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ORIGINAL ARTICLE – ENDOCRINE TUMORS

The Incidence and Survival of Rare Cancers of the Thyroid, Parathyroid, Adrenal, and Pancreas

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ABSTRACT

Purpose. With the exception of papillary and follicular thyroid cancer, malignant cancers of the thyroid, parathyroid, adrenal, and endocrine pancreas are uncommon. These rare malignancies present a challenge to both the clinician and patient, because few data exist on their incidence or survival. We analyzed the incidence and survival of these rare endocrine cancers (RECs), as well as the trends in incidence over time.

Methods. We used the NCI's SEER 18 database (2000–2012) to investigate incidence and survival of rare cancers of the thyroid, parathyroid, adrenal, and endocrine pancreas. Cancers were categorized using the WHO classification systems. We collected data on incidence, gender, stage, size, and survival. Time trends were evaluated from 2000–2002 to 2010–2012.

Results. We identified 36 types of rare cancers in the endocrine organs captured in the SEER database. RECs of the thyroid had the highest combined incidence rate (IR 8.26), followed by pancreas (IR 3.24), adrenal (IR 2.71), and parathyroid (IR 0.41). The incidence rate for all rare endocrine organs combined increased 32.4 % during the study period. The majority of the increase was attributable to rare cancers of thyroid, which increased in not only microcarcinomas, but in all sizes. The mean 5-year survival for RECs is 59.56 % (range 2.49–100 %).

Conclusions. This study is a comprehensive analysis of the incidence and survival for rare malignant endocrine cancers. There has been an increase in incidence rate of almost all RECs and their survival is low. We hope that our data will serve as a source of information for clinicians as well as bring awareness regarding these uncommon cancers.

Rare endocrine cancers (RECs) present a significant challenge to the clinician and patient.[1] It is possible that physicians may encounter a REC once in their entire career, making it difficult to be knowledgeable about RECs, some of which can be highly aggressive.[2] Additionally, rare cancers have traditionally received little allocation of funds for research.[3] The United States government has attempted to broadly address this problem via several avenues, including the implementation of the Rare Disease Act of 2002 and the United States Orphan Drug Act—both of which promote research on and development of drugs for rare diseases.[4,5] Furthermore, in 1993 the NIH established the Office of Rare Diseases Research, which supports the research of rare diseases. However, this office, while serving to broadly respond to the needs of rare diseases, has not formally focused on RECs outside of providing basic information to patients.

As a result of the lack of formalized initiatives to address RECs, much of what is known is derived from case reports and case series.[6–10] This is problematic, as these data generally do not provide enough information to make sound inferences about incidence and survival. With the development of national databases such as the Surveillance, Epidemiology, and End Results (SEER) database, information on incidence and survival trends of rare cancers have become more readily available. However, to our knowledge, there have been no comprehensive descriptive

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epidemiologic studies using the SEER database quantifying incidence and survival trends for RECs individually and as a group.

In the present study, our goal was to determine the incidence rate (IR) and survival of rare cancers of the thyroid, parathyroid, adrenal gland, and pancreas. We used the National Cancer Institute's (NCIs) Surveillance, Epidemiology and End Result (SEER) database with classification based on the most recent International Classification of Disease for Oncology (ICD-0) codes. We further considered demographic and tumor characteristics to provide information on the frequency and aggressiveness of these RECs. This work will illustrate the disease burden of RECs as well as provide a reference for clinicians treating these cancers.

METHODS

Cancers are defined as rare when occurring with an incidence of less than 60 cases per 1,000,000 person-years.[11,12] The NCI's SEER 18 Registries Database was used to analyze incidence and survival rates from 2000 to 2012.[13] The SEER 18 Registries Database includes registries in Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, Alaska Native Tumor Registry, Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia, which covers roughly 28 % of the U.S. population.

RECs were coded using the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3).[14] These codes categorize cancers based on both the topographic site and the histology of the tumor. The organs studied include the thyroid gland, parathyroid gland, adrenal gland, and endocrine pancreas (we did not include adenocarcinoma of the pancreas). Tumors were then stratified further based on histologic subtype groupings. A pathologist specialized in endocrine organs reviewed the subtypes. In cases where multiple names are used to describe the same histologic subtype, they were combined (Table 1). Each specific ICD-O code is listed in Table 2 for reference purposes. Benign neoplasms and neoplasms that are metastatic from other organs were excluded. In addition to histologic subtype, we evaluated patient demographics and tumor characteristics, including gender, tumor size, and stage for IR and survival (1, 5, and 10 year). SEER historic stage A is used to classify tumors as localized (limited to the organ), regional (limited to the surrounding tissue), and distant (systemic disease).[14] Beginning in 1988, SEER began collecting information on tumor size, which is defined as the cancer's greatest diameter as recorded on surgical pathology reports. Tumors were categorized as ≤ 1, >1 to ≤ 2, >2 to ≤ 4, and >4 cm based on the Extent of Disease-10 (EOD-10) codes for 1988–2003 and the Collaborative Staging (CS) codes for 2004–2006.[15]

