

# Risk factors for sporadic pancreatic neuroendocrine tumors (PNETs): A single-center case control study

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## BACKGROUND

- PNETs are uncommon tumors
- The annual incidence per 100,000 of PNETs in the US is 0.1 in females and 0.2 in males
- The clinical behavior of PNETs is variable, ranging from indolent to very aggressive tumors
- Little is known about risk factors for PNETs
- We evaluated smoking, alcohol use, family history of PNET and other cancers, and personal history of diabetes as potential risk factors

## METHODS

- Patients with PNETs seen for the first time at the Mayo Clinic Rochester between 2000 and 2005 were included
- Patients with insulinoma and high-grade PNETs were excluded
- Primary care patients seen for a general medical evaluation served as controls and were frequency matched (4:1 ratio) to patients with PNETs on age, sex and residence
- Patients and controls completed the same questionnaires at the time of their enrollment into the study
- Chi-square test or Fisher's exact test was used for comparing categorical variables; continuous variables were compared using a two-sample t test.

## RESULTS: PATIENT CHARACTERISTICS

- 178 patients with PNET were evaluated
- The mean age of patients was 59.2 years
- 50.6% were females
- 90.4% of tumors were clinically nonfunctional (defined as the absence of symptoms secondary to hormone overproduction)
- Most tumors were either not graded or well differentiated
- 16 patients (9%) had a diagnosis of MEN
- 60% were symptomatic at diagnosis, most commonly with abdominal pain

	Median age (years)	
Age	56.3 (23 – 84)	
	Number	Percent
<b>Sex</b>		
Male	88	49.4
<b>Grade</b>		
Not graded	88	49.4
Well differentiated	51	28.7
Moderately differentiated	39	21.9
<b>Stage</b>		
Localized	73	41.3
Locally advanced	6	3.4
Node metastases	33	18.8
Distant metastases	64	36.4
<b>Functional status</b>		
Nonfunctional	160	90.4
Functional	17	9.6
<b>MEN1</b>	16	9
<b>Symptoms at diagnosis</b>		
No	67	39.9
Yes	101	60.1

## RESULTS: CHARACTERISTICS OF CASES AND CONTROLS

- 111 patients were frequency matched to 420 controls
- Patients with MEN1 were excluded from the case control analysis
- The distribution of BMI, sex and race were similar among the two groups
- Fifty percent of the patients and controls came from Minnesota or the adjacent states but more controls than cases were from Minnesota

Characteristics	Controls (n=420)	Cases (n=111)	p
<b>Age</b>	60.5 ± 10.7	59.2 ± 11.1	0.26
<b>BMI</b>	26.8 ± 4.8	27.3 ± 4.2	0.38
<b>Male sex</b>	51%	50%	0.93
<b>Race</b>			
White	98%	96%	
Black	0%	2%	
Asian	1%	1%	
Other	1%	1%	
<b>Residence</b>			
Minnesota	163 (39%)	25 (23%)	<0.001
Iowa or Wisconsin	41 (10%)	21 (19%)	
No./So. Dakota	12 (3%)	8 (7%)	
Other states	204 (49%)	57 (51%)	

## RESULTS: ANALYSIS OF RISK FACTORS

Variable	Controls (n=420)	Cases (n=111)	p
<b>Ever smoker</b>			0.22
No	228 (55%)	44 (48%)	
Yes	187 (45%)	48 (52%)	
<b>ETS</b>			<0.001
No	98 (43)	1 (3%)	
Yes	130 (57%)	39 (98%)	
<b>Alcohol use</b>			<0.001
No	37 (14%)	71 (64%)	
Yes	229 (86%)	40 (36%)	
<b>Diabetes</b>			<0.001
No	390 (93%)	84 (76%)	
Yes	30 (7%)	27 (24%)	
<b>Family history of cancer*</b>			0.50
Hepatobiliary			
No	407 (98%)	91 (99%)	
Yes	9 (2%)	1 (1%)	
Pancreas			0.59
No	392 (94%)	88 (96%)	
Yes	24 (6%)	4 (4%)	
<b>PNETs</b>			0.033
No	416 (100%)	91 (99%)	
Yes	0 (0%)	1 (1%)	
<b>Sarcoma</b>			0.001
No	413 (99%)	87 (95)	
Yes	3 (1%)	5 (5%)	
<b>Unknown primary</b>			0.05
No	408 (98%)	87 (95%)	
Yes	8 (2%)	5 (5%)	

\*First degree family member.

ETS: Environmental tobacco exposure (Ever exposed to regular smoker >1 year), PNET: Pancreatic neuroendocrine tumor

- Personal smoking history was not associated with PNETs (p=0.22)
- Environmental tobacco exposure was more common among cases than controls (p<0.001)
- Alcohol use was less common among cases than controls (p<0.001)
- Cases were more likely to have a diagnosis of diabetes than controls (p<0.001)
- Cases were more likely to report a first degree family member with sarcoma (p=0.001), PNET (p=0.033) and cancer of unknown primary (p=0.05), though numbers are small.
- There was no association of PNET with other cancers in first degree relatives

## CONCLUSIONS

- The majority of patients had nonfunctional tumors with only 7% having clinically functional tumors
- Sporadic PNETs were metastatic in the majority of patients at the time of diagnosis
- There may be an association between smoking and exposure to environmental smoke and PNETs but this needs to be confirmed using a larger sample of patients
- Other studies have reported an association between smoking and carcinoid tumors of the small bowel but a recent case-control study using a large sample of GI neuroendocrine tumors did not observe such an association
- Although patients with PNET were more likely than controls to report a personal history of cancer, there was no association with any particular type of cancer
- The potential association of cancer in first degree relatives, particularly sarcoma, PNET and cancer of unknown primary needs to be explored using larger datasets