Cancer Causes Control (2010) 21:931–938
DOI 10.1007/s10552-010-9519-4

ORIGINAL PAPER

Epidemiology of neuroendocrine cancers in an Australian population

Colin Luke · Timothy Price · Amanda Townsend · Christos Karapetis · Dusan Kotasek · Nimit Singhal · Elizabeth Tracey · David Roder

Received: 26 August 2009 / Accepted: 4 February 2010 / Published online: 24 April 2010
© Springer Science+Business Media B.V. 2010

Abstract
Objective The aim was to explore incidence, mortality and case survivals for invasive neuroendocrine cancers in an Australian population and consider cancer control implications.
Methods Directly age-standardised incidence and mortality rates were investigated from 1980 to 2006, plus disease-specific survivals.
Results Annual incidence per 100,000 increased from 1.7 in 1980–1989 to 3.3 in 2000–2006. A corresponding mortality increase was not observed, although numbers of deaths were low, reducing statistical power. Increases in incidence affected both sexes and were more evident for female lung, large bowel (excluding appendix), and unknown primary site. Common sites were lung (25.9%), large bowel (23.3%) (40.9% were appendix), small intestine (20.6%), unknown primary (15.0%), pancreas (6.5%), and stomach (3.7%). Site distribution did not vary by sex ($p = 0.260$). Younger ages at diagnosis applied for lung ($p = 0.002$) and appendix ($p < 0.001$) and older ages for small intestine ($p < 0.001$) and unknown primary site ($p < 0.001$). Five-year survival was 68.5% for all sites combined, with secular increases ($p < 0.001$). After adjusting for age and diagnostic period, survivals were higher for appendix and lower for unknown primary site, pancreas, and colon (excluding appendix).
Conclusions Incidence rates are increasing. Research is needed into possible aetiological factors for lung and large-bowel sites, including tobacco smoking, and excess body weight and lack of exercise, respectively; and Crohn's disease as a possible precursor condition.

Keywords Incidence · Mortality · Survival · Aetiology · Risk factors

C. Luke (✉)
Epidemiology Branch, South Australian Department of Health, PO Box 6, Rundle Mall, Adelaide, SA 5000, Australia
e-mail: jowen@cancersa.org.au

T. Price · A. Townsend
Department of Haematology-Oncology, Queen Elizabeth Hospital, Woodville, SA, Australia

C. Karapetis
Department of Medical Oncology, Flinders Medical Centre, Bedford Park, SA, Australia

D. Kotasek
Ashford Cancer Centre, Ashford, SA, Australia

N. Singhal
Cancer Centre, Royal Adelaide Hospital, Adelaide, SA, Australia

E. Tracey
NSW Cancer Institute, Everleigh, NSW, Australia

D. Roder
Research and Information Science, Cancer Council South Australia, Eastwood, SA, Australia

Introduction

Neuroendocrine cancers are rare malignancies of the neuroendocrine system, reported in population and institutionally based studies to account for fewer than one per cent of all invasive cancers in Western populations [1, 2]. Annual incidence rates vary by study from around one to five per 100,000 persons [2–8]. Importantly, incidence has increased in the USA over time, and there appear to be variations by race with Afro-Americans having higher incidence rates than the white population [1, 7–9].

Because these cancers arise across the diffuse neuroendocrine system, almost any organ can be affected, but the commonest sites have been gastrointestinal, including the small intestine, rectum, appendix, colon, and stomach, plus broncho-pulmonary sites [2, 7, 9–11]. Neuroendocrine cancers often take an indolent course with the duration from symptom onset to diagnosis approximating 4–5 years and with much longer durations applying in some instances [12].

Although metastatic spread may affect around 20% or more of these cancers at diagnosis, survival duration post-diagnosis often exceeds that for other cancers of the same organ site due to the indolent behaviour of the disease [1, 13]. Surgical excision has been a mainstay of treatment although systemic therapies have an important role, depending on tumour size and location. Recent advances that may improve outcomes have included the use of the somatostatin analogues (e.g., octreotide), which although used for symptom control, may also reduce proliferation [14]. Results of a recent randomised, placebo-controlled study showed that the addition of octreotide LAR (long-acting release) reduced the risk of tumour progression by 67% [14]. Other technologies used to achieve earlier diagnosis and improved staging (e.g., octreoscanning) may also lead to better outcomes [13, 15].

In the present study, population-based registry data from Australia are used to describe incidence trends in 1980–2006 by socio-demographic characteristics and primary organ site. Disease-specific survivals are analysed by site, socio-demographic characteristics, and diagnostic period.

The extent to which site-specific age, sex, and secular distributions of neuroendocrine cancers reflect more closely the corresponding distributions for other neuroendocrine tumours, rather than the distributions for other cancers of the same organ sites, is explored. Where possible, descriptive features of the neuroendocrine cancers in this study are compared with those reported in previous investigations.