SEER data were used to calculate survival using the date of diagnosis and one of the following: date of death, date last known to be alive, or date of the study cutoff (December 31, 2012). For survival analysis, patients whose disease status is based on a death certificate or autopsy only, patients with second or later primaries, and patients who are not actively followed were excluded. To evaluate change in IR and survival over the study period, we evaluated the difference between two time periods: 2000–2002 to 2010–2012. IR and percent change were only included if there were greater than 10 cases. IRs were calculated using SEER*Stat software, version 8.2.1 and were expressed per 1,000,000 person-years and age-adjusted to the 2000 STD population (19 age groups; census P25-1130) standard.[16]

RESULTS

There were 36 unique RECs in the four endocrine organs reported in the SEER database between 2000 and 2012 (Table 2). The IR for all RECs combined was 17.23, and RECs were more common in females (IR 18.84) than males (IR 15.6). RECs increased over the study period from 2000–2002 to 2010–2012 (IR 14.61–32.38). RECs are most commonly localized with an overall IR of 4.66 (Table 3). The majority of RECs are >4 cm (IR 9.89) compared with RECs >2 to ≤ 4 cm (IR 4.01), >1 to ≤ 2 cm (IR 2.11), and ≤ 1 cm (IR 1.22; Table 4). The 5-year survival for all RECs combined is 59.56 % (range 2.49–100 %; Table 5).

Thyroid

There were 22 thyroid cancers that qualified as a REC. These included three variants of papillary thyroid cancer: diffuse sclerosing, columnar cell, and oxyphilic (oncocytic) variant. There were two follicular carcinoma variants: oxyphilic (oncocytic) and clear cell variant. The remaining 17 subtypes were not classified as papillary or follicular variants (Table 2).

Thyroid RECs had the highest combined IR of all the endocrine organs evaluated (IR 9.55). The IR of thyroid RECS increased in incidence by 23 % and was greater in women (IR 11.94) than men (IR 6.95), with an IRR of 1.7:1. The IR of localized and regional disease was roughly equal (IR 3.40 and 3.42, respectively). The IR of distant disease was 1.28. By size, thyroid RECs had a higher IR of cancers >4 cm (IR 4.66), followed by cancers >2 to ≤ 4 (IR 2.41), >1 to ≤ 2 (IR 1.5), and ≤ 1 cm (IR 0.99). The 5-year survival for all thyroid RECs combined was 72.02 %.

TABLE 1 Rare endocrine tumor combined terms

Rare endocrine cancer subtypes	Terms combined
Thyroid	
Follicular carcinoma (total)	
Classic (or NOS)	Follicular adenocarcinoma NOS, well-differentiated follicular adenocarcinoma, trabecular follicular adenocarcinoma and minimally-invasive follicular carcinoma
Poorly differentiated	Trabecular adenocarcinoma, insular carcinoma and poorly differentiated carcinoma
Undifferentiated	Undifferentiated carcinoma, carcinoma undifferentiated type NOS, carcinoma anaplastic type NOS, pleomorphic carcinoma, giant cell and spindle cell carcinoma, giant cell carcinoma, spindle cell carcinoma, pseudosarcomatous carcinoma, polygonal cell carcinoma, and carcinoma with osteoclast like giant cells
Medullary carcinoma	Medullary thyroid carcinoma, solid carcinoma NOS, neuroendocrine carcinoma, medullary carcinoma with amyloid stroma, and medullary carcinoma NOS
Mixed medullary and pap./follicular	Adenocarcinoma with mixed subtypes, mixed cell adenocarcinoma, mixed medullary follicular carcinoma, and mixed medullary papillary carcinoma
Squamous cell	Papillary squamous cell carcinoma, squamous cell carcinoma NOS, keratinizing squamous cell carcinoma, large cell nonkeratinizing squamous cell carcinoma, spindle cell squamous carcinoma, basaloid squamous cell carcinoma, adenosquamous carcinoma, adenocarcinoma with squamous metaplasia
Mucoepidermoid	Mucinous adenocarcinoma and mucin-producing adenocarcinoma
Malignant paraganglioma	Malignant paraganglioma and pheochromocytoma
Sarcoma	Sarcoma NOS, fibrosarcoma NOS, malignant fibrous histiocytoma, leiomyosarcoma, synovial sarcoma NOS, spindle cell synovial sarcoma, hemangiosarcoma, histiocytic sarcoma, and follicular dendritic cell sarcoma
Lymphoma and plasmacytoma	
Hodgkin lymphoma	HL NOS, nodular lymphocytic predominant HL and nodular sclerosis HL
Non-Hodgkin lymphoma	Malignant lymphoma NHL NOS, small cell B lymphocytic NHL NOS, lymphoplasmacytic NHL, mantle cell lymphoma, mixed small and large cell diffuse NHL, large B-cell diffuse NHL, large B-cell diffuse immunoblastic NHL NOS, Burkitt lymphoma NOS, follicular lymphoma NOS, follicular lymphoma grades 1, 2, and 3, marginal zone B-cell lymphoma NOS, mature T-cell lymphoma NOS, anaplastic large cell lymphoma T-cell and null cell type
Parathyroid	
Parathyroid carcinoma	Malignant parathyroid neoplasm, parathyroid carcinoma NOS, parathyroid adenocarcinoma NOS, parathyroid oxyphilic adenocarcinoma, and parathyroid clear cell adenocarcinoma NOS
Adrenal	
Adrenal cortical carcinoma	Carcinoma NOS, undifferentiated type carcinoma NOS, adenocarcinoma NOS and adrenal cortical carcinoma
Neuroblastoma	Neuroblastoma NOS and ganglioneuroblastoma
Malignant pheochromocytoma	Neuroendocrine carcinoma, malignant paraganglioma and pheochromocytoma
Sarcoma	Sarcoma NOS, spindle cell sarcoma, undifferentiated sarcoma, fibrosarcoma NOS, malignant fibrous histiocytoma, leiomyosarcoma NOS, hemangiosarcoma, Ewing sarcoma, peripheral neuroectodermal tumor, and primitive neuroectodermal tumor
Pancreas	
Well-differentiated	
Nonfunctioning (total)	Islet cell tumors and neuroendocrine tumors
Poorly differentiated (small cell)	
Mixed exocrine–endocrine	Mixed islet cell/exocrine adenocarcinoma and adenocarcinoid tumor

