Neuroendocrine Tumor Epidemiology

Contrasting Norway and North America

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BACKGROUND. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program has proven to be a significant resource in US neuroendocrine tumor (NET) epidemiology. Norway also holds a robust and detailed cancer registry: the Norwegian Registry of Cancer (NRC).

METHODS. SEER NET data were compared with corresponding NRC data in the time period 1993 to 2004 to determine whether there are differences in NET epidemiology between Norway and the United States.

RESULTS. The SEER and NRC reported 17,312 and 2030 NETs, respectively. The overall Caucasian SEER NET incidence was 4.44, compared with 3.24 in the NRC. In the SEER white subset, bronchopulmonary NETs were the most common (incidence = 1.42; 32% of all NETs), compared with small intestinal NETs in the NRC (0.81; 26%). A marked increase in SEER NET incidence (37%-40%) was observed in the period 2000 to 2004, compared with 1993 to 1997; an even more pronounced increase (72%) was seen in the NRC. African Americans exhibited a remarkably high overall NET incidence of 6.50; furthermore, among African Americans, rectal NETs were most common (1.65; 27%). Small intestinal NET incidence was ~30% higher in men compared with women in all populations. The highest 5-year survival rates were for rectal NETs (74%-88%) in both databases, whereas prostatic NETs had the worst outcome (0%-23%). At diagnosis, NETs were localized in 27% to 46% of patients.

CONCLUSIONS. NET incidence in the US Caucasian population and in Norway is similar, but considerably higher (~50%) among African Americans. NETs have been regarded as indolent tumors; however, the 5-year survival is only ~55%. ***Cancer* 2008;113:2655–64.** © *2008 American Cancer Society.*

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Neuroendocrine tumors (NETs) of the diffuse neuroendocrine cell system, previously referred to as carcinoid tumors, are neoplasms that originate from neuroendocrine cell compartments localized in numerous different organ systems. Most frequently these tumors are found in the gastrointestinal tract and the bronchopulmonary system,[1] reflecting the density of neuroendocrine cells in these tissues. Neuroendocrine cells, although a heterogeneous cell population, are characterized by amine and neuropeptide hormone production and dense core vesicles. Despite the diversity in tissue origin, all these tumors share common features, including growth pattern and expression of neuroendocrine markers.

Historically, Sigefried Oberndorfer (1876-1944) was the first to introduce the term carcinoid in 1907,[2] and in 1914 Andre Gosset (1872-1944) and Pierre Masson (1880-1959)[3] identified the endocrine nature of carcinoid tumors; however, in retrospect it is evident that neoplasms presenting neuroendocrine characteristics had been

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described in the 19th century by pathologists Theodor Langhans (1839-1915) in 1867,[4] Otto Lubarsch (1860-1933) in 1888,[5] and William B. Ransom (1860-1909) in 1890.[6] Despite the passage of almost a century, the classification of NETs is still under debate. This reflects the morphological and biological heterogeneity of these lesions and the advances that have been made in both cellular and molecular biology.

A comprehensive survey on neuroendocrine epidemiology based on data extracted from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (US) demonstrated an increasing incidence of NETs.[1] Similar results have been observed by others[7-9]; however, it is unclear if this trend is because of an increased awareness among physicians, improved diagnostic tools, or an actual increase in NET incidence. SEER reports also indicate racial disparities in the development and outcome of NET disease, reflecting both an increased incidence and poorer survival in blacks.[7,10] NETs have in general been considered indolent tumors with low metastatic potential; however, some NET subtypes are highly malignant and carry a grave prognosis.[1] Furthermore the outcome of NET disease has not improved in the past few decades despite improved diagnostics and new treatment modalities.[1]

Norway, a Scandinavian country with a total population of 4.7 million, has a reliable and robust population-based cancer registry.[11] Since the commencement of the Norwegian Registry of Cancer (NRC) in 1953, it has systematically collected notifications on cancer. The requirement that the registry follows the mandated legal obligation to report new cases has enabled the registry to attain a high degree of completeness: ~95% for solid tumors.[11]

To date it has not been clear if NET epidemiology is different in various countries. The main objective of this study was to compare SEER NET data with corresponding NRC data to determine whether there are differences in NET epidemiology between Norway and the US. Data were extracted from the SEER and NRC in the time period 1993 to 2004. The white subset of the SEER data were compared with the NRC given the principally Caucasian population of Norway. In addition, we performed a subanalysis of the SEER data to further investigate whether NET epidemiology differs between African Americans and Caucasians.

