of 49.9% of light and moderate/heavier drinker (Table 3). Light drinkers as well as moderate/heavier drinkers were significantly more frequent in male patients compared to female patients (44.7% vs 22.7% for light drinkers and 14.1% vs. 3.0% for

Table 3 Comorbidities and risk factors in the entire cohort and according to gender

Parameter	All patients	Males	Females	*p* value	Chi squared	[a]OR (95% CI)
T2DM, *n* available	219	101	118	0.08	3.11	1.32 (0.98–1.76)
Yes	57 (26.0)	32 (31.7)	25 (21.2)			
No	162 (74.0)	69 (68.3)	93 (78.8)			
CVD, *n* available	216	100	116	**0.006**	7.68	1.51 (1.20–2.05)
Yes	112 (51.9)	62 (62.0)	50 (43.1)			
No	104 (48.1)	38 (38.0)	66 (56.9)			
Pancreatitis, *n* available	212	99	113	0.17	1.86	1.41 (0.93–2.15)
Yes	14 (6.6)	9 (9.1)	5 (5.44)			
No	198 (93.4)	90 (90.9)	108 (95.6)			
Other diseases, *n* available	229	105	124	0.05	3.86	0.74 (0.48–1.03)
Yes	60 (26.4)	21 (20.0)	39 (31.5)			
No	169 (73.8)	84 (80.0)	85 (68.5)			
Other tumors[b], *n* available	117	54	63	0.21	3.14	–
Benign tumors	7 (6.0)	1 (1.9)	6 (9.5)			
Malignant tumors	39 (33.3)	18 (33.3)	21 (33.3)			
No	71 (60.7)	35 (64.8)	36 (57.1)			
Smoking status, *n* available	196	89	107	**<0.001**	24.0	–
Never smoker	111 (56.6)	34 (38.2)	77 (72.0)			
Former smoker	39 (19.9)	28 (31.5)	11 (10.3)			
Current smoker	46 (23.5)	27 (30.3)	19 (17.8)			
Drinking status, *n* available	186	85	101	**<0.001**	24.4	–
Abstainer/infrequent	110 (59.1)	35 (41.2)	75 (74.3)			
Light drinker	61 (32.8)	38 (44.7)	23 (22.7)			
Moderate/heavier	15 (8.1)	12 (14.1)	3 (3.0)			

CVD cardiovascular diseases, *n* number of patients, *T2DM* type 2 diabetes mellitus, – not evaluable

[a]The reported odds ratio (OR), together with the 95% confidence interval (CI), is referred to male in comparison to female patients

[b]The presence of other tumors was evaluated only in sporadic PNEN ($n = 186$). Variables are reported as numbers (percentages). Statistical analysis for the comparison of the evaluated variables between the male and female groups was performed by Chi square test. A *p* value in bold denotes a difference statistically significant

moderate/heavier drinkers; chi square = 24.4, $p < 0.001$). Considering the current light and moderate/heavier drinker as one group, males showed a significant increased risk of alcohol use (OR 2.07, 95% CI 1.50–2.84, chi square = 20.9, $p < 0.001$).

Estrogen therapy and pregnancy

The informations regarding the estrogen therapy (EP) were available in 81 of 124 female patients (65.3%), without differences between oral contraceptive and hormone replacement therapy. Particularly, 7 (8.4%) patients assumed EP. We did not find any correlation between EP treatment and tumor size and presence of metastasis. On the other hand, we observed that EP significantly correlated with tumor grade ($p = 0.034$, chi-squared = 4.47, OR = 1.2, 95% CI 1.05–1.37) and all the patients who assumed EP presented a G1 tumor. However, the number of patients who assumed EP was too low to draw final conclusions (Table 4a).

Data regarding pregnancy were available in 94 out 124 patients (75.8%). In detail, 66 (70.2%) patients had one or more pregnancy. We did not find any correlation between pregnancy and parameters of tumor aggressiveness (considering tumor size, tumor grading, and presence of metastasis). To note, we did not observe significant differences between patients who had single or multiple pregnancies (Table 4b).