Parathyroid

There was only one cancer of the parathyroid gland: parathyroid carcinoma. By definition, this cancer is considered a REC. The IR for parathyroid carcinoma was 0.36 and demonstrates a 19.5 % decrease in IR over the study period. Parathyroid carcinoma was more common in men (IR 0.41) than women (IR 0.33), with an IRR of 1.2:1. The majority of these cancers were localized (IR 0.06) compared with regional (IR 0.04) and distant (IR 0). Regarding size, parathyroid cancers were most commonly >4 cm (IR 0.18). However, this size category saw a 39.1 % decrease in IR, whereas cancers $\leq$1 cm and >1 to $\leq$2 cm saw a 100 and 20 % increase, respectively. The 5-year survival for parathyroid carcinoma was 82.57 %.

TABLE 2 Rare endocrine tumors incidence rate and percent change in incidence rate: 2000–2002 to 2010–2012 change

	ICD-0 code	Incidence rate (*N*)	Male incidence rate (*N*)	Female incidence rate (*N*)	% change in incidence rate (2000–2002 to 2010–2012)
Thyroid		9.55 (10,261)	6.95 (3444)	11.94 (6817)	22.76
Papillary Carcinoma-rare (total)		1.46 (1590)	0.80 (409)	2.11 (1191)	173.68
Variant: diffuse sclerosing	8350/3	0.34 (370)	0.13 (72)	0.54 (298)	91.30
Variant: columnar cell	8344/3	0.99 (1073)	0.60 (301)	1.37 (772)	187.76
Variant: oxyphilic (oncocytic)	8342/3	0.13 (147)	0.07 (36)	0.20 (111)	340.00
Follicular Carcinoma (total)		3.07 (3298)	1.96 (973)	4.10 (2325)	0.35
Variant: oxyphilic (oncocytic)	8290/3	3.05 (3278)	1.95 (966)	4.08 (2312)	0.35
Variant: clear cell	8310/3	0.02 (20)	* (7)	0.02 (13)	−33.33
Poorly Differentiated	8190/3, 8337/3	0.20 (218)	0.21 (101)	0.20 (117)	46.15
Undifferentiated (anaplastic)	8020/3, 8021/3, 8022/3, 8030/3, 8031/3, 8032/3, 8033/3, 8034/3, 8035/3	1.08 (1140)	0.95 (442)	1.17 (698)	15.31
Carcinosarcoma	8980/3	0.01 (10)	* (3)	* (7)	0
Medullary carcinoma	8230/3, 8246/3, 8345/3, 8510/3	2.08 (2254)	1.87 (949)	2.31 (1305)	31.49
Mixed medullary and Pap./follicular	8255/3, 8323/3, 8346/3, 8347/3	0.20 (218)	0.15 (77)	0.25 (141)	50
Squamous cell	8052/3, 8070/3, 8071/3, 8072/3, 8074/3, 8083/3, 8560/3, 8570/3	0.15 (162)	0.12 (58)	0.18 (104)	−6.67
Mucoepidermoid	8430/3	0.03 (28)	* (4)	0.04 (24)	−33.33
Mucinous	8480/3, 8481/3	* (6)	* (3)	* (3)	*
SETTLE	8588/3	* (2)	* (1)	* (1)	*
CASTLE	8589/3	* (5)	* (0)	* (5)	*
Malignant Paraganglioma	8680/3, 8700/3	* (4)	* (2)	* (2)	*
Malignant teratoma	9080/3	* (5)	* (1)	* (4)	*
Sarcoma	8800/3, 8810/3, 8830/3, 8890/3, 9040/3, 9041/3, 9120/3, 9755/3, 9758/3	0.02 (26)	0.03 (15)	0.02 (11)	50
Lymphoma and plasmacytoma					
Lymphoma, NOS	9590/3	0.04 (38)	* (7)	0.05 (31)	−60
Hodgkin lymphoma	9650/3, 9659/3, 9663/3	0.01 (15)	* (4)	0.02 (11)	0
Non-Hodgkin lymphoma	9670/3, 9671/3, 9673/3, 9675/3, 9680/3, 9684/3, 9687/3, 9690/3, 9691/3, 9695/3, 9698/3, 9699/3, 9702/3, 9714/3	1.18 (1256)	0.81 (394)	1.48 (862)	−18.25
Plasmacytoma	9731/3, 9734/3	0.01 (14)	* (5)	* (9)	−100
Parathyroid					
Parathyroid carcinoma	8000/3, 8010/3, 8140/3, 8290/3, 8310/3	0.36 (395)	0.41 (208)	0.33 (187)	−19.51
Adrenal		2.71 (2923)	2.68 (1402)	2.75 (1521)	−3.69
Adrenal cortical carcinoma	8010/3, 8020/3, 8140/3, 8370/3	1.26 (1364)	1.14 (569)	1.40 (795)	−7.41
Neuroblastoma	9490/3, 9500/3	1.06 (1141)	1.15 (630)	0.97 (511)	1.98
Malignant pheochromocytoma	8246/3, 8680/3, 8700/3	0.32 (346)	0.32 (168)	0.31 (178)	−13.33
Sarcoma	8800/3, 8801/3, 8805/3, 8810/3, 8830/3, 8890/3, 9120/3, 9260/3, 9364/3, 9473/3	0.06 (68)	0.06 (31)	0.07 (37)	40
Melanoma	8720/3, 8745/3	* (4)	* (4)	* (0)	*
Pancreas		4.60 (4963)	5.59 (2772)	3.82 (2191)	93.21
Well-differentiated		4.22 (4565)	5.12 (2548)	3.51 (2017)	105.59
Functioning (total)		0.16 (171)	0.15 (79)	0.16 (92)	−6.25
Insulin-secreting	8151/3	0.06 (67)	0.06 (29)	0.07 (38)	100