Materials and methods

Data collection

The Registry has received statutory notifications of invasive neuroendocrine cancers since 1977 [16]. The Registry covers all regions of South Australia (one of eight Australian states and territories) and all invasive cancers except non-melanoma skin cancers. Its procedures have been described previously [16]. Death data are collected through routine notifications, electronic searches of official State death records and the National Death Index at the Australian Institute of Health and Welfare, and from interstate registries [16]. Under-ascertainment has been checked through active follow-up, and with deaths reported independently, and found to be minimal at less than 1% [16, 17].

The present study included 943 invasive neuroendocrine cancers diagnosed between 1980 and 2006, plus 312 deaths from these 943 cancers occurring in that period. Following registry protocol, these were the first invasive cancers diagnosed with a primary site in the stated organs. Benign lesions were not reported to the Registry and were not included. Data for the 1970s were excluded due to uncertainty about consistency of histology coding in the early years of the Registry. Neuroendocrine cancers were defined as those with ICD-O-3 histology codes of 8,150–8,157, 8,240–8,246 or 8,249, as used in a comparative study of USA SEER data [8]. They mostly comprised carcinoid cancers, although islet cell carcinomas, glucagonomas, insulinomas, and other neuroendocrine cancers of the pancreas also were covered, together with gastrinomas that also were mostly sited in the pancreas. Merkel cell cancers and small-cell carcinomas were not included.

Socio-demographic descriptors included age at diagnosis; sex; region of residence, classified as 20 statistical subdivisions and as metropolitan or non-metropolitan [16]; country of birth (World Health Organization criteria [18]); and relative socio-economic disadvantage, as inferred from residential postcode characteristics using the SEIFA index categorised in quartiles (i.e., low, mid-low, mid-high, and high) [19].

Statistical analyses

A de-identified file was extracted and analysed in-house under provisions of the South Australian Health Care Act 2008, employing STATA 9.2 software [20].

Mean annual incidence and mortality rates were determined by sex for all sites combined for three broad periods, i.e., 1980–1989, 1990–1999, and 2000–2006, directly standardising by 5-year age group (with an open-ended category from 85 years) to the 2001 Australian reference population [20, 21]. Ninety-five per cent confidence limits were calculated assuming a Poisson distribution, as described previously [22].

Rates were calculated for all ages combined and for age categories under 50, 50–59, 60–69, and 70 years or more, respectively, to assist visualisation of trends. Mean annual incidence rates were also analysed by sex for individual primary sites for all ages combined for the same calendar year groupings, directly standardising by 5-year age group.

Differences in epidemiological characteristics of neuroendocrine cancers by organ site were investigated. Initially characteristics were analysed as univariate predictors, using the Pearson chi-square test for nominal variables and the Kruskal–Wallis ANOVA for ordinal variables [21].

Epidemiological differences were further explored using multiple logistic regression analysis, taking each organ site as the dependent variable in separate analyses [20, 21]. All socio-demographic variables were entered as predictors, with backwards elimination of those where the fit of the model did not reduce as a consequence ($p > 0.05$). Assumptions underlying each analysis, including an absence of co-linearity, were found to be satisfied [20]. Alternative models including generalised linear log binomial regression, Poisson regression, and negative binomial regression were tried but were not found to fit the data as well as logistic regression [20].

Distributions of neuroendocrine cancers by sex, age at diagnosis, and diagnostic period were compared for each organ site: (1) with corresponding distributions for cancers of other histological type of that same organ site and (2) with corresponding distributions for neuroendocrine cancers of other organ sites, in order to investigate their relative similarity. This was undertaken by comparing Spearman correlation coefficients (95% confidence intervals) for age and diagnostic period, and relative risks (95% confidence intervals) for sex [20, 21]. When 95% confidence intervals did not overlap, non-random differences were assumed, although the study was descriptive and the results regarded as hypothesis generating.

Case survivals were calculated, with a date of censoring of live cases of 31 December 2006. Kaplan–Meier product-limit estimates of disease-specific survival were calculated, treating deaths from other causes and people still alive at the end of 2006 as censored observations [20, 21]. This involved a life-table approach in which cases not followed for the full period of interest (say 5 years for 5-year survival) still contributed their shorter experience to the survival calculation [21].

Multivariable Cox proportional hazards regression also was undertaken to assess socio-demographic and histological predictors of survival from neuroendocrine cancer. The regression analysis employed the same censoring criteria as for the Kaplan–Meier analyses [20, 21]. All predictor variables were entered into the analysis, with backwards elimination. Assumptions underlying the analysis, including proportionality and an absence of co-linearity, were found to be satisfied [20, 21]. Because continuous variables were not used as predictors, assumptions about linear relations with the outcome variable did not apply. The results indicate the association of each predictor with death from neuroendocrine cancer, adjusting for other predictors in the model and follow-up period [20, 21].

Disease-specific survival was employed, not relative survival, because the life tables needed to undertake relative survival analyses were not available for many population sub-groups. Analyses have shown very similar survival estimates in South Australia, irrespective of disease-specific or relative survival method, such that disease-specific survivals presented here are regarded as a good proxy for relative survivals [23].

