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Risk Factors for Pancreatic Neuroendocrine Tumors (PNETs): A Clinic-Based Case-Control study

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Abstract

Objectives—Pancreatic neuroendocrine tumors (PNETs) are uncommon, and little is known about their risk factors and association with other cancers. We evaluated whether risk factors known to be associated with pancreatic adenocarcinoma are also associated with PNETs: smoking, alcohol use, family history of PNET and other cancers, and personal history of diabetes as potential risk factors.

Methods—Patients with PNETs seen at Mayo Clinic Rochester between 2000 and 2011 were compared to controls seen for a general medical evaluation. Patients and controls completed the same questionnaires. After excluding insulinoma and high-grade PNETs, 355 cases were evaluated, and 309 were matched to 602 controls (2:1) on age, sex, and region of residence.

Results—Personal smoking history was not associated with PNETs. Alcohol use was less common among cases (54% vs. 67%, $p<0.001$). Cases were more likely to report a family member with sarcoma ($p=0.02$), PNET ($p=0.02$), gall bladder cancer ($p=0.02$), ovarian cancer ($p=0.04$) and gastric cancer ($p=0.01$). There was no association with other cancers in family members. Diabetes was more commonly reported by cases than controls (19% vs. 11%, $p<0.001$).

Conclusions—With the exception of diabetes, risk factors that are associated with pancreatic adenocarcinoma are not risk factors for PNETs.

Introduction

Pancreatic neuroendocrine tumors (PNETs) are uncommon tumors of neuroendocrine origin arising in the pancreas. PNETs are generally more indolent than adenocarcinoma of the pancreas, although aggressive variants may be seen.[1] Population-based studies have reported a 5-year overall survival ranging from 15% to 60% based on disease stage but

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survival appears to be considerably more favorable in single-institution studies, possibly reflecting patients with better performance status and receiving more aggressive therapy.[2–4] Analysis of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) data show that the crude annual incidence per 100,000 of PNETs in the United States for all ages is 0.1 in females and 0.2 in males, and that incidence increases with age.[5] Although PNETs can be seen in association with inherited syndromes such as multiple endocrine neoplasia type 1 (MEN1)[6] and von Hippel-Lindau disease[7], most PNETs are sporadic. No risk factors other than inherited syndromes are known, and it is not known if PNETs share risk factors in common with adenocarcinoma of the pancreas, such as smoking, family history of pancreatic cancer, or personal history of diabetes. It has been suggested that there may be an association between sporadic PNETs and other gastrointestinal neuroendocrine tumors and other malignancies in first-degree relatives.[8, 9] One study reported that patients with non-functional PNETs were more likely to have a family history of pancreatic adenocarcinoma, but there was no comparison with a control group.[10] There are conflicting data on the association between smoking and alcohol use with risk of neuroendocrine tumors.[11, 12] The aim of our study was to identify potential risk factors for PNETs using a case-control design and in particular, to evaluate the potential role of smoking, alcohol consumption, diabetes, and family history of pancreatic and other cancers, which are associated with pancreatic adenocarcinoma.

Methods

The study was reviewed and approved by the Mayo Clinic Institutional Review Board, and written, informed consent was obtained from all cases and controls.[13]

The study utilized an existing patient registry database at the Mayo Clinic, Rochester, MN (Biospecimen Resource for Pancreas Research), supported by the Mayo Clinic SPORE in Pancreatic Cancer. Patients with pancreatic tumors were identified through an ultra-rapid patient identification system using an electronic patient schedule system and daily pathology reports from October, 2000 to May, 2011, with 71% consenting to participate. All eligible patients were contacted in the clinic at the time of their appointment, or later by mail or phone if clinic contact was not possible. All cases and controls provided written consent before participating. Cases were asked to complete a risk factor questionnaire that included detailed information on family history of malignancies, personal history of malignant and non-malignant disorders, and habits such as alcohol and tobacco use.[14] Only histologically or clinically confirmed cases with low to intermediate grade PNETs were included. Records on all cases were reviewed by a subspecialist physician for diagnosis coding.