Discussion

In this retrospective study the prevalence of PNENs was slightly increased in females than in males. This finding was consistent with previous data reporting a higher prevalence of PNENs in females in Italy [9], even though most of the

current literature reported that the prevalence of PNENs is higher in males worldwide [7, 22]. This reported prevalence seems to be due to the gender hormonal pattern; in fact, estrogen exposure has been identified as a protective factor against PNENs tumorigenesis [23]. However, although in our study the age at diagnosis was significantly younger in females than in males, most of the enrolled females were in menopause. Therefore, a clear role (if any) for the estrogen exposure cannot be establish by our data.

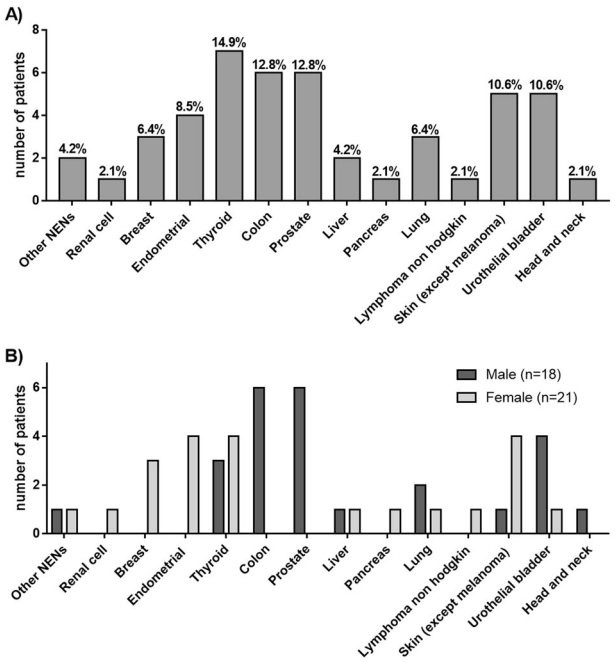

Fig. 2 Prevalence of secondary malignancy in patients with sporadic pancreatic neuroendocrine neoplasm (PNEN). **a** Prevalence of the different tumor types associated to sporadic PNENs considering the entire cohort of evaluated patients. **b** Prevalence of the different associated tumor types according to gender

This study underlines for the first time a younger age at diagnosis in females compared to male patients affected by PNEN. To the best of our knowledge, younger female age has been described only in carcinoid [24]. This could be explained by the fact that, in accordance with the previous literature [25, 26], females develop symptoms earlier than males because of a higher prevalence of insulinomas in females that usually is associated to an earlier onset of symptoms compared to the other hystotypes of PNENs. This in turn could result in a diagnosis at earlier stage. Furthermore, males are less prone to undergo to screening procedures delaying the diagnosis of cancer [23]. Moreover, although we did not observe significant difference in the site of distant metastases. Recently, it has been found no difference in terms of eating habits between men and women with gastro-entero-pancreatic NEN, although a lower adherence to Mediterranean diet have been reported in NEN patients (both men and women) compared to healthy subjects [27, 28]. This could explain the fact that we did not find differences in terms of BMI categories between the genders. According to Valente et al. [11], we observed that T2DM was associated to higher tumor grade and metastatic disease, although this was significant only for females. This could be due to the fact that at least in the early phase of pathogenesis of T2DM, insulin resistance is associated with compensatory hyperinsulinemia that could contribute to tumor growth, as observed in other tumor types [29–31]

In addition, our study found a significant increased prevalence of cardiovascular diseases in males. This finding could be explained by the fact that in males we detected a significant higher prevalence of both current and former smokers. An association between tobacco smoke and PNENs has been already reported in several

Table 4 Association between estrogen therapy (a) and pregnancy (b) with parameters of tumor aggressiveness