Results

Trends in incidence

Neuroendocrine tumours comprised 0.6% of all invasive cancers recorded on the Registry for 1980–2006, 0.4% of those in men and 0.6% of those in women. The proportion ranged from 0.5% in the 1980s to 0.6% in 2000–2006. Over half the neuroendocrine cancers (52.5%) occurred in women. The great majority (96.5%) were carcinoid, with most of the remainder being islet cell and like carcinomas of the pancreas.

The annual age-standardised incidence (95% confidence limits) per 100,000 increased by 86.8% from 1.74 (1.52, 1.99) in 1980–1989 to 3.25 (2.93, 3.59) in 2000–2006 (Table 1), with increases affecting all age groups and both sexes, although more evident in women. By comparison, annual age-standardised mortality rates per 100,000 did not show a clear trend over time, varying from 0.72 (0.58, 0.88) in 1980–1989 to 0.94 (0.79, 1.11) in 1990–1999 and 0.84 (0.69, 1.02) in 2000–2006.

Incidence rates increased steeply with age, with the rate for persons aged 70 or more being 10.4 times that for persons under 50 years of age (Table 1). Annual age-standardised mortality rates per 100,000 increased even more steeply with age from 0.12 (0.08, 0.17) in persons under 50 years to 0.98 (0.71, 1.32) in 50- to 59-year-olds, 2.73 (2.20, 3.35) in 60- to 69-year-olds, and 4.83 (4.14, 5.61) in persons aged 70 or more.

The most common incidence site for neuroendocrine cancers for both sexes combined was lung (25.9%) followed by large bowel (23.3%) (40.9% of large-bowel cancers were located in the appendix) (Table 2). Other common sites included the small intestine (20.6%), unknown primary site (15.0%), pancreas (6.5%), and stomach (3.7%).

Increases in incidence were evident by site between 1980–1989 and 2000–2006, with a 164.7% increase applying for female lung, a 136.4% increase for large bowel (excluding appendix), a 237.5% increase for unknown primary site, and with borderline evidence of increases also applying for the small intestine and female stomach (Table 2). Further analysis indicated that there was not a significant difference in the increase for large-bowel cancers between colon and rectum cancers ($p = 0.322$). Analyses of mortality trends by site were not undertaken due to small numbers.

Table 1 Mean annual age-standardised (Australia, 2001) incidence rates (95% confidence limits) for neuroendocrine tumours per 100,000 South Australians by age range, sex, and calendar year period

Ages (years)	Calendar year			Total
	1980–1989	1990–1999	2000–2006	
Males				
	[$n = 119$]	[$n = 152$]	[$n = 177$]	[$n = 448$]
<50 [$n = 95$]	0.56 [0.36, 0.83]	0.59 [0.40, 0.83]	1.07 [0.77, 1.46]	0.70 [0.57, 0.86]
50–59 [$n = 89$]	3.59 [2.32, 5.31]	3.46 [2.26, 5.07]	5.53 [3.92, 7.59]	4.05 [3.25, 4.98]
60–69 [$n = 113$]	5.99 [4.15, 8.37]	5.28 [3.63, 7.41]	10.16 [7.44, 13.55]	6.81 [5.61, 8.18]
70+ [$n = 151$]	9.04 [6.33, 12.51]	10.66 [8.17, 13.67]	10.81 [8.10, 14.14]	10.10 [8.55, 11.85]
Total [$n = 448$]	2.11 [1.75, 2.52]	2.21 [1.87, 2.59]	3.19 [2.74, 3.70]	2.43 [2.21, 2.66]
Females				
	[$n = 102$]	[$n = 187$]	[$n = 206$]	[$n = 495$]
<50 [$n = 125$]	0.51 [0.33, 0.77]	1.04 [0.78, 1.35]	1.27 [0.93, 1.68]	0.90 [0.75, 1.08]
50–59 [$n = 90$]	2.54 [1.50, 4.01]	3.86 [2.59, 5.55]	6.17 [4.46, 8.31]	3.97 [3.19, 4.88]
60–69 [$n = 120$]	6.43 [4.59, 8.76]	6.60 [4.78, 8.89]	7.79 [5.48, 10.74]	6.85 [5.68, 8.19]
70+ [$n = 160$]	3.52 [2.18, 5.38]	7.50 [5.74, 9.64]	11.52 [9.11, 14.38]	7.07 [6.02, 8.25]
Total [$n = 495$]	1.48 [1.21, 1.80]	2.39 [2.06, 2.76]	3.29 [2.85, 3.77]	2.29 [2.09, 2.50]
Persons				
	[$n = 221$]	[$n = 339$]	[$n = 383$]	[$n = 943$]
<50 [$n = 220$]	0.54 [0.39, 0.71]	0.81 [0.65, 1.00]	1.17 [0.94, 1.44]	0.80 [0.70, 0.92]
50–59 [$n = 179$]	3.07 [2.22, 4.14]	3.66 [2.76, 4.76]	5.86 [4.65, 7.28]	4.01 [3.45, 4.64]
60–69 [$n = 233$]	6.21 [4.87, 7.79]	5.95 [4.69, 7.45]	8.95 [7.13, 11.10]	6.82 [5.97, 7.76]
70+ [$n = 311$]	5.69 [4.31, 7.37]	8.90 [7.40, 10.62]	11.25 [9.41, 13.35]	8.32 [7.42, 9.30]
Total [$n = 943$]	1.74 [1.52, 1.99]	2.28 [2.05, 2.54]	3.25 [2.93, 3.59]	2.33 [2.19, 2.49]