TABLE 2 continued

	ICD-0 code	Incidence rate (*N*)	Male incidence rate (*N*)	Female incidence rate (*N*)	% change in incidence rate (2000–2002 to 2010–2012)
Glucagon-secreting	8152/3	0.03 (33)	0.03 (16)	0.03 (17)	−33.33
Somatostatin-secreting	8156/3	* (2)	* (1)	* (1)	*
Gastrin-secreting	8153/3	0.05 (58)	0.05 (29)	0.05 (29)	−16.67
VIP-secreting	8155/3	0.01 (11)	* (4)	* (7)	−100
Non-functioning (or unknown)	8150/3, 8246/3	4.06 (4394)	4.96 (2469)	3.35 (1925)	112.59
Poorly-differentiated (small cell)	8041/3	0.26 (273)	0.32 (148)	0.21 (125)	−20
Mixed exocrine–endocrine	8154/3, 8245/3	0.12 (125)	0.16 (76)	0.09 (49)	100

Rates are per 1,000,000 person-years and age-adjusted to the 2000 US STD population (19 age groups—Census P25-1130) standard; confidence intervals (Tiwari mod) are 95 % for rates

SETTLE spindle cell tumor with thymus-like differentiation, *CASTLE* carcinoma showing thymus-like differentiation, *VIP* vasoactive intestinal peptide

* IR was not calculated as $n < 10$

Adrenal

There were five RECs of the adrenal gland. These included adrenal cortical carcinoma (ACC), neuroblastoma, malignant pheochromocytoma, sarcoma, and melanoma. The overall IR for all RECs of the adrenal gland was 2.7, with a 3.69 % decrease in IR over the study period. The male-to-female IRR was 1:1. The majority of adrenal cancers presented with distant disease (IR 0.4) compared with localized and regional disease (IR 0.21 and 0.12, respectively). The majority of cancers were >4 cm (IR 2.38). The IR for cancers ≤1, >1 to ≤2, and >2 to ≤4 cm were 0.01, 0.06, and 0.26, respectively. The 5-year survival for all rare adrenal cancers combined was 45.83 %.

Pancreas

There were eight pancreas RECs, which included well-differentiated neuroendocrine cancers, poorly differentiated (small cell) carcinomas, and mixed exocrine–endocrine carcinomas. The well-differentiated cancers were divided into functioning cancers (insulin, glucagon, somatostatin, gastrin, and VIP-secreting), and nonfunctioning cancers. The overall IR for pancreatic RECs was 4.60, and there was a 93 % increase in incidence over the study period. These cancers were more common in men (IR 5.59) than women (IR 3.82), with an IRR of 1.5:1. The majority of pancreatic RECs had distant disease (IR 2.52) with a roughly equal IR for localized and regional cancers (IR 0.99 and 0.89, respectively). The majority of pancreatic RECs were >4 cm (IR 2.67) and illustrated a decreasing incidence with decreasing size. All size categories increased in incidence over the study period, with the highest rise in cancers ≤1 cm (720 %) and >1 to ≤2 cm (470.6 %). The 5-year survival for pancreatic RECs was 39.84 % (range 2.49–67.88 %).

DISCUSSION

To our knowledge, this study is the first to describe the incidence and survival of RECs of the thyroid, parathyroid, adrenal gland, and pancreas using a large national database. As a whole, these cancers were more common than we hypothesized. Many of these are very aggressive, with a 5-year survival rate as low as 2.5 %. Our analysis provides a definitive epidemiologic resource on the incidence and survival of RECs. These data may be valuable for clinicians caring for patients with these rare cancers.