Parameter	*n* available case	*p* value	Chi squared	OR	95% CI
(a) Estrogen therapy and tumor aggressiveness					
Tumor size	78	0.95	0.004	1.0	0.88–1.14
High grade	66	**0.03**	4.47	1.20	1.05–1.37
Metas(a) Estrogen therapy and tumor aggressivenesstasis	81	0.80	0.06	0.98	0.83–1.15
(b) Pregnancy and tumor aggressiveness					
Tumor size	91	0.86	0.03	0.97	0.37–2.32
High grade	69	0.22	1.49	1.22	0.90–1.67
Metastasis	94	0.79	3.09	1.30	1.01–1.64

Tumor size >15.5 mm, tumor grade G2, G3, and NEC (vs G1) and presence of metastasis were considered for the analysis. The evaluated OR is in (a) for patients who not assumed estrogen therapy, and in (b) for those who had history of pregnancy. Statistical analysis was performed by Chi square test. A *p* value in bold denotes a difference statistically significant. *n* number of patients, *OR* odds ratio, 95% CI 95% confident interval

studies [32–36]. However, these studies did not investigate if a different gender susceptibility according to tobacco smoke could be related to a higher risk of PNENs. It has been showed that cigarette smoking had a more harmful effects on males than on females since males who smoke experienced a higher number of cell mutations, which have been proven to lead to the loss of Y chromosomes that in turn predisposes to the risk of developing cancer [36].

We confirmed that alcohol use was significantly more frequent in males than in females; nevertheless, the association between alcohol use and the risk of developing PNENs is still under debate in the current literature [37]. Finally, we observed also a very higher incidence of secondary malignant tumor (above 30%) in sporadic PNENs compared to previous studies, which reported an incidence of 10–20% of secondary tumor in patients with PNENs [38, 39]. This discrepancy could be due by the fact that one-third of sporadic PNEN data regarding secondary tumor were not available; thus, the final group of evaluated patients was smaller than previous studies. To note, different patients presented more than two malignant tumors, underlying the fact that a potential unknown genetic predisposition, associated with environment exposure, could play a key role in tumor initiation.

The limit of the study is its retrospective nature. However, due the multicenter design, we were able to enroll a relatively large cohort of PNENs, considering the incidence of this disease in the general population. Another limit of the study was represented by the fact that we cannot investigate if there were difference in the associations of risk factors with PNEN between pre- and post-menopausal women, since we only enrolled post-menopausal women. To the best of our knowledge, this is the first study that focuses on gender difference in risk factors, clinical presentation, pathological tumor characteristics, and comorbidities of PNEN patients.

NIKE group Filomena Bottiglieri[14], Severo Campione[15], Federica de Cicco[14], Alessandra Dicitore[16], Francesco Ferraù[17], Federica Grillo[18], Erika Grossrubatscher[19], Elia Guadagno[14], Andrea M. Isidori[20], Andrea Lania[21], Andrea Lenzi[20], Fabio Lo Calzo[14], Luca Pes[22], Genoveffa Pizza[23], Riccardo Pofi[20], Giulia Puliani[20], Carmen Rainone[14], Paola Razzore[24], Laura Rizza[25], Manila Rubino[26], Emilia Sbardella[27], Franz Sesti[20], Giovanni Vitale[28], Maria Chiara Zatelli[29]

[14]Federico II University, Naples, Italy; [15]Ospedale Cardarelli, Naples, Italy; [16]Istituto Auxologico Italiano IRCCS, Milan, Milan, Italy; [17]University of Messina, Messina, Italy; [18]Ospedale Policlinico San Martino IRCCS, Genova, Italy; [19]ASST Grande Ospedale Metropolitano, Niguarda, Milan, Italy; [20]Sapienza University, Rome, Italy; [21]Humanitas Clinical and Research Center IRCCS, Rozzano, Italy; [22]University of Cagliari, Cagliari, Italy; [23]Landolfi Hospital, Solofra, Avellino, Italy; [24]Mauriziano Hospita, Turin, Italy; [25]AO San Camillo-Forlanini, Rome, Italy; [26]European Institute of Oncology, IEO, IRCCS, Milan, Italy; [27]University of Oxford, Oxford, UK; [28]University of Milan, Milan, Italy; [29]University of Ferrara, Ferrara, Italy

