Published in final edited form as:

Pancreas. 2019 February ; 48(2): 161–168. doi:10.1097/MPA.0000000000001232.

Risk of Primary Neuroendocrine Pancreatic Tumor Following a First Primary Cancer: A US Population-Based Study

Geetanjali R. Kamath, PhD^{*,†}, Michelle K. Kim, MD[‡], and Emanuela Taioli, MD, PhD^{*,†}

^{*}Department of Population Health Science and Policy and Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York, NY

[†]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

[‡]Department of Internal Medicine, Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY

Abstract

Objective: To describe the relative and excess risk of pancreatic neuroendocrine tumor (NET) at least six months after the first primary cancer among the US population.

Methods: Surveillance, Epidemiology, and End-Results Program data were analyzed for patients diagnosed with first primary cancer (FPC) from 2000–2015 (n = 4,008,092). Standardized incidence ratios, excess risk, and average time to diagnosis of a second primary pancreatic NET were reported by FPC site; stratified by sex and receipt of radiotherapy and chemotherapy.

Results: Risk of pancreatic NET was significantly higher following FPC at any site, any solid tumor (standardized incidence ratios, 1.3; 95% confidence interval, 1.2–1.5), pancreas, thymus, small intestine, liver, stomach, kidney, lung, female breast. Excess incidence of pancreatic NET was highest among those with FPC (especially NET) of the pancreas, bladder, thymus and female breast; received radiotherapy/chemotherapy for bladder, melanoma, and stomach cancers; received chemotherapy for uterine, cervical, prostate, and other genital cancers. Time to diagnosis was shortest after pancreatic, liver, lung, and stomach cancer.

Conclusions: Cancer survivors have increased risk and excess incidence of primary pancreatic NET compared to the population, particularly for certain primary sites. High-risk patients should receive regular follow-up screenings, counseling to reduce carcinogen exposure, and lifestyle interventions.

Keywords

pancreatic neoplasms; neuroendocrine tumors; second primary neoplasm; SEER Program

Address correspondence to: Emanuela Taioli, MD, PhD, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1133, New York, NY 10029-5674 (emanuela.taioli@mountsinai.org). Telephone: (212) 659-9590; Fax: (212) 423-2998.

Conflict of interest disclosure: The authors declare no conflict of interest.

Introduction

Pancreatic cancer is the eleventh most commonly diagnosed cancer and the fourth leading cause of cancer-related death in the United States (US).¹ An estimated 12.6 new cases are diagnosed per 100,000 persons, and 10.9 per 100,000 persons die from it every year.² Overall, the case fatality rate is high, with only 8.5% of pancreatic cancer patients living five years past diagnosis. Five-year survival is better for tumors diagnosed at the localized stage at 34.3%; however, these constitute only 10% of cases. Most cases (52%) are diagnosed at the distant stage, for which the survival rate is an abysmal 2.7%.²

Although less than 5% of all pancreatic cancers are neuroendocrine, the pancreas is one of the most common sites for neuroendocrine tumors (NET).^{3,4} Pancreatic NETs histologically resemble carcinoid gastrointestinal tract tumors, but respond differently to treatment, and are therefore recognized as a separate entity.³ They can be classified as functional (hormone-producing) and non-functional. Non-functional pancreatic NETs, making up about 15–53% of pancreatic NET, may initially be asymptomatic, and therefore detected at a late clinical stage. By the time of diagnosis, the tumor has often enlarged, and/or metastasized.^{5,6} Hence, identifying persons at highest risk for this cancer is crucial in reducing the fatality rate via screening, early detection and treatment.

Most cases of pancreatic NET are sporadic; however, some occur as part of the autosomal dominant multiple endocrine neoplasia type-1 (MEN-1) inherited syndrome, which includes neoplasia in the anterior pituitary, parathyroid, and endocrine pancreas.³ Risk factors for sporadic pancreatic NET include cigarette smoking, heavy alcohol drinking, a history of diabetes, and of cancer in a first-degree family member⁷, similar to risk factors for NETs at any site.⁸ A case/control study found that pancreatic NET patients were more likely than controls to report a family member with pancreatic NET, sarcoma, gallbladder, ovarian and gastric cancer.⁹ However, it is not known whether history of a previous cancer is associated with increased risk of pancreatic NET in the same individual.