Data source: South Australian Cancer Registry

Socio-demographic differences

Site distributions of neuroendocrine cancers were not found to vary by sex (chi-square $p = 0.260$), socio-economic status expressed in quartiles (KW $p = 0.114$), place of residence (chi-square $p = 0.589$ for statistical sub-division; chi-square $p = 0.684$ for metropolitan/non-metropolitan), but there were differences by age at diagnosis (KW $p < 0.001$), country of birth (chi-square $p < 0.001$), and diagnostic period (KW $p = 0.021$).

Multiple regression showed lower age distributions for neuroendocrine cases with a primary site of lung ($p = 0.002$) and appendix ($p < 0.001$) and older age distributions for those with a primary site of small intestine ($p < 0.001$) or of unknown primary site ($p < 0.001$). After adjusting for age, there was no longer a difference by site across diagnostic periods ($p > 0.100$). However, cancers of the appendix were less common in Australian than overseas-born cases ($p = 0.003$), whereas those of the small intestine tended to be less common in the overseas-born ($p = 0.056$), particularly those from Europe ($p = 0.020$).

Rank correlation coefficients did not show a stronger correlation between socio-demographic characteristics of neuroendocrine cancers of different sites than between socio-demographic characteristics of neuroendocrine and other histology types of the same site (i.e., 95% confidence ranges overlapped).

On three occasions, the correlation for age distribution was stronger between neuroendocrine and other histology types of the same site than between neuroendocrine cancers of different sites (i.e., 95% confidence ranges did not overlap). This applied for the appendix, small intestine, and unknown primary site.

Survivals

Survivals for all sites combined reduced from 68.5% at 5 years to 60.6% at 10 years, 55.9% at 15 years, and 49.9% at 20 years (Table 3). Five-year survivals were higher at 93.8% for appendix, 85.8% for rectum, 80.1% for lung, and 74.6% for small intestine, whereas comparatively low 5-year survivals presented at 27.8% for unknown primary site, 42.4% for pancreas, 64.6% for colon (excluding appendix), and 66.4% for stomach.

An increase in survival was evident for later calendar years of diagnosis for all sites combined ($p < 0.001$) and for the lung ($p = 0.012$), appendix ($p = 0.025$), stomach ($p = 0.008$), and potentially the colon (excluding appendix)

Table 2 Mean annual age-standardised (Australia, 2001) incidence rates (95% confidence limits) for neuroendocrine tumours per 100,000 South Australians by sex and calendar year period and primary site