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. G. Baggio, A. Corsini, A. Floreani, S. Giannini, V. Zagonel, Gender medicine: a task for the third millennium. Clin. Chem. Lab. Med. **51**(4), 713–727 (2013). https://doi.org/10.1515/cclm-2012-0849
2. S. Oertelt-Prigione, The influence of sex and gender on the immune response. Autoimmun. Rev. **11**(6–7), A479–A485 (2012). https://doi.org/10.1016/j.autrev.2011.11.022
3. M.T. Dorak, E. Karpuzoglu, Gender differences in cancer susceptibility: an inadequately addressed issue. Front. Genet. **3**, 268 (2012). https://doi.org/10.3389/fgene.2012.00268
4. M. Gallo, R.M. Ruggeri, G. Muscogiuri, G. Pizza, A. Faggiano, A. Colao, N. Group, Diabetes and pancreatic neuroendocrine tumours: which interplays, if any? Cancer Treat. Rev. **67**, 1–9 (2018). https://doi.org/10.1016/j.ctrv.2018.04.013
5. A. Dasari, C. Shen, D. Halperin, B. Zhao, S. Zhou, Y. Xu, T. Shih, J.C. Yao, Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. **3**(10), 1335–1342 (2017). https://doi.org/10.1001/jamaoncol.2017.0589
6. H. Scherubl, B. Streller, R. Stabenow, H. Herbst, M. Hopfner, C. Schwertner, J. Steinberg, J. Eick, W. Ring, K. Tiwari, S.M. Zappe, Clinically detected gastroenteropancreatic neuroendocrine tumors are on the rise: epidemiological changes in Germany. World J. Gastroenterol. **19**(47), 9012–9019 (2013). https://doi.org/10.3748/wjg.v19.i47.9012
7. M. Fraenkel, M. Kim, A. Faggiano, W.W. de Herder, G.D. Valk, N. Knowledge, Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. Endocr. Relat. Cancer **21**(3), R153–R163 (2014). https://doi.org/10.1530/ERC-13-0125
8. A.K. Clift, M. Kidd, L. Bodei, C. Toumpanakis, R.P. Baum, K. Oberg, I. Modlin, A. Frilling, Neuroendocrine neoplasms of the small bowel and pancreas. Neuroendocrinology (2019). https://doi.org/10.1159/000503721
9. A. Faggiano, P. Ferolla, F. Grimaldi, D. Campana, M. Manzoni, M.V. Davi, A. Bianchi, R. Valcavi, E. Papini, D. Giuffrida, D. Ferone, G. Fanciulli, G. Arnaldi, G.M. Franchi, G. Francia, G. Fasola, L. Crino, A. Pontecorvi, P. Tomassetti, A. Colao, Natural history of gastro-entero-pancreatic and thoracic neuroendocrine tumors. Data from a large prospective and retrospective Italian