We have shown the IR for all RECs combined was 17.23 per million. To put this in a clinically relevant context, the IR for papillary thyroid cancer is 121 per million and is rising in incidence every year.[17] While the IR of RECs is small, we found that they have doubled in incidence over the past 12 years, similar to papillary thyroid cancer. Additionally, they have increased in all sizes and their survival is poor. For these reasons, it is important to have a good clinical understanding of these cancers, because it is becoming increasingly likely that a physician will encounter one of these aggressive cancers. Our data also suggested that more research needs to be done to understand the underlying cause of the increase in these rare cancers. However, their overall IR still make up a relatively small amount of endocrine malignancies.

Parathyroid carcinoma is the only type of REC that exists in the parathyroid gland. We found the overall IR to be 0.36 with an increased IR in males compared with females. While a previous study showed an increase in IR

TABLE 3 Rare endocrine tumors incidence rate: localized, regional, distant, and unstaged

	Localized incidence rate (*N*)	Regional incidence rate (*N*)	Distant incidence rate (*N*)	Unstaged incidence rate (*N*)
Thyroid	3.4 (3677)	3.42 (3670)	1.28 (1368)	1.45 (1546)
Papillary carcinoma-rare (total)	0.49 (532)	0.84 (913)	0.12 (130)	0.01 (15)
Variant: diffuse sclerosing	0.12 (128)	0.20 (214)	0.03 (28)	* (0)
Variant: columnar cell	0.29 (314)	0.60 (651)	0.09 (96)	0.01 (12)
Variant: oxyphilic (oncocytic)	0.08 (90)	0.04 (48)	* (6)	* (3)
Follicular carcinoma (total)	1.63 (1754)	1.26 (1349)	0.12 (124)	0.07 (71)
Variant: oxyphilic (oncocytic)	1.63 (1752)	1.24 (1336)	0.12 (121)	0.06 (69)
Variant: clear cell	* (2)	0.01 (13)	* (3)	* (2)
Poorly differentiated	0.06 (68)	0.09 (97)	0.05 (48)	* (5)
Undifferentiated (anaplastic)	0.07 (73)	0.38 (393)	0.58 (614)	0.06 (60)
Carcinosarcoma	* (1)	* (3)	* (6)	* (0)
Medullary carcinoma	1.03 (1112)	0.69 (747)	0.31 (332)	0.06 (63)
Mixed medullary and Pap./follicular	0.09 (103)	0.08 (88)	0.02 (24)	* (3)
Squamous cell	0.02 (24)	0.06 (64)	0.06 (60)	0.01 (14)
Mucoepidermoid	0.01 (15)	* (5)	* (7)	* (1)
Mucinous	* (2)	* (1)	* (2)	* (1)
SETTLE	* (1)	* (0)	* (1)	* (0)
CASTLE	* (1)	* (4)	* (0)	* (0)
Malignant paraganglioma	* (1)	* (2)	* (0)	* (1)
Malignant teratoma	* (1)	* (2)	* (1)	* (1)
Sarcoma	* (4)	* (7)	0.01 (12)	* (3)
Parathyroid				
Parathyroid carcinoma	0.06 (64)	0.04 (41)	* (5)	0.01 (15)
Adrenal	0.21 (229)	0.12 (131)	0.40 (429)	0.07 (74)
Adrenal cortical carcinoma	0.13 (143)	0.06 (67)	0.14 (153)	0.04 (45)
Neuroblastoma	0.05 (49)	0.04 (39)	0.22 (241)	* (9)
Malignant pheochromocytoma	0.03 (32)	0.02 (21)	0.02 (25)	0.02 (18)
Sarcoma	* (4)	* (4)	* (8)	* (2)
Melanoma	* (1)	* (0)	* (2)	* (0)
Pancreas	0.99 (1068)	0.89 (968)	2.52 (2714)	0.20 (213)
Well-differentiated	0.96 (1033)	0.82 (891)	2.26 (2442)	0.19 (199)
Functioning (total)	0.05 (50)	0.04 (43)	0.06 (67)	0.01 (11)
Insulin-secreting	0.03 (31)	0.01 (10)	0.02 (22)	* (4)
Glucagon-secreting	* (8)	* (8)	0.01 (15)	* (2)
Somatostatin-secreting	* (1)	* (0)	* (1)	* (0)
Gastrin-secreting	* (8)	0.02 (23)	0.02 (23)	* (4)
VIP-secreting	* (2)	* (2)	* (6)	* (1)
Nonfunctioning (or unknown)	0.91 (983)	0.78 (848)	2.20 (2375)	0.18 (188)
Poorly differentiated (small cell)	0.01 (12)	0.03 (27)	0.21 (222)	0.01 (12)
Mixed exocrine–endocrine	0.02 (23)	0.05 (50)	0.05 (50)	* (2)

Rates are per 1,000,000 person-years and age-adjusted to the 2000 US STD population (19 age groups—Census P25-1130) standard; confidence intervals (Tiwari mod) are 95 % for rates. Thyroid lymphoma not presented in this table as incidence rates were not reported for localized vs. regional vs. distant disease

SETTLE spindle cell tumor with thymus-like differentiation, *CASTLE* carcinoma showing thymus-like differentiation, *VIP* vasoactive intestinal peptide

* IR was not calculated as $n < 10$

TABLE 4 Rare endocrine tumors incidence rate by size and percent change in incidence rate