Primary site	Sex	Calendar year			Total
		1980–1989	1990–1999	2000–2006	
Lung (ICD-10: C33-34)	Males [$n = 104$]	0.66 [0.46, 0.90]	0.48 [0.33, 0.67]	0.57 [0.39, 0.81]	0.57 [0.46, 0.69]
	Females [$n = 140$]	0.34 [0.22, 0.51]	0.83 [0.64, 1.06]	0.90 [0.68, 1.18]	0.67 [0.56, 0.79]
	Persons [$n = 244$]	0.48 [0.37, 0.62]	0.65 [0.53, 0.79]	0.75 [0.60, 0.92]	0.61 [0.54, 0.69]
Small intestine (ICD-10: C17)	Males [$n = 101$]	0.53 [0.35, 0.75]	0.42 [0.28, 0.60]	0.80 [0.58, 1.07]	0.56 [0.45, 0.68]
	Females [$n = 93$]	0.40 [0.26, 0.57]	0.28 [0.17, 0.42]	0.66 [0.48, 0.88]	0.42 [0.34, 0.51]
	Persons [$n = 194$]	0.45 [0.34, 0.58]	0.33 [0.25, 0.44]	0.72 [0.58, 0.89]	0.48 [0.41, 0.55]
Appendix (ICD-10: C18.1)	Males [$n = 36$]	0.17 [0.08, 0.31]	0.19 [0.10, 0.32]	0.23 [0.12, 0.39]	0.19 [0.13, 0.26]
	Females [$n = 54$]	0.10 [0.04, 0.20]	0.41 [0.28, 0.58]	0.30 [0.17, 0.48]	0.27 [0.20, 0.35]
	Persons [$n = 90$]	0.13 [0.07, 0.20]	0.30 [0.22, 0.40]	0.27 [0.18, 0.38]	0.23 [0.18, 0.28]
Large bowel (ICD-10: C18-20) (*minus appendix*)	Males [$n = 64$]	0.21 [0.11, 0.37]	0.25 [0.15, 0.40]	0.61 [0.42, 0.86]	0.33 [0.25, 0.42]
	Females [$n = 66$]	0.22 [0.12, 0.37]	0.30 [0.19, 0.44]	0.44 [0.29, 0.64]	0.31 [0.24, 0.39]
	Persons [$n = 130$]	0.22 [0.14, 0.32]	0.28 [0.20, 0.38]	0.52 [0.40, 0.67]	0.32 [0.27, 0.38]
Unknown (ICD-10: C80)	Males [$n = 73$]	0.17 [0.09, 0.31]	0.45 [0.30, 0.64]	0.58 [0.40, 0.82]	0.38 [0.30, 0.48]
	Females [$n = 68$]	0.14 [0.07, 0.26]	0.26 [0.17, 0.39]	0.50 [0.35, 0.69]	0.28 [0.22, 0.35]
	Persons [$n = 141$]	0.16 [0.10, 0.24]	0.36 [0.27, 0.46]	0.54 [0.42, 0.68]	0.33 [0.28, 0.39]
Stomach (ICD-10: C16)	Males [$n = 17$]	0.10 [0.04, 0.21]	0.11 [0.04, 0.23]	0.07 [0.02, 0.17]	0.10 [0.06, 0.15]
	Females [$n = 18$]	0.02 [0.00, 0.09]	0.08 [0.03, 0.16]	0.18 [0.09, 0.33]	0.08 [0.05, 0.13]
	Persons [$n = 35$]	0.05 [0.02, 0.11]	0.09 [0.05, 0.16]	0.13 [0.07, 0.21]	0.09 [0.06, 0.12]
Pancreas (ICD-10: C25)	Males [$n = 33$]	0.14 [0.06, 0.29]	0.17 [0.09, 0.29]	0.25 [0.13, 0.41]	0.18 [0.12, 0.25]
	Females [$n = 28$]	0.09 [0.04, 0.19]	0.12 [0.06, 0.23]	0.19 [0.09, 0.33]	0.13 [0.09, 0.19]
	Persons [$n = 61$]	0.11 [0.06, 0.18]	0.15 [0.09, 0.22]	0.22 [0.14, 0.32]	0.15 [0.11, 0.19]
Other (ICD-10: Rem C00-96)	Males [$n = 20$]	0.14 [0.05, 0.30]	0.14 [0.06, 0.27]	0.09 [0.03, 0.21]	0.13 [0.08, 0.19]
	Females [$n = 28$]	0.18 [0.09, 0.31]	0.12 [0.05, 0.22]	0.12 [0.05, 0.25]	0.14 [0.09, 0.20]
	Persons [$n = 48$]	0.15 [0.09, 0.23]	0.13 [0.08, 0.20]	0.11 [0.05, 0.18]	0.13 [0.10, 0.17]

Data source: South Australian Cancer Registry

($p = 0.056$). Five-year survivals (±standard errors) for 1980–1989, 1990–1999, and 2000–2006, respectively, were

1. All sites: 61.0 (±3.4)%, 67.4 (±2.6)%, and 73.4 (±3.0)%
2. Lung: 70.0 (±5.9)%, 78.8 (±4.2)%, and 90.3 (±3.5)%
3. Appendix: 87.4 (±8.4)%, 93.1 (±3.9)%, and 100%

Meanwhile, 20 stomach cancer cases diagnosed in 1980–1999 had a 5-year survival of 54.7 (±9.8)%, which was lower than the corresponding 84.8 (±0.10)% for 15 stomach cases diagnosed in 2000–2006, and 33 colon cancer cases diagnosed in 1980–1999 had a 5-year survival of 52.1 (±9.0)%, which was lower than the 80.9 (±8.8)% for 25 colon cases diagnosed in 2000–2006.

Multivariable Cox proportional hazards regression showed that risk of case fatality from neuroendocrine cancer increased with increasing diagnostic age and was lower in more recent diagnostic periods (Table 4). Meanwhile, a low relative risk was evident for cancers sited in the appendix and an elevated relative risk for colonic and pancreatic cases, and especially those of unknown primary site which presented the highest relative risk. Sex, region of residence, socio-economic status, and country of birth were excluded from the model in the backwards elimination process ($p > 0.100$).

Discussion

The mean annual incidence of 2.3 per 100,000 for neuro-endocrine cancers in 1980–2006 and the 3.3 per 100,000 for the more contemporary 2000–2006 period fall within the range of one to five per 100,000 reported in other studies [2–8].