epidemiological study: the NET management study. J. Endocrinol. Invest. **35**(9), 817–823 (2012). https://doi.org/10.3275/8102
10. A. Faggiano, R. Modica, F. Lo Calzo, L. Camera, V. Napolitano, B. Altieri, F. de Cicco, F. Bottiglieri, F. Sesti, G. Badalamenti, A.M. Isidori, A. Colao, Lanreotide therapy vs active surveillance in MEN1-related pancreatic neuroendocrine tumors <2 centimeters. J. Clin. Endocrinol. Metab. 105(1) (2020). https://doi.org/10.1210/clinem/dgz007
11. R. Valente, A.J. Hayes, S.P. Haugvik, P. Hedenstrom, D. Siuka, E. Korsaeth, D. Kammerer, S.M. Robinson, P. Maisonneuve, G. Delle Fave, B. Lindkvist, G. Capurso, Risk and protective factors for the occurrence of sporadic pancreatic endocrine neoplasms. Endocr. Relat. Cancer **24**(8), 405–414 (2017). https://doi.org/10.1530/ERC-17-0040
12. S.P. Haugvik, I. Basim Ibrahim, P. Hedenstrom, R. Valente, A.J. Hayes, D. Siuka, I.P. Gladhaug, G. Capurso, Smoking, alcohol and family history of cancer as risk factors for small intestinal neuroendocrine tumors: a systematic review and meta-analysis. Scand. J. Gastroenterol. **52**(8), 797–802 (2017). https://doi.org/10.1080/00365521.2017.1310290
13. M. Falconi, B. Eriksson, G. Kaltsas, D.K. Bartsch, J. Capdevila, M. Caplin, B. Kos-Kudla, D. Kwekkeboom, G. Rindi, G. Kloppel, N. Reed, R. Kianmanesh, R.T. Jensen, Vienna Consensus Conference Participants, ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology **103**(2), 153–171 (2016). https://doi.org/10.1159/000443171
14. N. Benetatos, J. Hodson, R. Marudanayagam, R.P. Sutcliffe, J.R. Isaac, J. Ayuk, T. Shah, K.J. Roberts, Prognostic factors and survival after surgical resection of pancreatic neuroendocrine tumor with validation of established and modified staging systems. Hepatobiliary Pancreat. Dis. Int, **17**(2), 169–175 (2018). https://doi.org/10.1016/j.hbpd.2018.03.002
15. G. Li, M.L. Tian, Y.T. Bing, L.Y. Tao, H.Y. Wang, B. Jiang, C.H. Yuan, D.R. Xiu, Clinicopathological features and prognosis factors for survival in elderly patients with pancreatic neuroendocrine tumor: A STROBE-compliant article. Medine (Baltimore) **98**(11), e14576 (2019). https://doi.org/10.1097/MD.0000000000014576
16. K. Tsutsumi, T. Ohtsuka, M. Fujino, H. Nakashima, S. Aishima, J. Ueda, S. Takahata, M. Nakamura, Y. Oda, M. Tanaka, Analysis of risk factors for recurrence after curative resection of well-differentiated pancreatic neuroendocrine tumors based on the new grading classification. J. Hepatobiliary Pancreat. Sci. **21**(6), 418–425 (2014). https://doi.org/10.1002/jhbp.47
17. P.J. Mazzaglia, E. Berber, M. Milas, A.E. Siperstein, Laparoscopic radiofrequency ablation of neuroendocrine liver metastases: a 10-year experience evaluating predictors of survival. Surgery **142**(1), 10–19 (2007). https://doi.org/10.1016/j.surg.2007.01.036
18. H.Y. Akyildiz, J. Mitchell, M. Milas, A. Siperstein, E. Berber, Laparoscopic radiofrequency thermal ablation of neuroendocrine hepatic metastases: long-term follow-up. Surgery **148**(6), 1288–1293 (2010). https://doi.org/10.1016/j.surg.2010.09.014. Discussion 1293
19. R.V. Lloyd, R.Y. Osamura, G. Klöppel, J. Rosai, WHO classification of tumours of endocrine organs. In: Press, I. (ed.) WHO Classification of Tumours, vol. 10, p. 355, Lyons, France (2017)
20. World Health Organization, Waist Circumference and Waist–Hip Ratio. Report of a WHO Expert Consultation, Geneva, Switzerland, 8–11 December 2008 (2008)
21. CDC, C.f.D.C.a.P.: National Health Interview Survey—Special Topics. https://www.cdc.gov/nchs/nhis/special_topics.htm
22. J.C. Yao, M. Hassan, A. Phan, C. Dagohoy, C. Leary, J.E. Mares, E.K. Abdalla, J.B. Fleming, J.N. Vauthey, A. Rashid, D.B. Evans, One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J. Clin. Oncol. **26**(18), 3063–3072 (2008). https://doi.org/10.1200/JCO.2007.15.4377