	Incidence rate over entire study period				Percent change in incidence rate 2000–2002 to 2010–2012			
	≤1 cm (*N*)	>1 to ≤2 cm (*N*)	>2 to ≤4 cm (*N*)	≤4 cm	≤1 cm	>1 to ≤2 cm	>2 to ≤4 cm	>4 cm
Thyroid	0.99 (1078)	1.5 (1634)	2.41 (2596)	4.66 (4953)	100	71.84	25.5	0
Papillary carcinoma- rare (total)	0.32 (350)	0.4 (439)	0.42 (456)	0.32 (345)	172.22	205	256.25	81.81
Variant: diffuse sclerosing	0.11 (119)	0.10 (104)	0.06 (69)	0.07 (78)	20.00	85.71	450	100
Variant: columnar cell	0.18 (191)	0.27 (292)	0.32 (341)	0.23 (249)	328.57	215.38	207.69	93.75
Variant: oxyphilic (oncocytic)	0.04 (40)	0.04 (43)	0.04 (46)	0.02 (18)	600	*	200	0
Follicular carcinoma (total)	0.18 (195)	0.54 (586)	1.11 (1196)	1.24 (1321)	−11.11	8.89	2	−2.42
Variant: oxyphilic (oncocytic)	0.18 (194)	0.54 (582)	1.10 (1192)	1.23 (1310)	−11.11	8.89	1	−2.46
Variant: clear cell	* (1)	* (4)	* (4)	0.01 (11)	*	*	*	0
Poorly differentiated	* (1)	0.02 (18)	0.05 (56)	0.13 (143)	*	0	25	85.71
Undifferentiated (anaplastic)	0.01 (14)	0.03 (30)	0.12 (131)	0.92 (965)	*	200	18.18	14.12
Carcinosarcoma	* (0)	* (0)	* (1)	* (9)	*	*	*	*
Medullary carcinoma	0.44 (476)	0.45 (487)	0.61 (656)	0.59 (635)	133.33	77.42	12.07	−8.82
Mixed medullary and Pap./follic.	0.03 (36)	0.05 (59)	0.06 (62)	0.06 (61)	0	100	50	75
Squamous cell	* (5)	0.01 (13)	0.03 (29)	0.11 (115)	*	*	−60	0
Mucoepidermoid	* (3)	* (6)	* (5)	0.01 (14)	*	*	−100	−50
Mucinous	* (0)	* (0)	* (4)	* (2)	*	*	*	*
SETTLE	* (0)	* (0)	* (0)	* (2)	*	*	*	*
CASTLE	* (1)	* (1)	* (1)	* (2)	*	*	*	*
Malignant paraganglioma	* (0)	* (1)	* (2)	* (2)	*	*	*	*
Malignant teratoma	* (0)	* (1)	* (1)	* (3)	*	*	*	*
Sarcoma	* (0)	* (0)	* (1)	0.02 (25)	*	*	*	0
Parathyroid								
Parathyroid carcinoma	0.02 (20)	0.06 (63)	0.11 (119)	0.18 (193)	100	20	−8.33	−39.13
Adrenal	0.01 (16)	0.06 (66)	0.26 (277)	2.38 (2564)	*	0	4.55	−5.35
Adrenal cortical carcinoma	* (7)	0.01 (16)	0.05 (58)	1.19 (1283)	*	−100	200	−10
Neuroblastoma	* (8)	0.03 (36)	0.16 (174)	0.86 (923)	*	0	−12.5	3.66
Malignant pheochromocytoma	* (1)	0.01 (14)	0.04 (43)	0.26 (288)	*	*	0	−23.08
Sarcoma	* (0)	* (0)	* (2)	0.06 (66)	*	*	*	75
Melanoma	* (0)	* (0)	* (0)	* (4)	*	*	*	*
Pancreas	0.2 (212)	0.49 (529)	1.24 (1333)	2.67 (2889)	720	470.58	221.67	22.31
Well-differentiated	0.19 (204)	0.47 (507)	1.16 (1248)	2.41 (2606)	680	564.29	234.55	28.3
Functioning (total)	0.02 (16)	0.04 (39)	0.03 (31)	0.08 (85)	100	66.67	50	−50
Insulin-secreting	* (9)	0.02 (26)	0.01 (13)	0.02 (19)	*	300	*	−50
Glucagon-secreting	* (2)	* (3)	* (9)	0.02 (19)	*	*	*	−66.67
Somatostatin-secreting	* (0)	* (0)	* (1)	* (1)	*	*	*	*
Gastrin-secreting	* (4)	* (9)	* (5)	0.04 (40)	*	*	*	−25
VIP-secreting	* (1)	* (1)	* (3)	* (6)	*	*	*	*
Nonfunctioning (or unknown)	0.17 (188)	0.43 (468)	1.13 (1217)	2.33 (2521)	825	641.67	241.51	32.84
Poorly differentiated (small cell)	* (5)	0.01 (12)	0.05 (49)	0.2 (207)	*	100	0	−36
Mixed exocrine–endocrine	* (3)	0.01 (10)	0.03 (36)	0.07 (76)	*	0	400	60