Data for the 1970s were excluded from this study due to uncertainty about consistency of histology coding in the early years of the Registry. Despite this precaution, it is possible than increases in incidence during 1980–2006 were affected by changes in diagnostic accuracy. Neuro-endocrine cancers frequently develop slowly, such that many years can elapse between symptom onset and

Table 3 Percentage survival (±standard error) from neuroendocrine cancer in SA by primary site and period from diagnosis: SA Cancer Registry, 1980–2006

Primary site (n = cases/dths)	Period from diagnosis (years)			
	5	10	15	20
Lung (n = 244/54)	80.1 ± 2.7	73.6 ± 3.3	72.3 ± 3.5	72.3 ± 3.5
Small intestine (n = 194/57)	74.6 ± 3.7	60.1 ± 5.2	47.8 ± 6.1	37.7 ± 7.1
Appendix (n = 90/7)	93.8 ± 2.7	90.2 ± 3.6	90.2 ± 3.6	90.2 ± 3.6
Colon (n = 58/22) (*excl. appendix*)	64.6 ± 6.6	49.1 ± 12.3	–	–
Rectum (n = 72/13)	85.8 ± 4.2	77.0 ± 6.2	77.0 ± 6.2	77.0 ± 6.2
Stomach (n = 35/11)	66.4 ± 8.8	58.1 ± 10.9	–	–
Pancreas (n = 61/32)	42.4 ± 7.3	39.4 ± 7.4	29.5 ± 10.2	–
Other (n = 48/20)	60.8 ± 7.3	56.1 ± 8.1	44.9 ± 11.9	44.9 ± 11.9
Unknown (n = 141/96)	27.8 ± 4.4	18.6 ± 4.5	16.0 ± 4.6	–
Total (n = 943/312)	68.5 ± 1.6	60.6 ± 2.0	55.9 ± 2.3	49.9 ± 3.4

Kaplan–Meier product-limit estimates

Date of censoring of live cases: 31 December 2006

Data source: South Australian Cancer Registry

Table 4 Relative risk (95% confidence limits) of death from neuroendocrine tumours: SA Cancer Registry, 1980–2006

Predictors (n = cases/dths)	Relative risk
Age at diagnosis (years)	
Under 50 (ref) [n = 220/37]	1.00
50–59 [n = 179/56]	1.74 [1.13, 2.66]
60–69 [n = 233/88]	2.03 [1.37, 3.01]
70–79 [n = 219/83]	2.66 [1.77, 3.99]
80+ [n = 92/48]	4.74 [2.99, 7.51]
Organ site	
Other (ref) [n = 593/155]	1.00
Appendix [n = 90/7]	0.22 [0.09, 0.53]
Colon [n = 58/22] (*excl. appen.*)	1.60 [1.02, 2.53]
Pancreas [n = 61/32]	3.16 [2.14, 4.66]
Unknown [n = 141/96]	4.09 [3.13, 5.36]
Period of diagnosis	
1980–1989 (ref) [n = 221/111]	1.00
1990–1994 [n = 169/60]	0.64 [0.46, 0.88]
1995–1999 [n = 170/64]	0.59 [0.42, 0.81]
2000–2006 [n = 383/77]	0.41 [0.30, 0.56]

Multivariable Cox proportional hazards regression

Variables entered into the model included age, sex, organ site, period of diagnosis, region of residence, country of birth, and socio-economic status, with age, organ site, and period of diagnosis retained as significant predictors (see text). Adjustment was made in the model for differences between cases in follow-up time [20, 21]

diagnosis [1, 12, 13]. If diagnosis were to be brought forward through gains in diagnostic technology, or increased clinical interest, then incidence figures might be inflated artificially through lead time and related effects. It is possible, for example, that advances in immunohistochemistry and neuroendocrine tumour markers could have contributed in this regard [24]. The extent to which incidence increases observed in this study were due to such effects, as opposed to real incidence increases, is not known and warrants separate investigation with data that include stage.

The annual increase of 3.4% during 1980–2006, although pronounced, was not as large as the 6.5% reported for North America in 1973–1997 [2]. The increase in our study applied to a broad cross-section of ages, and to both sexes, and supports the North American evidence for an increase.

Although there was not evidence of a corresponding increase in annual mortality, statistical power was limited due to small numbers of deaths (i.e., 338 deaths in 1980–2006; 312 from cancers diagnosed in 1980–2006, and 26 from cancers diagnosed before 1980). Moreover, increases in survival during the study period would tend to have offset the potential for mortality increases.

Increases in incidence during the study period exceeded twofold for neuroendocrine cancers of the female lung, large bowel (excluding appendix), and unknown primary site, with similar increases applying for colon and rectum cancers. Female lung and large-bowel cancers also showed increases in incidence for all histology types combined during this period [25], which raises the possibility of similar causal factors. Possible causes requiring further investigation include tobacco smoking, excess body weight, diet, lack of exercise, and trends in precursor conditions such as Crohn's disease [26].

Crohn's disease has been linked to tobacco smoking and to increased risk of carcinoid tumours [27]. Although the reliability of incidence data has been uncertain, and conflicting trends reported, Australian data have pointed to an increased incidence of Crohn's disease in children, and

confirmatory increases have been reported for other populations [28–30]. There is the possibility that trends in Crohn's disease itself, or risk factors common to Crohn's disease and neuroendocrine cancers, may have contributed to the increasing incidence of neuroendocrine cancers.

The stronger correlation of age at diagnosis of neuroendocrine cancers with ages for other histology types of the same sites (rather than with ages of other neuroendocrine cancers) may have causal implications. This was observed for the appendix and small intestine. Again, there is a need for research into potentially common dietary and environmental causes and precursor conditions, including Crohn's disease [26, 27].