Clinical information specific to the diagnosis of PNETs were extracted from clinical records. Cases of high-grade (grade 4) neuroendocrine tumors and benign insulinomas were excluded as these tumors have different clinical behavior and prognosis than low-grade PNETs. Patients with a clinical diagnosis of MEN1 or other inherited syndromes such as von Hippel-Lindau syndrome were also excluded.

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Control recruitment

Controls were recruited from the Mayo Rochester General Internal Medicine Clinic from May 2004 – May 2011. The control group consists of individuals being evaluated in a primary care clinic, many of whom come for a routine check-up visit. Exclusion criteria included any history of cancer except non-melanoma skin cancer, and history of pancreatitis. Two thousand five hundred six controls provided consent, and 2,099 (84%) of these completed questionnaires. For the current analysis, 602 controls were matched (2:1) to the PNET cases based on sex, age, and residence in a five-state region (MN, IA, ND, SD, WI) and other regions in the United States. The controls completed the same questionnaire as the cases with respect to risk factors.

Statistical Analysis

Continuous variables (i.e. age and body mass index) are presented as mean ± SD. Associations for continuous variables with case-control status were evaluated using the Wilcoxon rank-sum test. Categorical values are presented as counts and percentages. Associations for categorical characteristics with case-control status were evaluated using a chi-squared test. A univariate conditional logistic regression model was used to estimate risk for each factor of interest. Incident PNET cases defined as cases which either had their first biopsy within 1 year of their Mayo Clinic diagnosis date or had surgery at Mayo Clinic were used to calculate risk. Anyone with a previous diagnosis that preceded the Mayo diagnosis date by greater than 1 year was excluded. Odds Ratios and 95% confidence intervals along with p-values are presented. For all analyses, p-values ≤ 0.05 were considered significant. The data analyses for this paper were performed using SAS software v9.2.

Results

Three hundred nine cases and 602 controls were included in the case-control analysis of risk factors. A matching control could not be found for 46 cases and those cases were excluded from the analysis. These 46 unmatched PNET cases were younger (42.2 years), more likely to be female (59%) and more likely to be from outside the 5 state region (89%) when compared to the 309 matched cases, but no significant differences were observed for the risk factors of interest (data not shown). Cases and controls were comparable in terms of age, sex, race, and state of residence (Table 1). The mean age of this PNET case patient subgroup was 58.7 ± 11.6 years, and 54% were males. The results of the risk factor analysis are reported in Table 2. Fifty-three percent of patients with PNETs reported being ever-smokers (≥ 100 cigarettes in lifetime) versus 46% of controls (p=0.25). Alcohol use was significantly less common among cases than controls (56% vs. 67%, p=0.003). More cases had a body mass index (BMI) 30 or higher than controls (30% vs. 24%, p=0.013). Cases were more likely than controls to report being diagnosed with diabetes prior to being diagnosed with PNET (19% vs. 11% p=0.003). Information on the temporal association of diabetes and the diagnosis of PNETs was missing in 17 (33.3%) of cases. Six patients (11.8%) were diagnosed with diabetes at the same time or after the PNET diagnosis, 16 (31.4%) were diagnosed within three years prior to the PNET diagnosis and 12 (23.5%) were diagnosed with diabetes three years or more before the PNET diagnosis. Cases were also more likely than controls to report a family member with sarcoma (p=0.02), PNET (p=0.024), gall

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bladder cancer (p=0.024), ovarian cancer (p=0.04) and gastric cancer (p=0.01). Two patients (1%) reported a history of a PNET in a family member but none of the controls did. There was no association between PNETs and cancers at other organ sites.

Conclusions

Our study of 355 prospectively enrolled patients with PNETs had the goal of evaluating potential risk factors, which to date have not been systematically identified, with a special focus on risk factors associated with pancreatic adenocarcinoma. In this study, we have identified that a personal history of diabetes as well as family history of several malignancies are risk factors.

We limited our risk factor study to patients with low to intermediate-grade PNETs; patients with high-grade tumors and insulinomas were excluded because their biological behavior is strikingly different from the low- to moderate grade PNETs. For example, patients with insulinoma have an excellent prognosis once diagnosed and treated appropriately,[15] while patients with high grade PNETs have markedly inferior survival when compared with patients who have better differentiated PNETs.[5] We also made an attempt to exclude patients with MEN-1 who frequently develop PNETs and often have affected family members. The exclusion of patients with MEN-1 was on clinical grounds as data on patients' genetics was unavailable. Given the lack of information on gene mutations resulting in MEN-1, there is possibility that patients with clinically unrecognized MEN-1 may have been included.

Our analysis of lifestyle risk lifestyle factors suggests there may be an inverse association with alcohol use. We consider this to be a very preliminary finding that requires further investigation and validation, preferentially in a study allowing better quantification of alcohol consumption. Other studies have reported higher prevalence of alcohol use among patients with NETs. A recent study suggested an association of increased risk of gastrinoma in patients who reported alcohol abuse.[16] Although cases were slightly more likely to have a personal history of tobacco use than controls, this difference was not statistically significant. A recent case-control study evaluated risk factors in patients with five different types of neuroendocrine tumors and did not observe an association between smoking or alcohol consumption and development of neuroendocrine tumors.[11] This study included patients with PNETs but fewer cases than were identified in our study. Two population-based studies, both containing a limited number of patients with small bowel neuroendocrine tumors (carcinoid tumors), have suggested there may be an association between smoking and the risk of neuroendocrine malignancies.[12, 17] These inconsistent findings suggest that the effect of smoking on the risk of neuroendocrine tumors remains uncertain and merits further study. Our findings regarding the effects of tobacco smoke and alcohol should be viewed as hypothesis generating, given the limited size of the study sample and the fact that not all cases and controls responded to the questions regarding exposure.

We observed that patients with PNETs were more likely to report a family member with sarcoma, PNET, cancer of the gall bladder, stomach and ovary but not other tumors. We did not observe an association with pancreatic adenocarcinoma. Other studies have suggested

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that there may be an association between PNETs and pancreatic adenocarcinoma[10] or esophageal cancer[8] but our reports do not support an association with those malignancies. A recent, large population-based study suggested an association between the more common gastrointestinal carcinoid tumors and a family history of various other non-neuroendocrine malignancies, suggesting shared etiologic factors.[9]

Our finding that patients with PNETs are more likely than controls to have a history of diabetes is supported by other investigators.[11] Hassan et al. reported that patients with PNETs were more likely to have been diagnosed with diabetes in the year leading up to the PNET diagnosis.[11] Other investigators have reported an association between diabetes and the carcinoid syndrome.[11, 18] An association between recent-onset diabetes and pancreatic adenocarcinoma has been observed, which may represent the effect of proteins secreted by the tumor on beta-cell function and insulin resistance.[19] There are several potential explanations for this association. It is possible that there is a yet unexplained perturbation in the metabolism of glucose in patients with PNETs. Obesity defined as a body mass index (BMI) of 30 or more was more commonly observed in cases than controls but the difference was small and unlikely to explain the observed association between PNETs and diabetes.

The strengths of our study include the prospective and concurrent collection of data from both cases and controls, the rapid case finding process and high participation rates, and that both cases and controls self-completed similarly designed questionnaires. The diagnosis was confirmed in each patient by individually reviewing pathological data, and electronic medical record data were available on all patients. Limitations of this study include the sample size and the fact that this is a single-center study with risk factor data based upon questionnaires, which may be subject to biases such as recall bias. The controls for the study were patients seen for a general medical examination at our institution. These patients are seen for regular examination or for specific health care issues and may either reside in the region or travel to the Mayo Clinic for this reason. To minimize potential unmeasured differences, we matched patients to controls based on their state of residence.

The findings of a possible association between alcohol use and family history are intriguing but require confirmation in a larger study. The lack of more detailed information on both the duration and amount of tobacco and alcohol use in both cases and controls is also a limitation of our study.

In summary, our study shows no association of PNETs with smoking but possibly an inverse association with alcohol use. Patients with PNETs were more likely to report a personal history of diabetes and family members with PNETs, sarcoma and cancer of the gall bladder, stomach and ovary.

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References Cited

1. Halfdanarson TR, Rubin J, Farnell MB, et al. Pancreatic endocrine neoplasms: epidemiology and prognosis of pancreatic endocrine tumors. Endocr Relat Cancer. 2008; 15:409–427. [PubMed: 18508996]
2. Strosberg, JR.; Halfdanarson, TR. Survival analyses of pancreatic neuroendocrine tumors: Contrasting institutional databases with population-based studies. Presented at the 2010 North American Neuroendocrine Tumor Society (NANETS) Meeting; Santa Fe, New Mexico. 2010.
3. Strosberg JR, Cheema A, Weber J, et al. Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. J Clin Oncol. 2011; 29:3044–3049. [PubMed: 21709192]
4. Bilimoria KY, Bentrem DJ, Merkow RP, et al. Application of the pancreatic adenocarcinoma staging system to pancreatic neuroendocrine tumors. J Am Coll Surg. 2007; 205:558–563. [PubMed: 17903729]
5. Halfdanarson TR, Rabe KG, Rubin J, et al. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. Ann Oncol. 2008; 19:1727–1733. [PubMed: 18515795]
6. Lakhani VT, You YN, Wells SA. The multiple endocrine neoplasia syndromes. Annu Rev Med. 2007; 58:253–265. [PubMed: 17037976]
7. Lonser RR, Glenn GM, Walther M, et al. von Hippel-Lindau disease. Lancet. 2003; 361:2059–2067. [PubMed: 12814730]
8. Hassan MM, Phan A, Li D, et al. Family history of cancer and associated risk of developing neuroendocrine tumors: a case-control study. Cancer Epidemiol Biomarkers Prev. 2008; 17:959–965. [PubMed: 18398037]
9. Hiripi E, Bermejo JL, Sundquist J, et al. Familial gastrointestinal carcinoid tumours and associated cancers. Ann Oncol. 2009; 20:950–954. [PubMed: 19150948]
10. Gullo L, Migliori M, Falconi M, et al. Nonfunctioning pancreatic endocrine tumors: a multicenter clinical study. Am J Gastroenterol. 2003; 98:2435–2439. [PubMed: 14638345]
11. Hassan MM, Phan A, Li D, et al. Risk factors associated with neuroendocrine tumors: A U.S.-based case-control study. Int J Cancer. 2008; 123:867–873. [PubMed: 18491401]
12. Kaerlev L, Teglbjaerg PS, Sabroe S, et al. The importance of smoking and medical history for development of small bowel carcinoid tumor: a European population-based case-control study. Cancer Causes Control. 2002; 13:27–34. [PubMed: 11899115]
13. Halfdanarson TR, Wang L, Bamlet WR, et al. Mitochondrial genetic polymorphisms do not predict survival in patients with pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2008; 17:2512–2513. [PubMed: 18768524]
14. McWilliams RR, Bamlet WR, de Andrade M, et al. Nucleotide excision repair pathway polymorphisms and pancreatic cancer risk: evidence for role of MMS19L. Cancer Epidemiol Biomarkers Prev. 2009; 18:1295–1302. [PubMed: 19318433]
15. Grant CS. Insulinoma. Best Pract Res Clin Gastroenterol. 2005; 19:783–798. [PubMed: 16253900]
16. Wilson SD, Doffek KM, Krzywda EA, et al. Zollinger-Ellison syndrome associated with a history of alcohol abuse: coincidence or consequence? Surgery. 2011; 150:1129–1135. [PubMed: 22136832]
17. Chen CC, Neugut AI, Rotterdam H. Risk factors for adenocarcinomas and malignant carcinoids of the small intestine: preliminary findings. Cancer Epidemiol Biomarkers Prev. 1994; 3:205–207. [PubMed: 8019367]
18. Feldman JM, Plonk JW, Bivens CH, et al. Glucose intolerance in the carcinoid syndrome. Diabetes. 1975; 24:664–671. [PubMed: 125668]
19. Pannala R, Basu A, Petersen GM, et al. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. Lancet Oncol. 2009; 10:88–95. [PubMed: 19111249]

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Table 1

Characteristics of Pancreatic Neuroendocrine Tumor Subjects and Controls in the Case-Control Analysis

	Controls (N=602)		PNET Cases (N=309)		
Variable	**N**	**%**	**N**	**%**	**p-value**
Age, mean ± sd	59.9 ± 11.5		58.7 ± 11.6		0.15
Body Mass Index (BMI), mean ± sd	27.4 ± 5.4		28.4 ± 5.8		0.022
Sex					0.94
Female	275	46	142	46	
Male	327	54	167	54	
State of Residence					0.69
MN, IA, WI, ND, SD	361	60	181	59	
Outside 5-state	241	40	128	41	
Race					0.15
Non-Caucasian	12	2	11	4	
Caucasian	588	98	296	96	

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Table 2

Risk Factors of Pancreatic Neuroendocrine Tumors

Variable	Controls (N=602)		PNET Incident Cases (N=273)		OR (95% CI)*	p-value*
	N	%	N	%		
Smoking Status						0.2452
Never Smoker	320	54	97	47	1.00	
Ever Smoker	275	46	108	53	1.23 (0.87, 1.73)	
Alcohol Use						0.0031
No	164	33	82	44	1.00	
Yes	332	67	105	56	0.56 (0.38, 0.82)	
Self-Reported Diabetes						0.0025
No	538	89	222	81	1.00	
Yes	64	11	51	19	1.91 (1.26, 2.91)	
Body Mass Index (BMI)						0.0126
Non-obese: BMI < 30	440	76	141	70	1.00	
Obese: BMI ≥ 30	140	24	61	30	1.65 (1.11, 2.45)	

* - Based on a Univariate Conditional Logistic Regression Model.

Incident cases are defined as cases which either had their first biopsy within 1 year of their Mayo Diagnosis Date or had surgery at Mayo. Anyone with a previous diagnosis that preceded Mayo Diagnosis Date by greater than 1 year was excluded.

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Table 3

Association with malignancies in first-degree relatives of patients with PNETs.

	Controls (N=602)		PNET Cases (N=309)		
First Degree Family History	**N**	**%**	**N**	**%**	**p-value**
Gastric	11	2	12	5	0.010
Sarcoma	5	1	7	3	0.020
Gallbladder	0	0	2	1	0.024
Pancreas (PNET)	0	0	2	1	0.024
Ovarian	9	2	9	4	0.040
Bladder	13	2	4	2	0.65
Brain	11	2	9	4	0.09
Breast	93	16	33	14	0.56
Carcinoid	1	0	0	0	0.53
Cervix	11	2	4	2	0.88
Colorectal	69	12	29	12	0.77
Esophagus	3	1	2	1	0.56
Gynecologic – Non Ovarian	11	2	8	3	0.18
Head and Neck	11	2	5	2	0.80
Hepatobiliary	19	3	3	1	0.12
Kidney	9	2	6	3	0.31
Leukemia	11	2	9	4	0.09
Lung	48	8	23	10	0.43
Lymphoma	22	4	5	2	0.25
Myeloma	3	1	4	2	0.09
Other	9	2	2	1	0.45
Pancreas (Adenocarcinoma)	30	5	15	6	0.45
Prostate	66	11	32	14	0.32
Testes	8	1	1	0	0.25
Thyroid	11	2	6	3	0.52
Unknown	15	3	12	5	0.06

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	Controls (N=602)		PNET Cases (N=309)		
First Degree Family History	N	%	N	%	p-value
Urethral	2	0	0	0	0.37