MATERIALS AND METHODS

Cancer Registries

The Norwegian population is principally white Caucasian with an immigrant proportion of 8%, from 200 different countries, in 2005. Life expectancy at birth (2004) is 82.3 years for females and 77.5 years for males,[12] and the elderly (>65 years) represent an increasing proportion (14.7%) of the Norwegian population.[11] The life expectancy at birth in the US (2004) is 80.4 years for females and 75.2 years for males,[13] and is thus slightly less than in Norway. The elderly (>65 years) represent 12% of the US population, and this segment of the population is rapidly increasing, similar to Norway.[14]

The Norwegian healthcare system is tax-financed, which secures a universal coverage of the population and is comparable to the healthcare systems in other Nordic countries and the United Kingdom. Norway spends 10%[12] of the gross domestic product on healthcare compared with 16% in the US,[15] the most expensive healthcare system in the world. The US, however, has an insurance-based healthcare system and 15.8% of the population is without health insurance.[15]

The notification of new cases of cancer in the NRC has been compulsory and represents a legal obligation since its initiation in 1953. Hospitals, oncology centers, and individual physicians, as well as pathological and cytological laboratories are required to report every new case of cancer. Inaccurate, conflicting, or absent notifications are further investigated by the NRC. The NRC records are regularly matched with the *Cause of Death Registry* run by the Norwegian National Statistic Bureau.

The SEER program of the National Cancer Institute was initiated in 1973 and currently covers 18 geographical areas in the US, which comprise approximately 26% of the population. The SEER database reflects the population of US in terms of income and level of education; however, the SEER population is slightly more urban, and the proportion of foreign born is higher (6%) as compared with the NRC.

Data Extraction

Since 1993, tumor morphology NRC coding has used the International Classification of Disease for Oncology, second edition (ICD-O-2), with the topography axis standardized with section C of the ICD-10. It is therefore similar to the coding system used by the SEER since 1976. To facilitate the comparison between databases, NETs reported from 1993 to 2004 were evaluated.

The ICD-O codes used when extracting different NET subtypes are provided in Table 1. Only malignant tumors were registered. Small cell lung carcinomas (SCLCs), although acknowledged as part of the neuroendocrine tumor spectrum, were excluded

TABLE 1
Neuroendocrine Tumor-related International Classification of Disease for Oncology Codes Used in Database Extraction

Code Descriptor	Code
Carcinoid tumor, malignant	8240
Enterochromaffin cell carcinoid	8241
Goblet cell carcinoid	8243
Composite carcinoid	8244
Adenocarcinoid tumor	8245
Neuroendocrine carcinoma	8246
Atypical carcinoid tumor	8249
Large cell neuroendocrine carcinoma	8013
Adenocarcinoma with neuroendocrine differentiation	8574

Codes 8249, 8013, and 8574 were only found in the Surveillance, Epidemiology, and End Results program because of the implementation of the International Classification of Disease for Oncology, 3rd edition, in 2001.

from this survey because of the largely different etiological and histological properties of these tumors compared with other NETs covered in this survey.

Because of the implementation of ICD-O-3 in the SEER (2001), 3 of the codes (Table 1) used when extracting SEER data were not available in the NRC. Nevertheless, these tumors were present in the NRC database, but classified as malignant carcinoid tumor, according to ICD-O-2.

The SEER*Stat 6.3.5 (National Cancer Institute, Bethesda, Md) and SPSS 14.0 (SPSS, Chicago, Ill) programs were used to retrieve raw data from the SEER and NRC, respectively. Frequencies, age-adjusted incidence, observed 5-year survival, morphological distribution, and extension of disease were calculated for the most common NETs sites. The subgroup "other" includes NETs with unknown or unspecified sites of origin, for which diagnoses were principally based on metastatic tissue samples.

Statistics

All incidence rates (per 100,000 population per year) extracted from 1993 to 2004 were age-adjusted using the US 2000 standard population for both databases and presented in terms of site, sex, and race. To further examine trends in NET disease, incidence rates were calculated for separate time periods (1993-1997 and 2000-2004).

The observed 5-year survival was calculated using the actuarial method.[16] Tumors were staged as localized (localized to organ of origin), regional (local lymph nodes and nearby organ invasion), distal (disseminated disease), or unknown extent of disease.