Therefore, we conducted a study based on US population data with the following objectives: 1) To assess whether the risk of developing a primary pancreatic NET is increased in persons who previously had a primary cancer diagnosis compared with the general population; 2) To assess whether a history of a first primary cancer at specific sites increases the risk of developing a second primary pancreatic NET; 3) to describe the excess risk of developing a second primary pancreatic NET among those who previously had a primary cancer diagnosis at specific sites compared with the general population.

MATERIALS AND METHODS

Data were extracted from the Surveillance, Epidemiology, and End-Results (SEER) Program's November 2017 release of the SEER 18 registry.¹⁰ Geographic areas covered include Greater California, Greater Georgia, Kentucky, Louisiana, and New Jersey in addition to the SEER 9 (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah) and the SEER 13 areas (Los Angeles, San Jose-Monterey, Rural Georgia and the Alaska Native Tumor Registry).

Inclusion criteria were defined as patients who had a first cancer diagnosis of a primary malignant cancer from 2000 to 2015. Postmortem cases and non-microscopically confirmed cases were excluded. Secondary analyses were also conducted on a sub-cohort of patients, defined as those diagnosed with a primary malignant cancer of neuroendocrine histology. Neuroendocrine tumors (NET) were defined by cancers with the following *ICD-O3 histology/behavior* codes: 8150/3–8157/3, 8240/3–8250/3, and 9190/3.

The outcome was the occurrence of a second primary pancreatic neuroendocrine tumor, defined by an intersection of the SEER variable *Site recode B ICD-O3/WHO 2008* = “Pancreas” and the above reported NET histology codes, at least 6 months after diagnosis of the first primary cancer (FPC); this latency period was used to decrease the likelihood of the pancreatic NET being a pre-existing tumor or incidental finding. SEER uses a definition of multiple primaries that is outlined in the SEER coding manual, which takes account of histology, site, laterality and time since initial diagnosis to identify multiple primary cancers.

11

Statistical Analysis

A single outcome analysis was used, so that patients contributed person-time to the study starting 6 months after their FPC diagnosis and exited the study (i.e. stopped contributing person-time) at the earliest of the following events: a diagnosis of pancreatic NET, death, or loss to follow-up.

The distribution of demographic (age group, sex, race/ethnicity, marital status) and tumor characteristics (year of diagnosis, stage, histologic type, second primary tumor) among the overall and the NET cohort was obtained using a frequency session in SEER*Stat. Next, the Multiple Primary-Standardized Incidence Ratios (MP-SIR) session of the SEER*Stat program was used to calculate age-adjusted standardized incidence ratios (SIR), 95% confidence intervals (CI), and excess risk among the overall and the NET cohort. The SIRs represent the relative risk of developing a pancreatic NET among patients who had an FPC compared with the general population, according to the sex and anatomical site of first primary cancer as: $SIR = \text{observed number of pancreatic NET cases at a particular tumor site} / \text{expected number of pancreatic NET cases at that particular tumor site}$.¹² The expected number of pancreatic NET cases was calculated by multiplying age- and sex-specific population cancer incidence rates with the age- and sex-specific person-years at risk among the cohort, using the formula: $(\text{observed number of pancreatic NET cases in the population} / \text{population's person-years at risk}) \times \text{FPC patients' person-years at risk}$. The excess risk of second primary pancreatic NET per 10,000 persons per year for each FPC site was calculated as: $((\text{observed number of pancreatic NET among FPC patients} - \text{expected number of pancreatic NET cases}) \times 10,000) / \text{FPC patients' person years at risk}$. The average time to diagnosis of second primary pancreatic NET was calculated in months using the mean person-years at risk for each primary cancer site.

Statistical analyses were conducted using SEER*Stat software (National Cancer Institute, DCCPS, Surveillance Research Program SEER*Stat software (www.seer.cancer.gov/seerstat) version 8.3.4).

RESULTS

During 2000–2015, 4,008,092 persons were reported in SEER with a diagnosis of a primary malignant cancer, of which 67,414 (1.7%) had neuroendocrine histology (Table 1). The majority of patients was age 45+ years and White; the NET cohort had a slightly higher proportion of Blacks (13.2%) compared with the overall cohort (10.6%). The overall cohort had a balanced sex distribution, but a slight majority (54%) of the NET cohort was female.

A slightly higher proportion of NETs were diagnosed at the distant stage (17.6%) compared to the overall cohort (15.1%). Similar proportions of both cohorts were diagnosed with a second primary cancer, however, a much higher proportion of the second primary tumors in the NET cohort were of neuroendocrine histology (14.7%) compared with just 2.3% in the overall cohort.