Rates are per 1,000,000 person-years and age-adjusted to the 2000 US Std population (19 age groups—Census P25-1130) standard; Confidence intervals (Tiwari mod) are 95 % for rates. The subtype lymphoma was removed as size was not reported for this subtype

SETTLE spindle cell tumor with thymus-like differentiation, *CASTLE* carcinoma showing thymus-like differentiation, VIP vasoactive intestinal peptide

* IR was not calculated as $n < 10$

TABLE 5 Rare endocrine tumors survival—1, 5, and 10 years

	1-year survival	5-year survival	10-year survival
Thyroid	82.79	72.02	62.28
Papillary carcinoma-rare (total)	97.03	89.29	79.57
Variant: diffuse sclerosing	98.24	93.48	88.05
Variant: columnar cell	96.09	86.46	72.97
Variant: oxyphilic (oncocytic)	100	93.95	91.66
Follicular carcinoma (total)	96.4	87.77	78.31
Variant: oxyphilic (oncocytic)	96.54	88	78.62
Variant: clear cell	81.52	64.32	49.18
Poorly differentiated	93.56	66.93	45.78
Undifferentiated (anaplastic)	18.4	8.19	7.01
Carcinosarcoma	11.11	0	0
Medullary Carcinoma	93.14	81.13	71.04
Mixed medullary and Pap./follicular	93.7	86.62	70.92
Squamous cell	42.53	25.34	23.89
Mucoepidermoid	71.02	63.88	63.88
Mucinous	66.67	53.33	44.44
SETTLE	100	0	0
CASTLE	100	100	100
Malignant paraganglioma	100	*	*
Malignant teratoma	83.33	62.5	62.5
Sarcoma	39.02	19.61	19.61
Lymphoma and plasmacytoma			
Lymphoma, NOS	84.72	67.7	51.06
Hodgkin lymphoma	100	92.79	92.79
Non-Hodgkin lymphoma	84.83	72.27	56.48
Plasmacytoma	95.83	75	53.41
Parathyroid			
Parathyroid carcinoma	94.61	82.57	65.39
Adrenal	69.67	45.83	38.03
Adrenal cortical carcinoma	54.4	29.68	22.13
Neuroblastoma	84.75	61.57	57.64
Malignant pheochromocytoma	81.53	61.06	41.28
Sarcoma	59.24	29.96	11.33
Melanoma	40	0	0
Pancreas	68.85	39.84	26.5
Well-differentiated	72.6	42.82	28.36
Functioning (total)	85.93	57.99	44.43
Insulin-secreting	83.18	53.42	47.65
Glucagon-secreting	83.13	57.74	32.21
Somatostatin-secreting	100	*	*
Gastrin-secreting	88.25	59.07	45.47
VIP-secreting	90.91	67.88	51.97
Nonfunctioning (or unknown)	71.81	41.84	27.09
Poorly differentiated (small cell)	18.07	2.49	1.86
Mixed exocrine–endocrine	75.03	38.12	30.02

SETTLE spindle cell tumor with thymus-like differentiation, *CASTLE* carcinoma showing thymus-like differentiation, *VIP* vasoactive intestinal peptide

* $n<10$

from 1988–2003, our study has shown that the IR of parathyroid carcinoma has decreased by 19.5 % since 2000.[18] It is possible that some of this difference is related to the names used as Lee et al. combined three terms (carcinoma NOS, adenocarcinoma NOS, and malignant neoplasm) to classify cancers as parathyroid carcinoma, whereas we used those three terms as well as two additional terms (parathyroid oxyphilic adenocarcinoma, and parathyroid clear cell adenocarcinoma NOS). However, the 10-year survival in both our study and the previous study was similar (64.8 and 65.39 %, respectively). With similar survival findings, it can be inferred that survival has not changed over the past 25 years.

The most common REC of the adrenal gland was ACC although its IR decreased by 7.4 % during the study period. These findings are similar to previously published reports.[19,20] The 5-year survival was roughly 30 %, which is similar to a previous study that showed a 32 % 5-year survival.[20] Malignant pheochromocytomas occurred less frequently than either ACC or neuroblastoma, with an IR of 0.3. The 5-year survival for malignant pheochromocytoma found in this study, 58 %, is similar to that of previous reports.[21,22]

RECs of the pancreas consisted of functioning and nonfunctioning well-differentiated cancers, poorly differentiated cancers, and mixed endocrine–exocrine cancers. The most common functioning tumor was insulin-secreting carcinoma with an IR of 0.06, which is similar to previous reports.[23,24] The longest report on the long-term survival of malignant functioning insulinomas showed a 10-year survival of 29 %,[24] which differs significantly from our finding of 48 %. This difference may be related to improved treatment modalities.[25] We also found that poorly differentiated cancers had an abysmal 5-year survival of 2.49 %. These findings differ significantly from those of Garcia-Caronero et al. who found a 5-year survival of 39 %.[23] This difference may be related to differences in classification of poorly differentiated cancer; we combined trabecular and insular carcinoma in the same category as poorly differentiated carcinoma.

Our study is limited by the use of a large national cancer registry. These databases are limited by the lack of histopathologic external review and potential misclassification. This study also was limited to a 12-year period. However, the authors felt that the SEER 18 registry was the best database, because it included the largest number of centers with both incidence and survival data available for analysis. Finally, many of these cancers are so rare that it is difficult to make broad statements about the trends over time. However, using a large database, such as SEER, enabled us to make some general statements on trends over time, when possible.