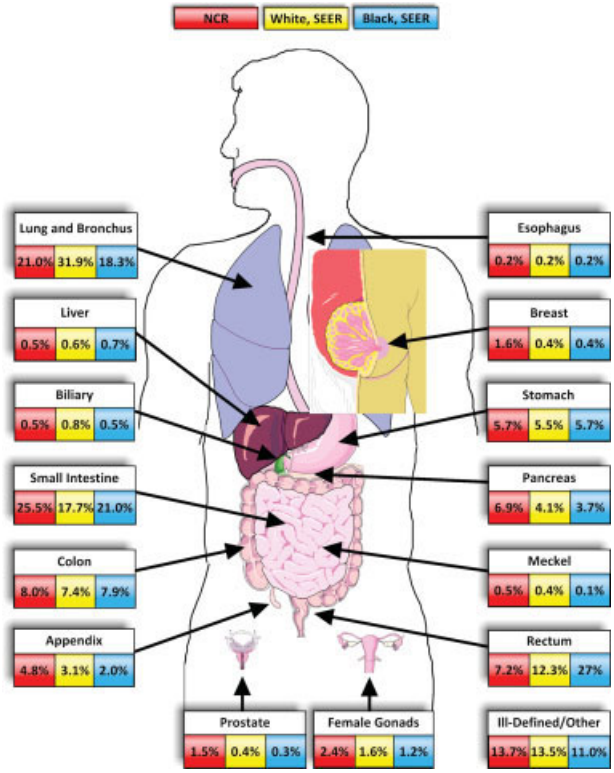

FIGURE 1. The distribution of neuroendocrine tumors (NETs) in the Norwegian Registry of Cancer (NCR) and the Surveillance, Epidemiology, and End Results program (SEER) is shown for 1993 to 2004. Results are presented as percentage of total NETs. A total of 17,312 and 2013 NETs were registered in the SEER and NRC, respectively. In the SEER, pulmonary (white) and rectal (black) NETs were more frequently reported, compared with small intestinal NETs in NRC.

RESULTS

Frequency

Between 1993 and 2004, a total of 2030 and 17,321 NETs were reported to the NRC and SEER databases, respectively. The frequencies of NETs and percentages of total NETs registered are shown in Figure 1. The most common NET location in the NRC is the small intestine (26%), in contrast to the SEER, where bronchopulmonary (BP)-NETs (32%) occur most frequently in the white population, and rectal NETs (27%) most commonly in the black population. Consequently, BP-NETs are the most frequently registered neuroendocrine neoplasms in the SEER and thereby the most common NET found in the US because of the large white proportion of the population (75%, Census 2000).

Incidence and Trends

Age-adjusted incidence rates by race and sex are presented in Tables 2 and 3, respectively. In the black

TABLE 2
Incidence Rates of Neuroendocrine Tumors: Norwegian Registry of Cancer and Surveillance, Epidemiology, and End Results Program, 1993 to 2004

		SEER	
NET Site	NRC	White	Black
All sites	3.24	4.44	6.50
Lung and bronchus	0.70	1.42	1.20
Small intestine	0.81	0.79	1.42
Rectum	0.24	0.54	1.65
Colon	0.25	0.33	0.53
Stomach	0.18	0.24	0.38
Pancreas	0.23	0.18	0.24
Appendix	0.16	0.13	0.11
Female gonads	0.09	0.07	0.08
Breast	0.05	0.02	0.03
Prostate	0.02	0.03	0.04
Biliary	0.02	0.04	0.03
Liver	0.05	0.02	0.02
Meckel	0.02	0.02	0.01
Esophagus	0.01	0.01	0.01
Other	0.43	0.60	0.73

Rates are per 100,000 and age-adjusted to the 2000 US standard population (19 age groups, Census P25-1130).
NET indicates neuroendocrine tumor; NRC, Norwegian Registry of Cancer; SEER, Surveillance, Epidemiology, and End Results program.

TABLE 3
Neuroendocrine Tumor Incidence Rates by Sex: Norwegian Registry of Cancer and Surveillance, Epidemiology, and End Results Program, 1993 to 2004

			SEER			
	NRC		White		Black	
NET Site	Male	Female	Male	Female	Male	Female
All sites	3.47	2.95	4.72	4.28	7.25	6.02
Lung and bronchus	0.75	0.67	1.33	1.51	1.21	1.2
Small intestine	0.98	0.67	0.94	0.68	1.83	1.14
Rectum	026	0.23	0.59	0.5	1.81	1.53
Colon	0.22	0.28	0.35	0.32	0.58	0.5
Stomach	0.19	0.16	0.23	0.26	0.41	0.39
Pancreas	0.29	0.17	0.24	0.13	0.27	0.21
Appendix	0.13	0.20	0.13	0.14	0.12	0.11
Breast	0.01	0.08	—	0.03	—	0.05
Biliary	0.01	0.02	0.03	0.04	0.05	0.03
Liver	0.02	0.02	0.03	0.02	0.06	0.03
Meckel	0.02	0.01	0.03	0.01	0.02	—
Esophagus	0.01	0.00	0.02	—	0.03	—
Other	0.56	0.32	0.76	0.49	0.79	0.7