Persons diagnosed with a first primary cancer at any site and for any solid tumor had a significantly higher risk of developing a second primary pancreatic NET compared with the general population (SIR, 1.3; 95% CI, 1.2–1.5). Site-specific results show a significantly higher risk of developing a second primary pancreatic NET following a primary cancer of the pancreas, thymus, adrenal gland and other endocrine organs, small intestine, liver and biliary organs, stomach, esophagus and other digestive organs, kidney, renal pelvis and other urinary organs, lung and other respiratory organs, female breast, and miscellaneous organs (Table 2). In the “miscellaneous” site group, the increased risk was due to cancers in the soft tissue including heart (SIR, 3.1; 95% CI, 1.1–6.7), and non-melanoma, non-epithelial skin cancer (SIR, 3.3; 95% CI, 1.1–7.6). The overall excess risk of having a second primary pancreatic NET was 0.07 per 10,000 person-years, and was highest for those with a primary cancer of the pancreas (1.9 cases per 10,000 person-years).

In the NET group, the relative risk of a second primary pancreatic NET was even higher after any NET primary (SIR, 8.0; 95% CI, 5.8–10.6), and after any solid NET (SIR, 8.2; 95% CI, 5.9–11.1). The risk of a second primary pancreatic NET was significantly increased following a primary in the same organs as in the general cohort, except for liver and biliary organs (1 case), and kidney, renal pelvis and other urinary organs (0 cases) (Table 2). In the “miscellaneous” site group, the increased risk was solely due to a primary non-melanoma, non-epithelial skin (SIR, 8.4; 95% CI, 1.7–24.5). Additionally, having a primary cancer of the urinary bladder significantly increased the risk of a second primary pancreatic NET. The excess risk of having a second primary pancreatic NET among those with a primary NET at any site was 1.3 per 10,000 person-years, and was highest for those with a primary cancer in the urinary bladder (27.1 cases/10,000 person-years), followed by the thymus (12.3 cases/10,000 person-years), female breast (11.8 cases per 10,000 person-years), and pancreas (6.9 cases per 10,000 person-years).

When data are stratified according to sex (Table 3), among males the risk of developing a second primary pancreatic NET was significantly increased following any primary cancer, any solid tumor, and primary cancer in the pancreas, thymus, adrenal gland, and other endocrine organs, small intestine, liver, and biliary organs, kidney, renal pelvis and other urinary organs, lung and other respiratory organs. Risk was also significantly increased

following non-melanoma, non-epithelial skin cancer (SIR, 3.8; 95% CI, 1.04–9.8), although not for the entire “Miscellaneous” group. The excess risk of having a second primary pancreatic NET among males with a primary cancer was 0.05 per 10,000 person-years, and was highest for those with a first primary cancer of the pancreas (1.4 cases per 10,000 person-years).

Among females, the risk of developing a second primary pancreatic NET was significantly increased following a primary cancer of the pancreas, small intestine, stomach, esophagus and other digestive organs, kidney, renal pelvis and other urinary organs, lung and other respiratory organs, female breast, and miscellaneous organs. The excess risk of a second primary pancreatic NET among females with a first primary cancer at any site was 1.6 per 10,000 person-years, and was highest for those with a first primary cancer of the pancreas (2.4 cases per 10,000 person-years).

On average, the second primary pancreatic NET was diagnosed 58 months after diagnosis of the first primary cancer at any site and 59 months after diagnosis of a solid tumor. Time to diagnosis of the pancreatic NET was shortest after first primary cancer of the pancreas (16 months), followed by liver and biliary organs, and lung and other respiratory organs (25 months), and stomach, esophagus and other digestive organs (30 months), while it was longest following female breast cancer (69 months). For all sites except thymus, adrenal gland and other endocrine organs, females developed second primary pancreatic NET at the same time or somewhat later than males.

The excess risk of second primary pancreatic NET was markedly greater in patients who had received radiotherapy for the first primary cancer, and specifically for first primary in the urinary bladder and melanoma, stomach, esophagus and other digestive organs, compared to those who had not received it (Fig. 1). The same was observed for those who received chemotherapy for cancer in the same sites, and additionally for cancer of the vulva and other female genitals, uterus, cervix, prostate, testes, penis and other male genitals (Fig. 2).

DISCUSSION

This study reports that there is an increased risk and excess incidence of second primary pancreatic neuroendocrine tumors in patients who were previously diagnosed with a primary cancer overall and in specific anatomical sites compared to the general population. To our knowledge, this is the first study to have assessed history of primary cancer as a risk factor for a second primary pancreatic NET.