CONCLUSIONS

We have provided a comprehensive analysis of the incidence and survival of all RECs of the thyroid, parathyroid, adrenal gland and pancreas. These cancers are more common than one might suspect and that the incidence of almost all RECs is on the rise, which should prompt further research and support for these rare cancers. We hope that this study will aid clinicians and patients in understanding the risk and prognosis for these rare cancers, which will ultimately guide decisions regarding treatment and manage long-term expectations.

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REFERENCES

1. Very rare cancers—a problem neglected. *Lancet Oncol.* 2001;2(4):189.
2. Gatta G, van der Zwan JM, Casali PG, RARECARE Working Group, et al. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer.* 2011;47(17):2493–511.
3. Miller RC. Problems in rare tumor study: a call for papers. *Rare Tumors*. 2010;2(1):e16.
4. Rare Diseases Act of 2002. Public law 170-280. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=170_cong_public_laws&docid=f:publ280.107.
5. Orphan Drug Act. Washington, DC: US House of Representatives; (September 17), 1982. US House of Representatives report 97-840.
6. Baloch ZW, Solomon AC, LiVolsi VA. Primary mucoepidermoid carcinoma and sclerosing mucoepidermoid carcinoma with eosinophilia of the thyroid gland: a report of nine cases. *Mod Pathol*. 2000;13(7):802–7.
7. Lam KY, Lo CY, Liu MC. Primary squamous cell carcinoma of the thyroid gland: an entity with aggressive clinical behaviour and distinctive cytokeratin expression profiles. *Histopathology*. 2001;39(3):279–86.
8. Lam KY, Lo CY, Chan KW, et al. Insular and anaplastic carcinoma of the thyroid: a 45-year comparative study at a single institution and a review of the significance of p53 and p21. *Ann Surg*. 2000;231(3):329–38.
9. Phukan C, Nirmal TJ, Kumar RM, et al. Peripheral primitive neuroectodermal tumor of the adrenal gland: a rare entity. *Indian J Urol*. 2013;29(4):357–9.
10. Lam S, Liew H, Khor HT, et al. VIPoma in a 37-year-old man. *Lancet*. 2013;382(9894):832.

11. Van der Zwan JM, Mallone S, Van Dijk B, et al. Carcinoma of endocrine organs: results of the RARECARE project. *Eur J Cancer*. 2012;48(13):1923–31.
12. Greenlee RT, Goodman MT, Lynch CF, et al. The occurrence of rare cancers in US adults, 1995-2004. *Public Health Rep*. 2010;125(1):28–43.
13. Surveillance, Epidemiology, and End Results (SEER) Program. Public-Use Database (1973–2009), National Cancer Institute DCCPS, Surveillance Research Program, Cancer Statistics Branch, Released April 2012, based on the November 2011 submission. http://seer.cancer.gov. Accessed Aug 2013.
14. Johnson CH, Adamo M, eds. SEER program coding and staging manual 2007 (NIH Publication number 07-5581). Bethesda: National Cancer Institute; 2007.
15. Fritz A, Percy C, Jack A, et al. International classification of diseases for oncology. 3rd ed. Geneva: World Health Organization; 2000.
16. Surveillance Research Program, National Cancer Institute SEER*Stat software. Version 8.1.5. www.seer.cancer.gov/seerstat. Accessed Sept 2014.
17. Aschebrook-Kilfoy B, Schechter RB, Shih YC, Kaplan EL, Chiu BC, Angelos P, Grogan RH. The clinical and economic burden of a sustained increase in thyroid cancer incidence. *Cancer Epidemiol Biomarkers Prev*. 2013;22(7):1252–9.
18. Lee PK, Jarosek SL, Virnig BA, et al. Trends in the incidence and treatment of parathyroid cancer in the United States. Cancer. 2007;109(9):1736–41.
19. Brennan MF, Schulick RD. Long-term survival after compete resection and repeat resection in patients with adrenocortical carcinoma. *Ann Surg Oncol*. 1999;6(8):719–26.
20. Kerkhofs TM, Verhoeven RH, Van der Zwan JM. Adrenocortical carcinoma: a population-based study on incidence and survival in the Netherlands since 1993. *Eur J Cancer*. 2013;49(11):2579–86.
21. Esiashvili N, Goodman M, Ward K. Neuroblastoma in adults: incidence and survival analysis based on SEER data. *Pediatr Blood Cancer*. 2007;49:41–46.
22. Chrisoulidou A, Kaltsas G, Ilias I, et al. The diagnosis and management of malignant phaeochromocytoma and paraganglioma. *Endocr Relat Cancer*. 2007;14:569–85.
23. Service FJ, McMahon MM, O'Brien PC, et al. Functioning insulinoma incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc*. 1991;66:711–9.
24. Boukhman MP, Karam JH, Shaver J, et al. Insulinoma—experience from 1950 to 1995. *West J Med*. 1998;169:98–104.
25. Nikfarjam M, Warshaw AL, Axelrod L, et al. Improved contemporary surgical management of insulinomas: a 25-year experience at the Massachusetts General Hospital. *Ann Surg*. 2008;247(1):165–72.