Rates are per 100,000 and age-adjusted to the 2000 US standard population (19 age groups, Census P25-1130).
NET indicates neuroendocrine tumor; NRC, Norwegian Registry of Cancer; SEER, Surveillance, Epidemiology, and End Results program.

subset of the SEER, the total NET incidence was considerably higher (46%-100%) compared with the white population of the SEER and NRC. In the NRC, small intestinal (SI)-NETs had the highest incidence (0.81), in contrast to the SEER, where BP-NETs (1.42) and rectal NETs (1.65) were most common in Caucasians and African Americans, respectively. The incidence of NETs in total was higher in men (male: female ratio, 1.1-1.2). In the more frequently occurring NETs, the most evident sex disparities (male predominance) were found for SI-NETs (male:female ratio, 1.38-1.61) and pancreatic NETs (male:female ratio, 1.29-1.85). These sex differences were consistent in all populations. The incidence rate of SI-NET disease in African Americans (1.83) was the single highest rate of all. The trends presented in Table 4 indicate a further increase (37%-72%, Fig. 2) of total NET incidence in the new millennium compared with the 1990s, especially in Norway (72%). The incidence of all of the more common NETs appears to be increasing and is most evident in gastric (39%-88%) and appendiceal (70%-133%) NET disease.

Extent of Disease, Morphology, and Therapy

The extent of disease at diagnosis is given in Figure 3. The overall proportion of localized NET disease was lower in the NRC (27%) compared with the SEER (40%-46%); however, the proportion with regional disease was correspondingly higher in the NRC (39%) compared with the SEER (17%-20%). There was a similar distribution of distant disease in both populations (18%-22%). The highest proportion of localized disease was evident in rectal NETs (60%-83%) and Meckel diverticulum (67%-80%), which corresponds well to their propitious prognosis. Among prostatic and pancreatic NETs, however, only ~10% presented with localized disease, reflecting their subsequent poor outcome.

Analysis of the distribution of morphological subtypes was only performed by the NRC (Fig. 4). The tumors were mainly classified as malignant carcinoid tumors (65%) or neuroendocrine carcinomas (31%).

Data for therapy were not available in the SEER database, and therefore only data from the NRC are presented. In the NRC, 58% received primary tumor surgery, and 16% underwent palliative surgery. Five percent received hormone or radiation therapy, and 12% were treated with chemotherapy; however, with the exception of surgery, these data were 30% incomplete.

Survival

Observed 5-year survival rates are presented in Table 5 and Figure 5. Among some of the exceedingly rare

TABLE 4
Incidence Trends of Neuroendocrine Tumors: Norwegian Registry of Cancer and Surveillance, Epidemiology, and End Results Program (SEER), 1993 to 1997 and 2000 to 2004

	NR	NRC	Change	SEER White	Population	Change	SEER Black	Population	Change
NET site	93-97	00-04	%	93-97	00-04	%	93-97	00-04	%
All sites	2.35	4.06	72	4.22	5.79	37	5.48	7.67	40
Lung & bronchus	0.49	0.90	85	1.21	1.59	31	0.9	1.37	52
Small intestine	0.60	1.01	69	0.7	0.87	24	1.29	1.59	23
Rectum	0.22	0.25	15	0.39	0.68	74	1.36	1.89	39
Colon	0.19	0.33	73	0.27	0.39	44	0.46	0.64	39
Stomach	0.15	0.20	39	0.17	0.32	88	0.32	0.46	44
Pancreas	0.15	0.30	101	0.26	0.33	27	0.2	0.44	120
Appendix	0.10	0.23	125	0.1	0.17	70	0.06	0.14	133
Female gonads	0.05	0.12	130	0.07	0.07	0	0.07	0.07	0
Breast	0.03	0.05	75	0.01	0.02	100	0.02	0.04	100
Prostate	0.02	0.08	389	0.01	0.02	100	0.02	0.03	50
Biliary	0.01	0.03	165	0.03	0.04	33	0.03	0.05	67
Liver	0.02	0.01	−51	0.02	0.03	50	0.02	0.06	200
Meckel	0.02	0.01	−57	0.02	0.02	0	0	0.01	—
Esophagus	—	0.01	—	0.01	0.01	0	0.02	0.01	−50
Other	0.31	0.52	69	0.94	1.24	32	0.7	0.88	26

Rates are per 100,000 and age-adjusted to the 2000 US standard population (19 age groups, Census P25-1130).
NET indicates neuroendocrine tumor; NRC, Norwegian Registry of Cancer; SEER, Surveillance, Epidemiology, and End Results program.

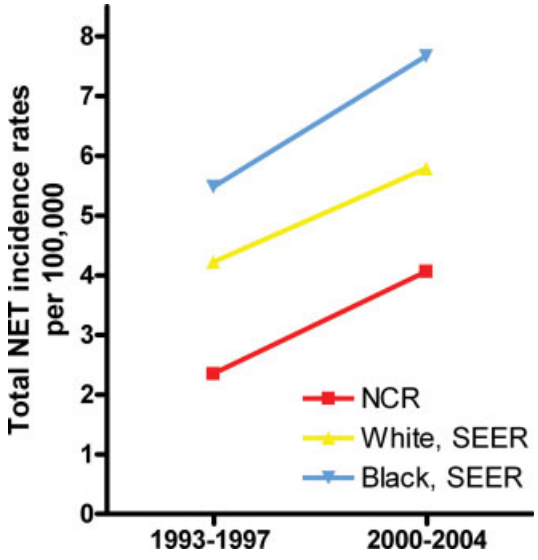

FIGURE 2. Trends in neuroendocrine tumor (NET) incidence are shown. There was a marked increase in Surveillance, Epidemiology, and End Results program (SEER) total incidence (~40%) and an even more pronounced increase (72%) in the Norwegian Registry of Cancer (NRC).

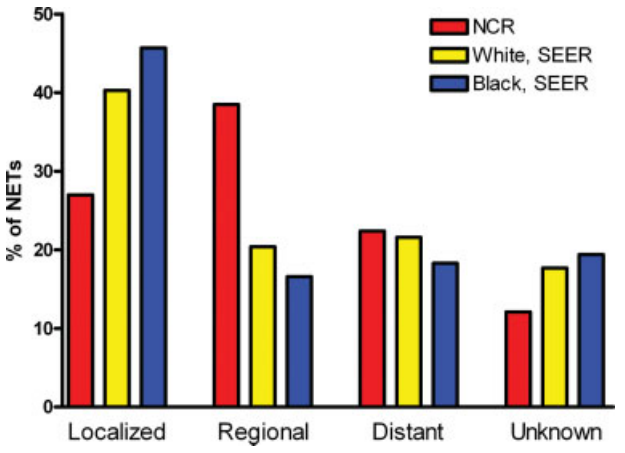

FIGURE 3. The extent of neuroendocrine tumor (NET) disease at the time of diagnosis is shown for the Norwegian Registry of Cancer (NCR) and the Surveillance, Epidemiology, and End Results program (SEER), 1993 to 2004.

NETs (liver, biliary, Meckel, and esophagus), the registered numbers were too low to provide reliable estimates, and these tumors were therefore excluded from the survival analysis. The overall 5-year survival rates for NET disease were similar in the studied populations (50%-59%). Rectal (74%-88%) and appendiceal (70%-79%) NETs had the best prognosis, whereas the outcomes for prostatic (0%-23%) and pancreatic (27%-43%) NETs were the worst. The "other" group also had low survival rates; however, in this fraction the primary tumor was often not identified, and the diagnosis was based on metastatic tissue, which most likely would explain the poor outcome.

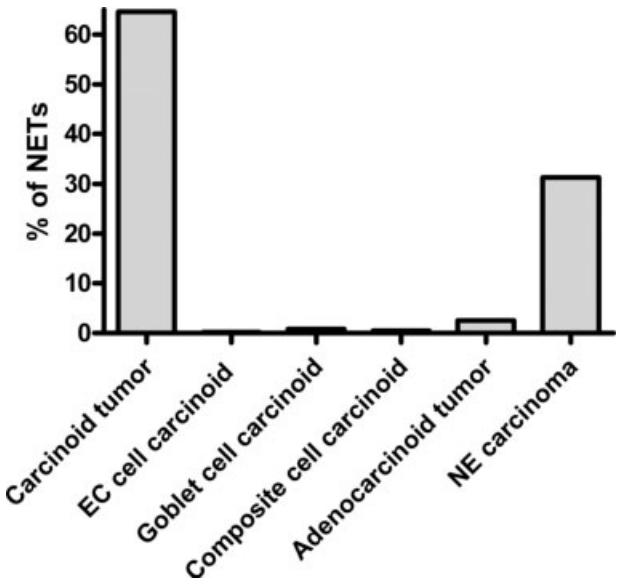

FIGURE 4. Morphological distribution of neuroendocrine tumors (NETs) is shown for the Norwegian Registry of Cancer, 1993 to 2004. EC indicates enterochromaffin cell; NE, neuroendocrine.

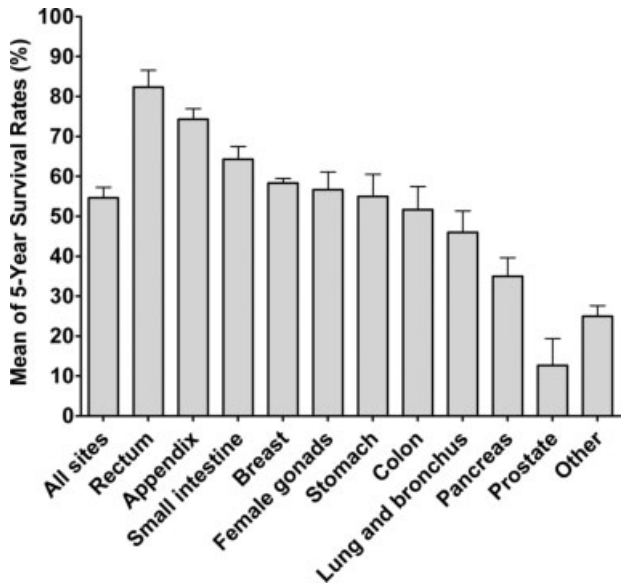

FIGURE 5. The survival rates in the Surveillance, Epidemiology, and End Results program and the Norwegian Registry of Cancer were similar. The diagram represents the mean 5-year survival rates of all 3 populations.

TABLE 5
Observed 5-Year Survival Rates: Norwegian Registry of Cancer and Surveillance, Epidemiology, and End Results Program, 1993 to 2004

		SEER, %	
NET Site	NRC, %	White	Black
All sites	50	55	59
Rectum	74	88	85
Appendix	74	79	70
Small intestine	59	70	64
Breast	56	59	60
Female gonads	63	48	59
Stomach	45	64	56
Colon	41	53	61
Lung and bronchus	54	48	36
Pancreas	43	35	27
Prostate	23	15	0
Other	21	24	30

Actuarial method.NET indicates neuroendocrine tumor; NRC, Norwegian Registry of Cancer; SEER, Surveillance, Epidemiology, and End Results program.

Histological subclassification of tumors generally reflects different malignant potential. The observed 5-year survival estimates for the 2 main morphological subtypes in the NRC, malignant carcinoid tumor and neuroendocrine carcinoma, were 60% and 25%, respectively. The poor prognosis of neuroendocrine carcinoma was expected, as these tumors are less differentiated compared with malignant carcinoid tumors.

DISCUSSION

This survey of NET epidemiology compares 2 well-organized databases from each side of the Atlantic Ocean and provides new insight into potential differences in NET epidemiology between a European country and the US. Because the survey has cumulatively assessed 19,342 NET notifications, it is to date the most comprehensive and updated study on the subject. The overview of this transatlantic comparison of NET epidemiological material is particularly relevant, because several reports have previously identified a general increase in North American NET disease,[1,7] and this information serves to confirm that this phenomenon is evident in Europe as well. The current data are noteworthy because they highlight what may also be an increase that reflects an increased awareness of NET disease in general and the wider availability of improved diagnostic techniques.

The total NET incidence among Caucasians was 37% higher in the SEER database compared with the NRC, principally because of the higher rates of BP-NETs and rectal NETs. However, overall the Norwegian population is approaching that of the US, because it is evident that the total NET incidence rate is increasing more rapidly in the NRC (72%) compared with the SEER (37%-40%). Ethnic differences in cancer risk are well known[17] and are also evident in NET disease. There are substantial data to support the higher incidence of NET disease in Afri-

can Americans,[1,7] including the current study (46%-100%); however, the potential genetic factors responsible are mostly unknown.[18] The databases investigated only register malignant tumors. NETs show a spectrum from benign to highly malignant tumors. When diagnosed at an early stage, such as insulinomas, the proportion of benign tumors is high. Both the SEER and NRC may therefore underestimate the real number of NETs, and the survival rates could consequently be more favorable than estimated in our study.

Because this was a retrospective study, we had to use the morphological classification system (ICD-0) implemented in the cancer registries at the time period investigated. There may be a correlation between malignant carcinoid tumors and neuroendocrine carcinomas in ICD-O with well-differentiated and poorly differentiated neuroendocrine carcinomas within the World Health Organization classification system (2000). These correlations were supported by the differences in survival rates found in our study. However, a direct comparison between 2 different classification systems is not advisable.

Recently new and more detailed NET classification systems have been designed,[19] and in the coming years it will be of interest to evaluate if these new systems will change the epidemiological data in NET disease when implemented in large cancer databases.

Lung and Bronchus

The incidence of BP-NETs has been increasing over the past 30 years,[1] and in the current study this lesion was noted to be the most common NET in the US.

The reason for the 2-fold higher rate of BP-NETs found in the SEER compared with the NRC is unknown; however, overall incidence rates of lung cancer in general are substantially higher in the US compared with Norway (2.25 times higher in men, 2.48 times higher in women).[11,20] Despite the higher lung cancer incidence in the US, tobacco smoking is more common in Norway compared with the US. In 2005, 25% of the adult population in Norway[12] were daily smokers compared with 17% in the United States,[21] and even in the 1950s Norwegians had higher tobacco consumption.[22,23]

The prognosis of BP-NETs is overall favorable as reported in a previous analysis of SEER data, which demonstrated a 5-year survival rate of 74% (1973-1991).[1] However, in recent years, as demonstrated by this report, survival rates have declined substantially to 36% to 48% in the SEER database. The exact cause of the declining survival is unknown. A plausible explanation, however, is that the increased use of more sensitive and specific neuroendocrine tumor markers in routine histopathology now identifies poorly differentiated BP-NETs, which were previously mischaracterized as non-neuroendocrine lung cancer. In addition the histological distinction between neuroendocrine carcinomas and the highly malignant SCLCs (not included in this survey) is sometimes difficult, and it is likely that there has been a dilution of the original more benign BP-NET group with this more aggressive tumor type.

Small Intestine

The classic carcinoid tumor is synonymous with SI-NETs, a neoplasm derived from the serotonin-producing enterochromaffin cells.[24] Although the small intestine was previously the most predominant NET location,[1,7] this survey indicates that SI-NETs are now second to BP-NETs in the American population. The SI-NET incidence rate was similar in the NRC and the white population of the SEER, indicating that geographical influences are probably of little importance in SI-NET etiology. In the current study, we demonstrated a considerably higher SI-NET incidence rate (80%) in African Americans compared with Caucasian Americans, indicating a possible genetic susceptibility.

Furthermore, sex seems to influence SI-NET disease, as a consistently higher incidence rate (30%) was found in men regardless of ethnicity.

Rectum

The rectum is 1 of the most frequent NET locations, particularly among African Americans, where the incidence was 3- and 6-fold higher than among Caucasians in SEER and NRC, respectively. A predominance of rectal NETs among African Americans is well recognized, although no causation has been identified.[1,25] Indeed, gastrointestinal (GI)-NETs in general occur more frequently in the African American population, and the incidence rate for all major GI locations were higher (60%-300%) with the exception of the appendix, where rates are similar.

In contrast to the high rates among African Americans, rectal NET is only the forth most common NET in the Norwegian population. Moreover, the incidence rates are 2-fold higher in the SEER Caucasian population compared with the NRC. The reason for the relatively low rates of rectal NETs in Norway is unknown, but may be partially explained by population-based colonoscopy screening programs for colon cancer in the US.

Rectal NETs are indolent tumors with a relatively low metastatic potential, reflected by the highest observed survival rate among the NETs in our survey (74%-88%). However, some tumors are reported to behave more aggressively.[26] In the NRC, 84% of the rectal NETs were morphologically classified as malignant carcinoid tumors and 14.3% as neuroendocrine carcinomas. When performing a subanalysis on survival, patients with tumors classified as malignant carcinoid tumors have a 5-year observed survival rate of 85%, compared with only 5% with tumors classified as neuroendocrine carcinomas.

Colon

Colon NETs comprise ~7.5% of all NETs in our survey regardless of the population, with a considerably higher incidence in the African American population (60%-100%) compared with the SEER Caucasian population and the NRC.

The incidence of colonic NETs is increasing compared with previous data.[7,9] Trend analysis of the current data indicates a 39% to 73% increase from 1993-1997 to 2000-2004. Colonic NETs have a relatively poor prognosis (5-year survival, 41%-61%) compared with SI-NETs (5-year survival, 59%-70%). This may represent the more aggressive histology of colonic NETs, because in the NRC 31.5% of colonic NETs were classified as neuroendocrine carcinomas compared with only 4% of SI-NETs.

Stomach

The incidence rates of gastric NETS in Norway and in the US Caucasian population are comparable (0.18-0.24). In the African American population, however, incidence rates are higher (60%) and consistent with the overall higher rates identified in African Americans for GI-NETs in general. The occurrence of gastric NETs has been increasing during the past 50 years,[27] in contrast to the decrease in gastric adenocarcinomas.[11,28,29] In this study, we noted that during the past decade there has been a further increase in incidence from 39% to 88%. Although this may reflect an increased awareness, greater access to endoscopic procedures, and improved immunohistochemical techniques, the possibility of the effects of acid suppressive therapy on the gastric mucosa remain an unresolved issue. In recent years, there has been an increasing discussion of the relation between the use of profound acid suppression induced by the proton pump inhibitor class of agents, the associated hypergastrinemia, and the development of gastric carcinoids.[30] Although it is well recognized that the worldwide use of acid-inhibiting drugs has substantially increased in the same time period as the increase in gastric NET incidence, our data does not allow any direct conclusions to be derived regarding the influence of these drugs on gastric NET development. Indeed the 2 observations may be no more than correlating epiphenomena, although the relation between hypergastrinemia and the induction of enterochromaffin-like cell proliferation provides compelling scientific credibility to the likelihood of a potential relation.[30,31]

Pancreas

The incidence of pancreatic NETs was similar in each population (0.18-0.24); however, there has been a ~10-fold increase in incidence compared with the SEER data from 1973 to 1991.[1] Consistently higher incidence rates were found in men (29%-85%), which are comparable to the general male predominance in pancreatic cancer (male:female ratio:1.3).[11] The prognosis of pancreatic NET was among the poorest of the NET subtypes and reflects the late diagnosis and limited treatment options that generally characterize malignant pancreatic disease.[32] The 5-year survival data (27%-43%) in this survey are in the same range as other reports[33] and have not improved during the past 20 years.[1] Pancreatic endocrine tumors (PETs), also known as islet cell tumors, are also considered NETs[10]; however the SEER and NRC data only record malignant tumors, therefore PETs were primarily excluded from this survey. However, if the malignant endocrinoma group is included for purposes of analysis, the incidence rate only increases to 0.29 (25%) in the NRC data, reflecting the very low incidence of these lesions. Overall, islet cell carcinoma is by far the most frequent PET, comprising 14% of pancreatic NETs, followed by the substantially rarer malignant gastrinoma (2%) and glucagonoma (2%).

Appendix

Previously considered as 1 of the most frequent NETs, appendiceal NETs currently comprise only 2.0% to 5.0% of total NETs, compared with 17% to 28% in older datasets.[7,9,34] Although the incidence of appendiceal NETs has increased in the past decade (70%-133%), the overall percentage has decreased, which reflects the overall increase in the incidence of other NETs. The relatively good survival rates in both registers (70%-79%) probably reflect the early diagnosis and prompt surgical therapy provided for acute appendicitis consequent upon obstruction of the appendiceal lumen by the tumor. Similarly, the serendipitous identification of early lesions at laparoscopy during gynecological surgery probably influences the outcome.[35] Appendiceal goblet cell NETs represent a complex group that are also considered

under the rubric of adenocarcinoids and are believed to constitute a separate pathological entity. In comparison to well-differentiated carcinoids, these lesions exhibit more aggressive behavior and phenotypically represent a spectrum of tumors that resemble adenocarcinomas.[36] A subanalysis of the NRC data indicates that these tumors comprise 44.3% of NETs in the appendix and, similar to previous reports,[37] occur at an incidence rate of 0.07.

Rare Sites

Because of their very low frequency, the accuracy of data on rare NETs is associated with some uncertainty. The morphological classification of some of these tumors is still controversial, and has the potential to cause errors in database registration and classification. Primary NETs of the breast are exceedingly uncommon, and little is known about the etiology and epidemiology of these lesions; tumors considered to be primary NETs have in some circumstances represented unrecognized metastatic disease.[38] We performed a subanalysis (NRC) and found no breast NET that had coexisting NET disease elsewhere, supporting that the breast NETs in this study were truly primary.

Prostatic adenocarcinomas with neuroendocrine differentiation are relatively common,[39,40] whereas pure NETs of the prostate are exceedingly rare. Neuroendocrine differentiation is a negative prognostic factor in prostatic cancer, and prostatic NETs have been reported to behave in a more aggressive fashion compared with other NETs.[41] Prostatic NETs had the worst outcome of all NETs (5-year survival, 0%-23%).

CONCLUSIONS

To our knowledge, this study represents the first comparison of NET epidemiology in a European country with the US. SI-NETs have previously been regarded as the most common NET; in the US, however, BP-NETs are now most frequent, and their incidence is also rapidly increasing in Norway. The current survey shows a predominance of GI-NETs in African Americans and when assessed with previously reported data indicates that racial and ethnic disparities exist in respect of NET disease.

Overall, it is evident that NET incidence has increased in the past decades, and continues to do so in the 21st century. Whether this represents a true increase in incidence or improved diagnostic precision still remains uncertain. Nevertheless, from the perspective of the physician and public health authorities, the prevalence of the disease must be considered to have undergone a significant alteration. Given the transatlantic evidence of an increasing incidence of the disease, it seems warranted that emphasis on early diagnosis and the introduction of novel molecular strategies are necessary to improve treatment and outcome in this enigmatic disease.

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