23. M.A. De Leon-Nava, K. Nava, G. Soldevila, L. Lopez-Griego, J. R. Chavez-Rios, J.A. Vargas-Villavicencio, J. Morales-Montor, Immune sexual dimorphism: effect of gonadal steroids on the expression of cytokines, sex steroid receptors, and lymphocyte proliferation. J. Steroid Biochem. Mol. Biol. **113**(1–2), 57–64 (2009). https://doi.org/10.1016/j.jsbmb.2008.11.003
24. K. Hemminki, X. Li,, Incidence trends and risk factors of carcinoid tumors: a nationwide epidemiologic study from Sweden. Cancer **92**(8), 2204–2210 (2001). https://doi.org/10.1002/1097-0142(20011015)92:83.0.co;2-r
25. F.J. Service, M.M. McMahon, P.C. O'Brien, D.J. Ballard, Functioning insulinoma-incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin. Proc. **66**(7), 711–719 (1991). https://doi.org/10.1016/s0025-6196(12)62083-7
26. S. Patel, M. Narwari, D. Parekh, V. Shah, Insulinoma: case report and review of diagnostic and treatment modalities. J. Assoc. Physicians India **61**(6), 423–426 (2013)
27. L. Barrea, B. Altieri, G. Muscogiuri, D. Laudisio, G. Annunziata, A. Colao, A. Faggiano, S. Savastano, Impact of nutritional status on gastroenteropancreatic neuroendocrine tumors (GEP-NET) aggressiveness. Nutrients **10**(12) (2018). https://doi.org/10.3390/nu10121854
28. B. Altieri, L. Barrea, R. Modica, G. Muscogiuri, S. Savastano, A. Colao, A. Faggiano, Nutrition and neuroendocrine tumors: an update of the literature. Rev. Endocr. Metab. Disord. **19**(2), 159–167 (2018). https://doi.org/10.1007/s11154-018-9466-z
29. B.J. Rolls, I.C. Fedoroff, J.F. Guthrie, Gender differences in eating behavior and body weight regulation. Health Psychol. **10**(2), 133–142 (1991). https://doi.org/10.1037//0278-6133.10.2.133
30. B. Altieri, G. Tirabassi, S. Della Casa, C.L. Ronchi, G. Balercia, F. Orio, A. Pontecorvi, A. Colao, G. Muscogiuri, Adrenocortical tumors and insulin resistance: What is the first step? Int J. Cancer **138**(12), 2785–2794 (2016). https://doi.org/10.1002/ijc.29950
31. E.J. Gallagher, D. LeRoith, Insulin, insulin resistance, obesity, and cancer. Curr. Diab Rep. **10**(2), 93–100 (2010). https://doi.org/10.1007/s11892-010-0101-y
32. R. Vigneri, I.D. Goldfine, L. Frittitta, Insulin, insulin receptors, and cancer. J. Endocrinol. Invest **39**(12), 1365–1376 (2016). https://doi.org/10.1007/s40618-016-0508-7
33. G. Capurso, M. Falconi, F. Panzuto, M. Rinzivillo, L. Boninsegna, R. Bettini, V. Corleto, P. Borgia, P. Pederzoli, A. Scarpa, G. Delle Fave, Risk factors for sporadic pancreatic endocrine tumors: a case-control study of prospectively evaluated patients. Am. J. Gastroenterol. **104**(12), 3034–3041 (2009). https://doi.org/10.1038/ajg.2009.466
34. T.R. Halfdanarson, W.R. Bamlet, R.R. McWilliams, T.J. Hobday, P. A. Burch, K.G. Rabe, G.M. Petersen, Risk factors for pancreatic neuroendocrine tumors: a clinic-based case-control study. Pancreas **43**(8), 1219–1222 (2014). https://doi.org/10.1097/MPA.0000000000000234
35. H.X. Zhan, L. Cong, Y.P. Zhao, T.P. Zhang, G. Chen, Risk factors for the occurrence of insulinoma: a case-control study. Hepatobiliary Pancreat. Dis. Int. **12**(3), 324–328 (2013). https://doi.org/10.1016/s1499-3872(13)60051-x
36. J.P. Dumanski, C. Rasi, M. Lonn, H. Davies, M. Ingelsson, V. Giedraitis, L. Lannfelt, P.K. Magnusson, C.M. Lindgren, A.P. Morris, D. Cesarini, M. Johannesson, E. Tiensuu Janson, L. Lind, N. L. Pedersen, E. Ingelsson, L.A. Forsberg, Mutagenesis. Smoking is associated with mosaic loss of chromosome Y. Science **347**(6217), 81–83 (2015). https://doi.org/10.1126/science.1262092
37. R. Pezzilli, Alcohol abuse and pancreatic diseases: an overview. Recent Pat. Inflamm. Allergy Drug Discov. **9**(2), 102–106 (2015). https://doi.org/10.2174/1872213x09666150430125052