As cancer survivorship has increased, the proportion of incident primary cancers that are second or higher-order has also steadily increased from 6% in 1973¹³ to 15% in the present data set, which covers 2000 to 2015. We also observed that 8% of people diagnosed with a first primary cancer developed a second primary tumor. Second primary cancers can be grouped according to predominant etiologic influences as syndromic, cancer treatment-related, and shared etiologic exposures.¹⁴ Syndromic cancers are associated with mutations in major susceptibility genes identified in the familial setting, whose penetrance is influenced by the location of the specific mutation, gene-gene interactions, and gene-

environment interactions.¹⁴ In case of pancreatic NET, associated genetic syndromes include multiple endocrine neoplasia type 1 (*MEN1*), Von-Hippel-Lindau disease (*VHL*) and neurofibromatosis type 1 (*NFI*).¹⁵ The *MEN1* syndrome is associated with increased risk of cancers in the endocrine pancreas, anterior pituitary, and parathyroid gland.³ People with *VHL* have an increased risk of pancreatic NET along with certain subtypes of kidney cancer (clear cell renal cell carcinoma) and adrenal gland cancer (pheochromocytoma).¹⁶ Although the majority of tumors associated with the *NFI* mutation are benign nerve and skin lesions, the risk of breast cancer is 3.5 folds in women with *NFI*, and five times in younger women.¹⁷ In this study, we observed that there was increased risk of second primary pancreatic NET among patients with first primary tumor of the breast (female), kidney and the thymus, adrenal, and other endocrine organs group, which could be possibly consistent with the above syndromes.

Other than direct genetic mutations, host factors such as impaired immune function and hormonal imbalances may also increase risk of second primary cancers. Shared etiological exposures are those that may increase the risk of the first and all subsequent primary tumors in the same individual, including lifestyle or behavioral factors such as tobacco, alcohol, and diet; and environmental factors such as contaminants, pollution, and occupational exposures.¹⁴ In this study, pancreatic NET was associated with first primary cancer of the lung, stomach, esophageal, kidney, and urinary bladder, all of which share an important etiological factor, tobacco use.^{7,18} Additionally, certain environmental exposures associated with pancreatic tumors (pesticides, cadmium, nickel, metalworking fluids and mineral oil) also increase the risk of cancer in some of the associated first primary cancer sites, including kidney, stomach, esophagus, breast, lung, soft tissues.¹⁹ Due to the nature of the data set, no information on environmental exposures or smoking habits is available.

Radiation and chemotherapy cancer treatments are known to be potentially carcinogenic because of the widespread genetic damage that overwhelms the DNA repair mechanism.²⁰ Radiotherapy may also interact with genetic susceptibility and tobacco use to increase the risk of a second primary cancer.²¹ For most secondary cancer sites, a linear dose-response relationship has been documented for radiotherapy, but the magnitude and shape of this relationship is less clear for pancreatic cancer.²² The pancreas does not appear to be particularly sensitive to radiation, except when very high doses are used.²¹ The total radiation dosage used to treat urinary bladder cancer is typically quite high at 55–70 Gy.²³ This may partly explain our observation of increased excess risk in bladder cancer survivors who underwent radiotherapy.

Chemotherapeutic drugs, particularly alkylating agents, topoisomerase II inhibitors and antimetabolites, have been associated with an increased risk of mainly leukemia, but also non-hematological tumors.^{22,24} The observed increase in the number of second primary tumors may be partially attributable to greater surveillance in cancer survivors, particularly for certain sites. Surveillance bias may occur if some cancer survivors are followed up more closely or undergo more follow-up diagnostic tests than others, leading to more frequent detection of a second primary cancer.²⁵

This study has some limitations. Since a very small proportion of first primary cancers were neuroendocrine, it was difficult to reliably measure excess risk of a second primary pancreatic NET in this sub-cohort. Cancer therapy data on the use of different chemotherapeutic agents or radiation dosage were not available in the SEER database. However, an important strength of the study is the large sample size, resulting in robust risk estimates for the overall cohort. The use of the most recent SEER 18 registry provided data for 16 years, with the widest possible coverage of the US population available in the SEER databases. Considering the complex mechanisms of carcinogenesis, the risk of a second primary pancreatic NET may be increased depending upon not only the site of the first primary cancer and the treatment used, but also on interactions with genetic predispositions, environmental exposures and risk behaviors. More longitudinal studies are needed to confirm the findings from this study and establish clear risk factors for a second primary pancreatic NET.

Cancer survivors should undergo regular follow up to monitor the pancreas, particularly during the first five years after first cancer diagnosis, since that is the average time to occurrence of most second pancreatic NET cases observed in our data. However, the carcinogenic effects of chemotherapy and radiotherapy may be delayed up to and beyond ten years.²⁶ Therefore, continued screening is recommended, particularly in survivors with known risk factors such as family history, presence of genetic mutations, and in those with increased excess risk (first primary cancers in the urinary bladder, pancreas, gastrointestinal tract, liver and gallbladder, female breast, thymus and other endocrine organs). Although environmental and occupational health interventions are mostly at the policy level, individual cancer survivors should be counseled on reducing their exposure to known and suspected carcinogens and endocrine-disrupting chemicals.²⁷ Lifestyle interventions including smoking cessation, diet and physical activity may reduce risk of developing a second cancer.²⁸

Acknowledgment of financial support:

This work was supported by a grant from the National Cancer Institute at the National Institutes of Health [P30 CA196521].

REFERENCES

1. American Cancer Society: Cancer Facts and Figures 2018. Atlanta, GA: American Cancer Society, 2018 Available at: <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf>. Accessed May 8, 2018.
2. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2015, National Cancer Institute. Bethesda, MD, based on November 2017 SEER data submission. 4 2018 Available at: https://seer.cancer.gov/csr/1975_2015/. Accessed May 8, 2018.
3. Davies K, Conlon KC. Neuroendocrine tumors of the pancreas. *Curr Gastroenterol Rep*. 2009;11:119–127. [PubMed: 19281699]
4. Ro C, Chai W, Yu VE, et al. Pancreatic neuroendocrine tumors: biology, diagnosis, and treatment. *Chin J Cancer*. 2013;32:312–324. [PubMed: 23237225]

5. Hochwald SN, Zee S, Conlon KC, et al. Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *J Clin Oncol*. 2002;20:2633–2642. [PubMed: 12039924]
6. O'Grady HL, Conlon KC. Pancreatic neuroendocrine tumours. *Eur J Surg Oncol*. 2008;34(3):324–332. [PubMed: 17967523]
7. Ben Q, Zhong J, Fei J, et al. Risk Factors for Sporadic Pancreatic Neuroendocrine Tumors: A Case-Control Study. *Sci Rep*. 2016;6:36073. [PubMed: 27782199]
8. Leoncini E, Carioli G, La Vecchia C, et al. Risk factors for neuroendocrine neoplasms: a systematic review and meta-analysis. *Ann Oncol*. 2016;27:68–81. [PubMed: 26487581]
9. Halfdanarson TR, Bamlet WR, McWilliams RR, et al. Risk factors for pancreatic neuroendocrine tumors: a clinic-based case-control study. *Pancreas*. 2014;43:1219–1222. [PubMed: 25291526]
10. Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (1973–2015 varying) - Linked To County Attributes - Total U.S., 1969–2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission. Available at: <https://www.seer.cancer.gov>. Accessed November 5, 2018.
11. Adamo M, Dickie L, Ruhl J. SEER Program Coding and Staging Manual 2016. 2016; Available at: https://seer.cancer.gov/archive/manuals/2016/SPCSM_2016_maindoc.pdf. Accessed November 5, 2018.
12. Rose Ragin CC, Taioli E. Second primary head and neck tumor risk in patients with cervical cancer--SEER data analysis. *Head Neck*. 2008;30:58–66. [PubMed: 17657793]
13. Travis LB. The epidemiology of second primary cancers. *Cancer Epidemiol Biomarkers Prev*. 2006;15:2020–2026. [PubMed: 17057028]
14. Travis LB, Rabkin CS, Brown LM, et al. Cancer survivorship--genetic susceptibility and second primary cancers: research strategies and recommendations. *J Natl Cancer Inst*. 2006;98:15–25. [PubMed: 16391368]
15. Carrera S, Sancho A, Azkona E, et al. Hereditary pancreatic cancer: related syndromes and clinical perspective. *Hered Cancer Clin Pract*. 2017;15:9. [PubMed: 28670351]
16. American Society of Clinical Oncology. Von Hippel-Lindau Syndrome. 2017; Available at: <https://www.cancer.net/cancer-types/von-hippel-lindau-syndrome>. Accessed June 4, 2018.
17. Howell SJ, Hockenhull K, Salih Z, et al. Increased risk of breast cancer in neurofibromatosis type 1: current insights. *Breast Cancer (Dove Med Press)*. 2017;9:531–536. [PubMed: 28860858]
18. Centers for Disease Control. Vital Signs: Cancer and Tobacco Use. 2016; Available at: <https://www.cdc.gov/vitalsigns/cancerandtobacco/index.html>. Accessed November 5, 2018.
19. Clapp RW, Jacobs MM, Loechler EL. Environmental and occupational causes of cancer: new evidence 2005–2007. *Rev Environ Health*. 2008;23:1–37. [PubMed: 18557596]
20. Behjati S, Gundem G, Wedge DC, et al. Mutational signatures of ionizing radiation in second malignancies. *Nat Commun*. 2016;7:12605. [PubMed: 27615322]
21. Travis LB. Therapy-associated solid tumors. *Acta Oncol*. 2002;41:323–333. [PubMed: 12234023]
22. Morton LM, Swerdlow AJ, Schaapveld M, et al. Current knowledge and future research directions in treatment-related second primary malignancies. *EJC Suppl*. 2014;12:5–17. [PubMed: 26217162]
23. Moonen L, vd Voet H, de Nijs R, et al. Muscle-invasive bladder cancer treated with external beam radiation: influence of total dose, overall treatment time, and treatment interruption on local control. *Int J Radiat Oncol Biol Phys*. 1998;42:525–530. [PubMed: 9806510]
24. Travis LB, Demark Wahnefried W, Allan JM, et al. Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors. *Nat Rev Clin Oncol*. 2013;10:289–301. [PubMed: 23529000]
25. Haut ER, Pronovost PJ. Surveillance bias in outcomes reporting. *JAMA*. 2011;305:2462–2463. [PubMed: 21673300]
26. Brower V Tracking chemotherapy's effects on secondary cancers. *J Natl Cancer Inst*. 2013;105:1421–1422. [PubMed: 24052617]

27. US Department of Health and Human Services. Reducing environmental risk: what we can do now. 2008–2009 Annual Report, President’s Cancer Panel 2010; Available at: https://deainfo.nci.nih.gov/advisory/pcp/annualreports/pcp08-09rpt/pcp_report_08-09_508.pdf. Accessed November 5, 2018.
28. Stull VB, Snyder DC, Demark-Wahnefried W. Lifestyle interventions in cancer survivors: designing programs that meet the needs of this vulnerable and growing population. *J Nutr.* 2007;137:243S–248S. [PubMed: 17182834]

FIGURE 1.

Excess risk of second primary pancreatic NET by site of first primary cancer and radiotherapy treatment (per 1000 patients)

FIGURE 2.

Excess risk of second primary pancreatic NET by site of first primary cancer and chemotherapy treatment (per 1000 patients)

TABLE 1.**Demographic Characteristics of Persons Diagnosed With First Primary Cancer During 2000–2015**

Demographic Characteristic	Overall Cohort (N = 4,008,092)	Neuroendocrine Tumor Cohort (N = 67,414)
	N (%)	N (%)
Age group, y		
0–19	58,611 (1.5)	388 (0.6)
20–44	426,472 (10.6)	7,627 (11.3)
45–64	1,689,039 (42.1)	31,106 (46.1)
65+	1,833,970 (45.8)	28,293 (42.0)
Race		
White	3,261,454 (81.4)	52,686 (78.2)
Black	423,571 (10.6)	8,887 (13.2)
American Indian/Alaska Native	17,259 (0.4)	276 (0.4)
Asian or Pacific Islander	255,884 (6.4)	4,409 (6.5)
Unknown	49,924 (1.2)	1156 (1.7)
Ethnicity		
Non-Hispanic	3,615,308 (90.2)	60,844 (90.3)
Hispanic	392,784 (9.8)	6,570 (9.7)
Sex		
Male	2,058,705 (51.4)	31,078 (46.1)
Female	1,949,387 (48.6)	36,336 (53.9)
Marital Status		
Single (never married)	605,701 (15.1)	9,596 (14.2)
Married or domestic partner	2,268,666 (56.6)	38,147 (56.6)
Divorced/separated/widowed	820,108 (20.5)	13,907 (20.6)
Unknown	313,617 (7.8)	5,764 (8.6)
Year of diagnosis		
2000–2005	1,478,470 (36.9)	22,180 (32.9)
2006–2010	1,328,951 (33.2)	22,619 (33.6)
2011–2015	1,200,671 (30.0)	22,615 (33.5)
SEER historic stage [*]		
In situ/Localized	1,467,957 (37.0)	34,504 (51.4)
Regional	783,930 (19.8)	13,533 (20.2)
Distant	600,566 (15.1)	11,802 (17.6)
Localized/regional (prostate cases)	692,467 (17.5)	47 (0.1)
Unstaged	421,634 (10.6)	7,245 (10.8)
Neuroendocrine histology		
Yes	67,414 (1.7)	-
No	3,940,678 (98.3)	-
Second primary malignancy following first		
None	3,695,300 (92.2)	61,796 (91.7)
Any cancer	312,792 (7.8)	5,618 (8.3)

	Overall Cohort (N = 4,008,092)	Neuroendocrine Tumor Cohort (N = 67,414)
Demographic Characteristic	N (%)	N (%)
Neuroendocrine cancer [†]	7,149 (2.3)	826 (14.7)
Pancreatic neuroendocrine cancer [†]	519 (0.2)	45 (0.8)

* Percentage of non-blank values (Blanks = 1% of overall cohort, 0.4% of neuroendocrine cancer)

[†] Percentage of those with any second primary cancer

TABLE 2.

Risk of Second Primary Pancreatic NET According to Site of First Primary Cancer

Site of First Primary Cancer	Overall Cohort (N = 4,008,092)			Neuroendocrine Tumor Cohort (N = 67,414)		
	PNET Cases*	SIR [†] (95% CI)	Excess Risk Per 10,000	PNET Cases*	SIR [†] (95% CI)	Excess Risk Per 10,000
All sites	519	1.3 (1.2–1.5)	0.07	45	8 (5.8–10.6)	1.3
All solid tumors	481	1.3 (1.2–1.5)	0.07	42	8.2 (5.9–11.1)	1.33
Head and neck	9	0.7 (0.3–1.4)	–0.06	0	-	-
Stomach, esophagus, other digestive	10	2.3 (1.1–4.1)	0.27	3	9.4 (2.0–27.6)	1.56
Small Intestine	7	4.8 (1.9–9.8)	0.76	7	6.7 (2.7–13.8)	1.2
Colon and rectum	42	1.2 (0.8–1.6)	0.03	4	2.3 (0.6–6.0)	0.24
Anus, anal canal and anorectum	0	-	-	0	-	-
Liver and biliary	10	3.6 (1.7–6.5)	0.52	1	23.7 (0.6–131.8)	4.03
Pancreas	16	10.6 (6.0–17.2)	1.9	12	37.5 (19.4–65.6)	6.86
Lung, bronchus, pleura, other respiratory	32	2.1 (1.4–3.0)	0.23	12	7.7 (4.0–13.4)	1.21
Female breast	74	1.3 (1.0–1.6)	0.04	1	75 (1.9–417.9)	11.82
Cervix	2	0.9 (0.1–3.1)	–0.01	0	-	-
Uterus	13	1.1 (0.6–1.9)	0.02	0	-	-
Ovary	2	0.7 (0.1–2.3)	–0.05	0	-	-
Vulva, vagina, other female genital	3	2.8 (0.6–8.1)	0.24	0	-	-
Male breast	1	1.6 (0.0–9.1)	0.17	0	-	-
Prostate	153	1.1 (0.9–1.3)	0.03	0	-	-
Testes, penis, other male genital	3	1.5 (0.3–4.4)	0.04	0	-	-
Urinary bladder	29	1.5 (1.0–2.1)	0.12	1	103.8 (2.6–578.5)	27.12
Kidney, renal pelvis, ureter, other urinary	27	2.2 (1.4–3.2)	0.24	0	-	-
Brain, eye & orbit, other nervous system	2	0.9 (0.1–3.4)	–0.01	0	-	-
Thyroid	13	1.4 (0.8–2.5)	0.05	0	-	-
Thymus, adrenal gland, other endocrine	3	7.7 (1.6–22.6)	0.74	1	75.9 (1.9–422.9)	12.32
Hematopoietic and lymphatic tissue	30	1.1 (0.7–1.5)	0.01	0	-	-
Melanoma skin	22	1.2 (0.7–1.8)	0.03	0	-	-
Lining membranes	1	1.6 (0.0–8.8)	0.09	0	-	-
Miscellaneous	15	2.4 (1.3–4.0)	0.21	3	5.7 (1.2–16.8)	1.03

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Patients diagnosed with second primary pancreatic NET

* Standardized Incidence Ratio for risk of second primary pancreatic NET compared to general population (95% confidence interval)

TABLE 3.

Risk of and Average Time to Second Primary Pancreatic NET According to Site of First Primary Cancer (Overall Cohort), by sex

Site of First Primary Cancer	Males (N = 2,058,705)				Females (N = 1,949,387)			
	PNET Cases*	SIR [†] (95% CI)	Excess Risk Per 10,000	Average Months to Diagnosis	PNET Cases*	SIR [†] (95% CI)	Excess Risk Per 10,000	Average Months to Diagnosis
All sites	309	1.2 (1.1–1.3)	0.05	58	210	1.6 (1.4–1.8)	0.08	59
All solid tumors	287	1.2 (1.1–1.4)	0.06	58	194	1.6 (1.4–1.8)	0.08	59
Head and neck	5	0.5 (0.2–1.2)	−0.12	50	4	1.7 (0.5–4.4)	0.1	52
Stomach, esophagus, other digestive	3	0.9 (0.2–2.7)	−0.02	28	7	6.1 (2.5–12.6)	0.76	34
Small intestine	4	4.3 (1.2–11.1)	0.81	52	3	5.5 (1.1–16.0)	0.7	53
Colon and rectum	25	1.1 (0.7–1.6)	0.02	55	17	1.3 (0.8–2.1)	0.04	57
Anus, anal canal and anorectum	0	-	-	-	0	-	-	-
Liver and biliary	7	3.4 (1.4–7.0)	0.56	25	3	4 (0.8–11.7)	0.45	26
Pancreas	6	6.5 (2.4–14.2)	1.36	16	10	16.9 (8.1–31.1)	2.42	16
Lung, bronchus, pleura, other respiratory	17	1.9 (1.1–3.0)	0.23	23	15	2.4 (1.3–3.9)	0.22	28
Female breast	n/a	-	-	-	74	1.3 (1.0–1.6)	0.04	69
Cervix	n/a	-	-	-	2	0.9 (0.1–3.1)	−0.01	63
Uterus	n/a	-	-	-	13	1.1 (0.6–1.9)	0.02	64
Ovary	n/a	-	-	-	2	0.7 (0.1–2.3)	−0.05	49
Vulva, vagina, other female genital	n/a	-	-	-	3	2.8 (0.6–8.1)	0.24	53
Male breast	1	1.6 (0.0–9.1)	0.17	58	n/a	-	-	-
Prostate	153	1.1 (0.9–1.3)	0.03	74	n/a	-	-	-
Testes, penis, other male genital	3	1.5 (0.3–4.4)	0.04	78	n/a	-	-	-
Urinary bladder	21	1.3 (0.8–1.9)	0.07	56	8	2.6 (1.1–5.1)	0.25	58
Kidney, renal pelvis, ureter, other urinary	18	2 (1.2–3.2)	0.25	54	9	2.5 (1.1–4.7)	0.23	57
Brain, eye and orbit, other nervous system	2	1.5 (0.2–5.4)	0.05	43	0	-	-	-
Thyroid	5	1.7 (0.6–4.1)	0.13	67	8	1.3 (0.6–2.6)	0.03	71
Thymus, adrenal gland, other endocrine	2	8.7 (1.1–31.4)	0.91	59	1	6.4 (0.2–35.4)	0.54	57
Hematopoietic and lymphatic tissue	17	0.9 (0.5–1.5)	−0.02	55	13	1.3 (0.7–2.2)	0.04	57

Site of First Primary Cancer	Males (N = 2,058,705)					Females (N = 1,949,387)				
	PNET Cases*	SIR [†] (95% CI)	Excess Risk Per 10,000	Average Months to Diagnosis	PNET Cases	SIR [†] (95% CI)	Excess Risk Per 10,000	Average Months to Diagnosis	PNET Cases	SIR [†] (95% CI)
Melanoma skin	11	0.9 (0.4–1.5)	−0.03	63	11	1.8 (0.9–3.3)	0.1	71		
Lining membranes	0	-	-	-	1	2.8 (0.1–15.7)	0.26	37		
Miscellaneous	9	2.1 (1.0–4.0)	0.2	52	6	3.1 (1.1–6.7)	0.23	51		

* Patients diagnosed with second primary pancreatic NET

[†] Standardized Incidence Ratio for risk of second primary pancreatic NET compared to general population (95% confidence interval)

n/a indicates not applicable.