Although neuroendocrine cancers are often diagnosed late [1, 13], their survivals from diagnosis are comparatively high, with a 5-year survival of 68.5%, reducing to around 50% at 20 years. Collective survivals for all neuroendocrine cancers combined were similar in this study to those reported for North America [2]. Although the higher survivals evident for the more recent diagnostic periods are encouraging and may reflect clinical advances such as the introduction of somatostatin analogues, they could have been influenced artificially by lead time and related effects of earlier diagnosis. They are not regarded as artefacts of shorter follow-up time, given the life-table approach that was taken and the short time intervals employed in the analyses (i.e., intervals of 1 day) [21]. Had stage, tumour grade, proliferative index, and other prognostic indicators been collected by the Registry, this secular trend could have been investigated in greater depth.

It was recommended at a recent workshop that the surgical management of neuroendocrine cancers of gastero-pancreatic sites be undertaken by specialists in high volume centres with the support of octrieotide scintigraphy, triple-phase CT, MRI, and echocardiograms [31]. The extent to which this is occurring and contributing to survival gains is not clear.

The lower survival from these cancers demonstrated in this study in the older age ranges is similar to that seen for other cancers [16]. The extent to which this finding is due to later diagnoses or to compromising effects of increased co-morbidity and frailty is not known. The better outcomes for neuroendocrine cancers sited in the appendix, and poorer outcomes for those in the pancreas or of unknown primary site, are consistent with the survival differences observed for all histology types combined [16]. For example, 5-year survivals for all histology types combined have approximated 5% for pancreatic cancers and 9% for cancers of unknown primary site.

After adjusting for age, multiple logistic regression indicated that neuroendocrine cancers of the appendix were less common in Australian than overseas-born cases, whereas those of the small intestine were less common in the overseas born, particularly those from Europe. These findings may reflect the impact of environment and diet. They warrant confirmation in separate studies.

The distribution of neuroendocrine cancers by site was similar to those reported for other populations [2, 7]. The distribution by organ site did not vary between men and women. The most common primary site for neuroendocrine cancers for both sexes combined was lung (26%) followed by large bowel (23%) (41% of large-bowel cancers were located in the appendix). Other common sites included the small intestine (21%), unknown primary site (15%), pancreas (7%), and stomach (4%). Similar findings presented in a preliminary analysis of NSW Central Cancer Registry data, in that the most common sites were the lung (24%) and gastrointestinal sites (43%), with less common sites including unknown primary sites (15%), pancreas (7%), and oesophagus (5%).

Earlier clinical reports from North America suggested that the most common gastro-intestinal site was the appendix [2, 30]. This clinical view is still commonly reported and may reflect observations of benign together with invasive lesions. It is not supported by more contemporary USA data or the results of this study for invasive cancers [2, 32].

The management of neuroendocrine cancers warrants further investigation. Linkage of cancer registry data with hospital admission data would enable the prevalence of cardiac complications to be investigated and the extent to which liver-related treatments are provided. Information on accompanying imaging and use of somatostatin analogues could be obtained through linkage with health insurance data. These are rare cancers where national investigations of secular trends in incidence, mortality, survival, and patterns of care would be beneficial by site and histological characteristics.

Conclusions

Incidence rates and increases observed in this study confirm those reported for other Western populations. The causes of increases are not known but parallel increases for other histology types of the lung and large-bowel site may be due to common causal factors, such as tobacco smoking, excess body weight, diet, and lack of exercise. Further research is needed into possible roles of precursor conditions like Crohn's disease and dietary variation. The present results support recent literature reports of secular improvements in survival. Factors increasing survival may include improvements in imaging and access to somatostatin analogues. Further research that explores effects of these factors and changes in stage and cancer biology is needed.

References

1. Taal BG, Visser O (2004) Epidemiology of neuroendocrine tumours. Neuroendocrinology 80(Suppl. 1):3–7
2. Maggard MA, O'Connell JB, Ko CY (2004) Updated population-based review of carcinoid tumors. Ann Surg 240:117–122
3. Levi F, Te V-C, Randimbison L, Rindi G, La Vecchia C (2000) Epidemiology of carcinoid neoplasms in Vaud, Switzerland, 1974–1997. Br J Cancer 83:952–955
4. Quaedvlieg PF, Visser O, Lamers CB, Janssen-Heijen ML, Taal BG (2001) Epidemiology, survival in patients with carcinoid disease in the Netherlands. An epidemiological study with 2391 patients. Ann Oncol 12:1295–1300
5. Kim T, Grobmyer SR, Liu C, Hochwald SN (2007) Primary presacral neuroendocrine tumor associated with imperforate anus. World J Surg Oncol 5:115
6. Modlin IM, Moss SF, Chung DC, Jensen RT, Snyderwine E (2008) Priorities for improving the management of gastroenteropancreatic neuroendocrine tumors. J Natl Cancer Inst 100: 1282–1289
7. Hauso O, Gustafsson BI, Kidd M, Waldum HL, Drozdov I, Chan AK, Modlin IM (2008) Neuroendocrine tumor epidemiology: contrasting Norway and North America. Cancer 113: 2655–2664
8. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB (2008) One hundred years after "carcinoid": epidemiology and prognostic factors for neuroendocrine tumors in 35, 825 cases in the United States. J Clin Oncol 26:3063–3072
9. Modlin IM, Lye KD, Kidd M (2003) A 5-decade analysis of 13, 715 carcinoid tumors. Cancer 97:934–959
10. Lauffer JM, Zhang T, Modlin IM (1999) Review article: current status of gastrointestinal carcinoids. Aliment Pharmacol Ther 13:271–287
11. Modlin IM, Shapiro MD, Kidd M (2005) An analysis of rare carcinoid tumors: clarifying these clinical conundrums. World J Surg 29:92–101
12. Horton KM, Kamel I, Hofmann L, Fishman EK (2004) Carcinoid tumors of the small bowel: a multitechnique imaging approach. AJR Am J Roentgenol 182:559–567
13. Modlin IM, Latich I, Zikusoka M, Kidd M, Eick G, Chan AK (2006) Gastrointestinal carcinoids: the evolution of diagnostic strategies. J Clin Gastroenterol 40:572–582
14. Muller H, Schade-Brittinger C, Rinke A et al. (2009) Placebo-controlled, double-blind, prospective, randomized study of the effect of Octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. Proceedings of gastrointestinal symposium: 120, aster 121
15. Massironi S, Sciola V, Peracchi M, Ciafardini C, Spampatti MP, Conte D (2008) Neuroendocrine tumors of the gastro-entero-pancreatic systems. World J Gastroenterol 14:5377–5384
16. South Australian Cancer Registry (SACR) (2000) Epidemiology of Cancer in South Australia. Incidence, mortality and survival 1977 to 1999. Incidence and mortality 1999. Openbook, Adelaide
17. Bonett A, Roder D, Esterman A (1988) Cancer case-survival rates for South Australia: a comparison with US rates and a preliminary investigation of time trends. Med J Aust 148:556–559
18. Ferlay J, Bray F, Pisani P, Parkin DM (2001) GLOBOCAN 2000: cancer incidence, mortality and prevalence worldwide. Version 1.0. IARC Press, IARC CancerBase No. 5, Lyon
19. Australian Bureau of Statistics (ABS) (1998) 1996 census of population and housing. Socio-economic indexes for areas. Australian Bureau of Statistics, Canberra
20. StataCorp (2005) Stata statistical software. Release 9.2. StataCorp LP, College Station
21. Armitage P, Berry G (1987) Statistical methods in medical research. Blackwell, Oxford
22. Dobson AJ, Kuulasmaa K, Eberle E, Scherer J (1991) Confidence intervals for weighted sums of Poisson parameters. Stat Med 10(3):457–462
23. South Australian Cancer Registry (SACR) (1997) Epidemiology of cancer in South Australia. Incidence, mortality and survival 1977 to 1996. Incidence and mortality 1996. Openbook, Adelaide
24. Scott N, Millward E, Carwright EJ, Preston SR, Coletta PL (2004) Gastrin releasing peptide and gastrin releasing peptide receptor expression in gastrointestinal carcinoid tumours. J Clin Pathol 57:189–192
25. Australian Institute of Health, Welfare (AIHW) (2008) Cancer incidence data cubes. Australian Institute of Health and Welfare, Canberra
26. Centre for Cancer Control Research (CCCR) (2001) Cancers of the digestive system. South Australian Cancer Statistics Monograph No 1. Anti-Cancer Foundation, Adelaide
27. West NE, Wise PE, Herline AJ, Muldoon RL, Chopp WV, Schwartz DA (2007) Carcinoid tumors are 15 times more common in patients with Crohn's disease. Inflamm Bowel Dis 13:1129–1134
28. Perminow G, Frigessi A, Rydning A, Nakstad B, Vatn MH (2006) Incidence and clinical presentation of IBD in children: comparison between prospective and retrospective data in a selected Norwegian population. Scand J Gastroenterol 41:1433–1439
29. Nguyen GC, Tuskey A, Dassopoulos T, Harris ML, Brant SR (2007) Rising hospitalization rates for inflammatory bowel disease in the United States between 1998 and 2004. Inflamm Bowel Dis 13:1529–1535
30. Ponsonby AL, Catto-Smith AG, Pezic A, Dupuis S, Halliday J, Cameron D, Morley R, Carlin J, Dwyer T (2008) Association between early-life factors and risk of child-onset Crohn's disease among Victorian children born 1983–1998: a birth cohort study. Inflamm Bowel Dis, December 23 [Epublication ahead of print]
31. Evans A (2008) Neuroendocrine tumours (NETS) consensus workshop, Melbourne, July 28th 2008. Clinical Oncological Society of Australia, Sydney
32. Schwartz SI (1994) Appendix. In: Schwartz SI, Shires GT, Spencer FC (eds) Principles of surgery, 6th edn. McGraw-Hill, New York, pp 1307–1318

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.