38. M. Krausch, A. Raffel, M. Anlauf, M. Schott, N. Lehwald, A. Krieg, F. Kropil, K. Cupisti, W.T. Knoefel, Secondary malignancy in patients with sporadic neuroendocrine neoplasia. Endocrine **44**(2), 510–516 (2013). https://doi.org/10.1007/s12020-013-9911-4

39. H.J. Tsai, C.C. Wu, C.R. Tsai, S.F. Lin, L.T. Chen, J.S. Chang, Second cancers in patients with neuroendocrine tumors. PLoS ONE **8**(12), e86414 (2013). https://doi.org/10.1371/journal.pone.0086414

Affiliations

Giovanna Muscogiuri[1] · Barbara Altieri[1,2] · Manuela Albertelli[3,4] · Andrea Dotto[5] · Roberta Modica[1] · Luigi Barrea[1] · Giuseppe Fanciulli[6] · Tiziana Feola[7] · Roberto Baldelli[8] · Rosaria Maddalena Ruggeri[9] · Marco Gallo[10] · Valentina Guarnotta[11] · Pasqualino Malandrino[12] · Erika Messina[13] · Mary Anna Venneri[7] · Elisa Giannetta[7] · Diego Ferone[3,4] · Annamaria Colao[1] · Antongiulio Faggiano[7] · on behalf of NIKE group

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

2 Division of Endocrinology and Diabetes, Department of Internal Medicine I, University Hospital, University of Würzburg, Würzburg, Germany

3 Endocrinology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

4 Endocrinology Unit, Department of Internal Medicine and Medical Specialities (DIMI) and Centre of Excellence for Biomedical Research (CEBR), University of Genoa, Genoa, Italy

5 Endocrinology Unit, Department of Internal Medicine and Medical Specialities (DIMI), University of Genoa, Genoa, Italy

6 Department of Surgical, Medical and Experimental Sciences, University of Sassari-Endocrine Unit, AOU Sassari, Sassari, Italy

7 Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

8 Endocrinological Oncology, Service of Endocrinology, A.O. San Camillo-Forlanini, Rome, Italy

9 Endocrine Unit, University Hospital AOU Policlinico G. Martino, Messina, Italy

10 Department of Medical Sciences, Oncological Endocrinology Unit, University of Turin, Turin, Italy

11 Section of Endocrine-Metabolic Diseases, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE), University of Palermo, Palermo, Italy

12 Endocrinology, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

13 Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy