Cancer Epidemiology 63 (2019) 101598

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Epidemiological trends of neuroendocrine tumours over three decades in Queensland, Australia

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ARTICLE INFO

Keywords:
Neuroendocrine neoplasms
Incidence
Survival
Population-based

ABSTRACT

Introduction: While neuroendocrine tumours (NETs) account for only a small proportion of cancer diagnoses, incidence has been rising over time. We examined incidence, mortality and survival over three decades in a large population-based registry study.

Methods: This retrospective study included all cases (n = 4580) of NETs diagnosed from 1986 to 2015 in Queensland, Australia. We examined directly age-standardised incidence and mortality rates. The impact on overall survival according to demographic factors and primary site was modelled using multivariable Cox proportional hazards regression (HR). Cause-specific and relative survival were estimated using the Kaplan-Meier survival function.

Results: Annual incidence increased from 2.0 in 1986 to 6.3 per 100,000 in 2015, while mortality remained stable. The most common primary site was appendix followed by lung, small intestine and rectum. Rectal, stomach, appendiceal and pancreatic NETs had the greatest rate increase, while lung NETs decreased over the same period. Five-year cause-specific survival improved from 69.4% during 1986–1995 to 92.6% from 2006 to 2015. Survival was highest for appendiceal and rectal NETs and lowest for pancreas and unknown primary sites. The risk of dying within five years of diagnosis was about 40% higher for males (HR = 1.41, 95%CI 1.20–1.65) and significantly higher for patients aged over 40 years compared to younger patients ($p < 0.001$).

Conclusion: This study, including 30 years of data, found significantly increasing rates of NETs and confirms results from elsewhere. Increasing survival over time in this study, likely reflects increased awareness, improvements in diagnostic imaging, greater use of endoscopy and colonoscopy, and the development of new therapies.

1. Introduction

Neuroendocrine Neoplasms (NENs) are a group of heterogeneous tumours with complex presentations. [1] Classification of NENs is based on grade, differentiation and other pathological factors [2]. Clinically, NENs broadly comprise two subgroups, neuroendocrine tumours (NETs) and neuroendocrine carcinomas (NECs). These subgroups have vastly different prognoses and survival rates [3]. In 2010, the World Health Organisation (WHO) introduced a new classification to accurately reflect the well-recognised differences in prognosis between NETs and NECs and to integrate a grading system with historical histopathological criteria to recognise the malignant potential of these tumours [2].

NENs are relatively rare, however their incidence has been increasing in European, North American and Asian countries over the past several decades. [4–10] Despite the rising incidence, mortality has remained stable. Similar to trends observed worldwide, a retrospective Australian state-based study showed an increasing incidence of neuroendocrine cancers without an increase in mortality [11]. The rising incidence may be related to several factors such as: a true increasing incidence of this malignancy, changes in histological classifications over time, increased detection due to greater use of new and existing imaging techniques (e.g. Ultrasound, CT, MRI) and the use of endoscopy and colonoscopy [2,12].

While the rise in incidence has been observed across most primary sites, site-specific incidence varies by geographical populations. For example, gastrointestinal NENs have the highest incidence in western countries while lung NENs have the highest incidence in Asian

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https://doi.org/10.1016/j.canep.2019.101598
Received 17 April 2019; Received in revised form 19 August 2019; Accepted 5 September 2019

Table 1
Sociodemographic characteristics of 4580 patients with neuroendocrine tumours in Queensland, Australia.

	Year of diagnosis 1986-1995 N (%)	1996-2005 N (%)	2006-2015 N (%)	Total N (%)
Sex				
Males	365 (48.8%)	572 (44.5%)	1170 (45.9%)	2107 (46.0%)
Females	383 (51.2%)	714 (55.5%)	1376 (54.1%)	2473 (54.0%)
Median age	58	56	57	57
Age Group				
0-19	45 (6.0%)	72 (5.6%)	152 (6.0%)	269 (5.9%)
20-29	71 (9.5%)	81 (6.3%)	147 (5.8%)	299 (6.5%)
30-39	69 (9.2%)	110 (8.6%)	230 (9.0%)	409 (8.9%)
40-49	71 (9.5%)	212 (16.5%)	332 (13.0%)	615 (13.4%)
50-59	135 (18.1%)	279 (21.7%)	535 (21.0%)	949 (20.7%)
60-69	184 (24.6%)	264 (20.5%)	541 (21.3%)	989 (21.6%)
70-79	134 (17.9%)	199 (15.5%)	428 (16.8%)	761 (16.6%)
80+	39 (5.2%)	69 (5.4%)	181 (7.1%)	289 (6.3%)
Indigenous status				
Indigenous	10 (1.3%)	27 (2.1%)	85 (3.3%)	122 (2.7%)
Non-Indigenous	554 (74.1%)	1253 (97.4%)	2452 (96.3%)	4259 (93.0%)
Unknown	184 (24.6%)	6 (0.5%)	9 (0.3%)	199 (4.3%)
Socioeconomic status[a]				
Affluent	123 (16.3%)	218 (17.0%)	412 (16.2%)	752 (16.5%)
Middle	488 (65.4%)	806 (62.7%)	1619 (63.6%)	2913 (63.6%)
Disadvantage	135 (18.1%)	262 (20.3%)	515 (20.2%)	912 (19.9%)
Residence				
Urban	524 (70.1%)	918 (71.4%)	1708 (67.1%)	3150 (68.8%)
Rural	224 (29.9%)	368 (28.6%)	838 (32.9%)	1430 (31.2%)
Primary site				
Appendix	165 (22.1%)	322 (25.1%)	654 (25.7%)	1142 (24.9%)
Small intestine	90 (12.0%)	263 (20.0%)	539 (21.2%)	892 (19.5%)
Colon	54 (7.2%)	80 (6.2%)	138 (5.4%)	272 (5.9%)
Rectum	60 (8.0%)	214 (16.6%)	396 (15.6%)	670 (14.6%)
Stomach	15 (2.0%)	56 (4.4%)	127 (5.0%)	198 (4.3%)
Pancreas	31 (4.1%)	52 (4.0%)	167 (6.6%)	250 (5.5%)
Lung	272 (36.4%)	217 (16.9%)	383 (15.0%)	872 (19.0%)
Other sites	23 (3.1%)	34 (2.6%)	62 (2.4%)	119 (2.6%)
Unknown primary	38 (5.1%)	47 (3.7%)	80 (3.1%)	165 (3.6%)

[a] Socioeconomic status unknown for two patients in the period 1986–1995.

countries. [3–5,7,13–16] North American studies also show incidence and clinical outcomes differ by gender, ethnicity, age and socio-economic status [4,5]. From these studies several factors including geography, environment and genetics likely play a role in the incidence and outcomes of NENs.

While studies examining incidence and survival from NENs have been conducted across several countries, only one earlier study using a population-based approach has been conducted in Australia. [11] Other published Australian-based studies have been based on small cross-sectional cohorts, single institutions or included only gastrointestinal NENs [17–19]. To address this, we conducted a retrospective population-based study describing incidence and mortality trends, demographic characteristics and cause-specific survival of NETs over three decades.

2. Methods

2.1. Setting

Queensland is the third most populous, and the most decentralised, Australian state whereby approximately 40% of the population live outside a major city.

2.2. Data sources

Data was obtained from the Queensland Oncology Repository (QOR), a database containing state-wide information on cancer incidence, mortality, treatment and outcomes. Data on cancer diagnoses and deaths within QOR are collected in the Queensland Cancer Register (QCR). In Queensland, notification of a cancer diagnosis (excluding basal and squamous cell carcinoma of the skin) is a statutory requirement. The QCR is population-based and maintains a register of all cases of cancer and tumours of uncertain behaviour diagnosed in Queensland since the beginning of 1982. Cancer registration is a statutory requirement for all Australian registries. All registries conduct national death matching annually and this identifies where a patient is diagnosed in one state but dies in another. The state where the original cancer notification was recorded is notified of the death, including the details (such as date and cause[s]) of the death. Thus, the entire Australian population is covered ensuring accurate follow-up of the entire dataset. All patients with a diagnosis of a NET between 1/1/1986 and 31/12/2015 and registered as Queensland residents were included.

2.3. Classification of NETs

To address the heterogeneous nature of NENs and their prognosis, we used the WHO 2010 classification to differentiate NETs from NECs for all cases including those of uncertain behaviour. In this study we particularly wanted to focus on NETs as they are a distinct group not often reported on using registry-based data. Thus, NETs with an ICD-O code of 8150–8157, 8240–8245, and 8249 were included. We excluded NECs (ICD-O 8246) (n = 972) and Merkel cell carcinomas (ICD-O 8247) (n = 1552) as they have very different clinical and biological behaviours. Sites were grouped as: stomach; small intestine; colon/rectosigmoid junction; appendix; rectum; pancreas; lung; other sites and unknown primary.

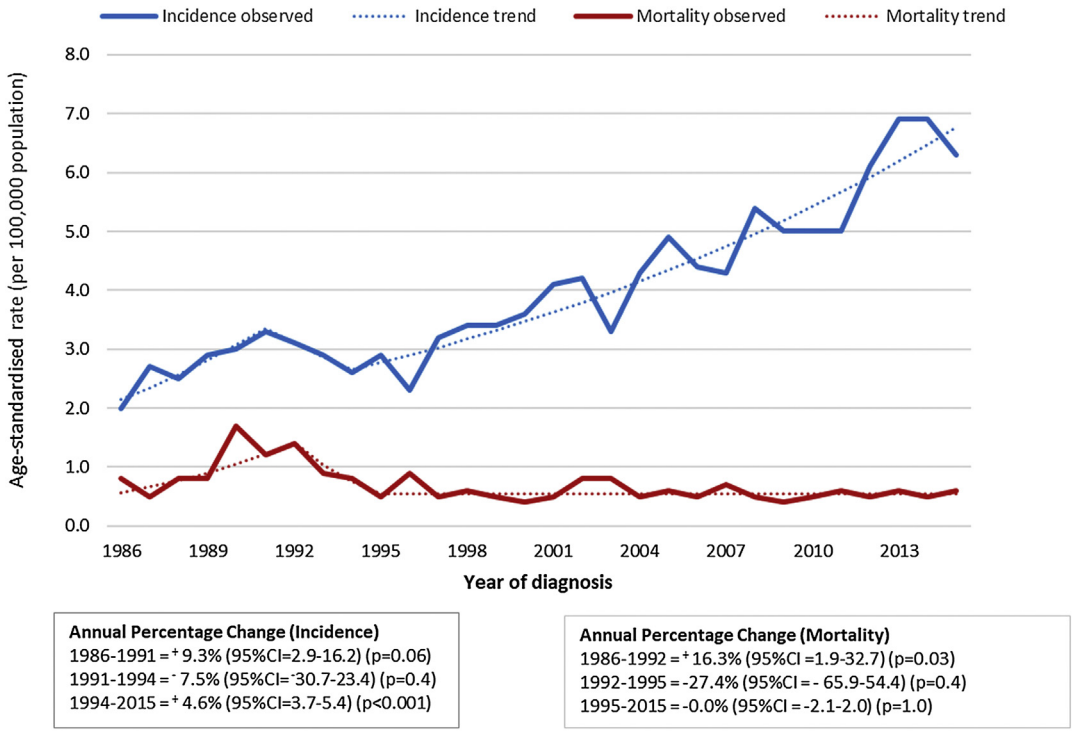

Fig. 1. Age-standardised incidence and mortality rates per 100,000 for NETs diagnosed from 1986 to 2015 in Queensland, Australia.

Table 2
: Average incidence and mortality rates over time adjusted to various reference populations.

	Period of diagnosis					
	1986–1995		1996–2005		2006–2015	
Population	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality
Australian 2001	2.8 (2.6–3.0)	1.0 (0.9–1.1)	3.7 (3.5–3.9)	0.6 (0.5–0.7)	5.6 (5.4–5.8)	0.5 (0.5–0.6)
World	2.2 (2.0–2.3)	0.7 (0.6–0.7)	2.9 (2.7–3.1)	0.4 (0.3–0.4)	4.3 (4.2–4.5)	0.3 (0.3–0.4)

2.4. Statistical analysis

Incidence and mortality rates were directly standardised to the 2001 Australia population distribution and to the world population. JoinPoint regression package (Statistical Research and Applications Branch, National Cancer Institute, Maryland, United Stated) was used to examine trends in age-standardised rates over time. Results were expressed as annual percentage change (APC) with 95% confidence intervals. Cases were grouped into three 10-year time periods (1986–1995, 1996–2005, 2006–2015).

Cancer-specific survival was calculated from the date of diagnosis and censored at December 31, 2015. The Kaplan-Meier method was used to plot cause-specific survival. Cox proportional hazards regression was used to examine factors associated with risk of death. Sex, age, residential location, socioeconomic status, primary site and year of diagnosis (grouped) were included in the model. In Cox proportional hazards regression, the measure of effect is the hazard rate (HR) (risk of death in this study) given the patient has survived up to specified time. In Cox regression the risk of the event is constant over time. The model evaluates the effect of the included covariates on survival. [20]

2.5. Ethics

This study was approved by the Metro South Hospital and Health Service Human Research Ethics Committee.

3. Results

From 1986–2015, 4580 cases of NETs were diagnosed accounting for 0.8% of all invasive cancers in Queensland. Table 1 provides a description of the cohort over time. Overall, 46.0% occurred in males, median age was 57 years (range 6–95 years) and 1.0% of patients identified as Aboriginal or Torres Strait Islander (Indigenous status). Indigenous representation increased over time due to improvement in the identification and collection of Indigenous status since the late 1990s.

3.1. Trends in incidence and mortality

Fig. 1 shows annual age-standardised (Australian population) incidence and mortality rates (ASR) from 1986 to 2015. Incidence increased from 2.0/100,000 (95%CI 1.4–2.6) in 1986 to 6.3/100,000 (95%CI 5.6–7.0) in 2015. A significant annual percentage (APC) increase of 9.3% (95%CI 2.9–16.2) (p = 0.06) from 1986 to 1999 and +4.6% (95%CI 3.7–5.4) from 1994 to 2015 was observed. Mortality was 0.7/100,000 in 1986 and 0.6/100,000 in 2015. We observed a sharp increase in mortality for the period 1986–1992 (+16.3%, 95%CI = 1.9–32.7), however overall, the numbers were relatively small. No other significant mortality trends were observed over time. The average incidence and mortality rates for the three time periods (1986–1995, 1996–2005 and 2006–2015) standardised to the Australian 2001 and the World population are presented in Table 2.

Table 3
: Average annual age–standardised incidence rates per 100,000 population by sex, age group and period of diagnosis.

	1986 – 1995 ASR (95%CI)	1996 – 2005 ASR (95%CI)	2006 – 2015 ASR (95%CI)	Total
Persons				
< 40	1.0 (0.9–1.2)	1.3 (1.1–1.4)	2.2 (2.0–2.4)	1.6 (1.5–1.7)
40–49	1.8 (1.4–2.2)	4.1 (3.5–4.6)	5.3 (4.7–5.9)	4.0 (3.7–4.3)
50–59	5.1 (4.2–5.9)	6.6 (5.8–7.4)	9.6 (8.8–10.4)	7.6 (7.1–8.1)
60–69	8.1 (7.0–9.3)	9.7 (8.5–10.9)	12.8 (11.7–13.8)	10.7 (10.1–11.4)
70–79	9.1 (7.6–10.7)	10.3 (8.9–11.8)	17.7 (16.0–19.3)	13.1 (12.2–14.0)
80 +	6.3 (4.3–8.3)	7.0 (5.3–8.6)	12.7 (10.8–14.5)	9.5 (8.4–10.6)
Total	2.8 (2.6–3.0)	3.7 (3.5–3.9)	5.6 (5.4–5.8)	4.3 (4.2–4.4)
Males				
< 40	0.8 (0.6–1.0)	(0.8–1.2)	1.6 (1.4–1.8)	1.2 (1.0–1.3)
40–49	1.4 (0.9–1.9)	3.4 (2.7–4.1)	4.8 (4.0–5.6)	3.5 (3.0–3.9)
50–59	5.6 (4.3–6.8)	6.2 (5.1–7.2)	9.2 (8.1–10.3)	7.4 (6.7–8.0)
60–69	8.6 (6.9–10.3)	8.5 (7.0–10.1)	12.8 (11.3–14.3)	10.5 (9.6–11.5)
70–79	11.8 (9.2–14.4)	11.3 (9.1–13.5)	18.0 (15.6–20.5)	14.3 (12.9–15.8)
80 +	7.8 (4.6–11.6)	7.1 (4.4–9.8)	15.6 (12.4–18.8)	11.4 (9.5–13.4)
Total	2.9 (2.6–3.2)	3.4 (3.1–3.6)	5.3 (4.9–5.5)	4.1 (3.9–4.2)
Females				
< 40	1.2 (1.0–1.5)	1.5 (1.3–1.8)	2.8 (2.5–3.1)	1.9 (1.8–2.1)
40–49	2.2 (1.6–2.9)	4.7 (3.9–5.5)	5.8 (5.0–6.7)	4.6 (4.1–5.0)
50–59	4.5 (3.4–5.7)	7.1 (6.0–8.2)	9.9 (8.8–11.1)	7.9 (7.2–8.5)
60–69	7.7 (6.1–9.3)	10.9 (9.2–12.7)	12.7 (11.2–14.3)	10.9 (10.0–11.9)
70–79	7.0 (5.2–8.8)	9.5 (7.6–11.4)	17.3 (15.0–19.6)	12.0 (10.8–13.2)
80 +	5.7 (3.4–8.1)	6.8 (4.7–8.8)	10.8 (8.6–13.0)	8.3 (7.0–9.7)
Total	2.8 (2.5–3.0)	4.0 (3.7–4.3)	6.0 (5.7–6.3)	4.5 (4.3–4.7)

Incidence rates increased markedly with increasing age, being highest in the 60–69 and 70–79 age groups (ASR = 10.7, 95%CI = 10.1–11.4 and ASR = 13.1, 95%CI = 12.2–14.0, respectively). While incidence increased across the three time periods, the increase was greatest when comparing 1996–2005 and 2006–2015 (Table 3).

3.2. Incidence by site

Overall, the most common sites were appendix (24.9%), followed by small intestine (19.5%), lung (19.0%) and rectum (14.6%). ASRs for most sites increased markedly over time (Table 4).

Greatest increases in incidence were observed for rectal, stomach, appendiceal and pancreatic NETs (Table 4). For example, percentage increase in ASRs from 1986/95 to 2006/15 was 176% for appendix, 367% for stomach, 222% for small intestine and 278% for rectal NETs. A 48% decrease in rates for male lung NETs over the same period was observed.

Site distribution of NETs varied according to some socio-demographics. Appendiceal, stomach and lung NETs were more common in females (65%, 62% and 57%, respectively) (Table 5). For males however, NETs of the small intestine and rectum were more common (58% and 54%, respectively). Of appendiceal NETs, 82% occurred in those under 60 years of age.

3.3. Survival

Overall, one-year, two-year and five-year cause-specific survival was 94.5% (95%CI 93.8–95.2), 91.8% (95%CI 91.0–92.6) and 87.5% (95%CI 86.5–88.5), respectively. Relative survival for one, two and five years was 97.6% (95%CI 96.6–98.5), 95.9% (95%CI 94.4–98.1) and 92.7% (95%CI 90.9–94.6), respectively. Five-year survival increased significantly over time from 69.4% (95%CI 66.0–72.8%) in the period 1986–1995 to 87.9% (95%CI 86.1–89.8) from 1996 to 2005, to 92.6% (95%CI 91.5–93.7) from 2006 to 2015 ($p < 0.001$) (Fig. 2).

Fig. 3 shows 25-year cause-specific survival according to primary site. Survival was highest for NETs of the appendix (96.1%) and rectum (94.5%) and lowest for unknown primary (33.2%) and pancreas (47.8%).

Patients with appendiceal, small intestine, rectal and stomach NETs had a significantly lower risk of death compared to those with lung NETs (Table 6). Other factors associated with a higher risk of death included older age ($p < 0.001$) and male compared to female sex ($p < 0.001$). Further, there was a significant trend towards a lower risk of death for patients diagnosed during 1996–2015 compared to 1986–1995 ($p < 0.001$).

4. Discussion

This study analyzed 4580 NET cases diagnosed in Queensland, Australia from 1986 to 2015. Incidence rose from 2.0/100,000 to 6.3/1000,00 over the thirty-year period. One difficulty in comparing epidemiological studies of neuroendocrine neoplasms is the variety of data sources, populations and morphological inclusions/exclusions used. [21] In this study we elected to focus on NETs only, and while many other studies reporting incidence include both NETs and NECs, some have reported separate mortality and survival rates. The rise in incidence we found in our study is broadly in line with others who have reported incidence by tumour grade [6,8,22].

4.1. Potential factors explaining rising incidence of NETs

Several factors may explain the rising incidence in NET diagnoses observed here and elsewhere. These include improvements in, and development of new imaging technologies, increased use of endoscopy and colonoscopy (additional to bowel cancer screening programs), increased awareness in clinical practice, and introduction of 2010 WHO classification for NETs.

Increased use of colonoscopy and endoscopy have been reported across several jurisdictions. [22,23] In Australia, rates of colonoscopy and endoscopy have increased approximately 50% from 1996-05 to 2006-15 [24]. While the introduction of the National Bowel Screening program in 2006 has likely contributed in some part to this increase, participation in the program is relatively low (37%) with about 8% of participants requiring further investigation [25]. Rates of CT scans have also increased some 240% in the period 1993/4 to 2012/13 [26] There has also been advances in, and increased use of localization enhancement techniques including endoscopic ultrasonography and single positron emission tomography (PET) [27,28]. For example, while the availability of Gallium Dotatate PET imaging is very variable worldwide, Australia has relatively good access to this diagnostic tool. While it has been suggested the increased use of such technologies has led in some part to the increased incidence of lower grade and localized NETs, Sackstein et al reported an increase in the incidence of lower grade and higher grade more aggressive tumours over the same period [22]. We did not include grade in our analyses.

In addition to the factors described above, there have also been increased efforts to formalize nomenclature and staging for NETs. In contrast to the 2000 WHO classification, in which morphological differentiation was the first criteria, the 2010 WHO classification of digestive NETs is largely based on the histological grade. [5] The purpose of these changes was to more accurately reflect the well-recognised differences in prognosis of NETs versus NECs and to integrate a proliferation-based grading system with the historical histo-pathological criteria to more precisely represent the malignant potential of these tumors. Prior to the WHO 2010 classification, incidence of NENs had been steadily increasing across several countries [3,4,7,8,10,13], including Australia.

Table 4
: Annual age-standardised site-specific incidence rates (95% confidence limits) per 100,000 for neuroendocrine tumours by sex and period of diagnosis, Queensland, Australia.

Primary site	Period of diagnosis			Total
	1986–1995	1996–2005	2006–2015	
Appendix				
Males	0.37 (0.27–0.46)	0.63 (0.51–0.74)	1.07 (0.94–1.21)	0.74 (0.67–0.82)
Females	0.71 (0.57–0.84)	1.18 (1.02–1.34)	1.91 (1.73–2.09)	1.34 (1.25–1.44)
Persons	0.54 (0.46–0.62)	0.91 (0.81–1.00)	1.49 (1.38–1.60)	1.04 (0.98–1.10)
Small intestine				
Males	0.46 (0.34–0.58)	0.95 (0.80–1.09)	1.37 (1.22–1.53)	1.03 (0.94–1.11)
Females	0.25 (0.17–0.34)	0.60 (0.49–0.72)	0.97 (0.84–1.09)	0.67 (0.61–0.74)
Persons	0.36 (0.29–0.44)	0.77 (0.67–0.86)	1.16 (1.06–1.26)	0.84 (0.79–0.90)
Colon				
Males	0.23 (0.14–0.32)	0.21 (0.14–0.27)	0.32 (0.24–0.39)	0.26 (0.22–0.31)
Females	0.20 (0.13–0.28)	0.25 (0.18–0.33)	0.28 (0.22–0.35)	0.25 (0.21–0.30)
Persons	0.21 (0.16–0.27)	0.23 (0.18–0.28)	0.30 (0.25–0.35)	0.26 (0.23–0.29)
Rectum				
Males	0.28 (0.18–0.37)	0.67 (0.55–0.79)	0.92 (0.80–1.05)	0.69 (0.61–0.76)
Females	0.20 (0.12–0.27)	0.56 (0.45–0.67)	0.82 (0.70–0.94)	0.58 (0.52–0.65)
Persons	0.23 (0.17–0.29)	0.61 (0.53–0.69)	0.87 (0.78–0.96)	0.63 (0.58–0.68)
Stomach				
Males	0.06 (0.01–0.11)	0.09 (0.04–0.14)	0.25 (0.18–0.31)	0.15 (0.12–0.19)
Females	0.06 (0.02–0.11)	0.24 (0.17–0.31)	0.31 (0.23–0.38)	0.22 (0.18–0.26)
Persons	0.06 (0.03–0.09)	0.16 (0.12–0.21)	0.28 (0.23–0.32)	0.19 (0.16–0.21)
Pancreas				
Males	0.13 (0.06–0.19)	0.13 (0.07–0.18)	0.41 (0.33–0.49)	0.25 (0.20–0.29)
Females	0.14 (0.08–0.21)	0.17 (0.11–0.23)	0.32 (0.25–0.39)	0.23 (0.19–0.27)
Persons	0.13 (0.08–0.17)	0.15 (0.11–0.19)	0.36 (0.31–0.42)	0.23 (0.21–0.26)
Lung				
Males	1.22 (1.03–1.42)	0.48 (0.37–0.58)	0.63 (0.52–0.73)	0.71 (0.64–0.79)
Females	0.91 (0.74–1.07)	0.77 (0.64–0.90)	1.04 (0.91–1.17)	0.91 (0.83–0.99)
Persons	1.05 (0.92–1.17)	0.62 (0.54–0.71)	0.84 (0.75–0.92)	0.81 (0.75–0.87)
Other known sites				
Males	0.05 (0.01–0.09)	0.09 (0.04–0.13)	0.08 (0.05–0.12)	0.08 (0.05–0.10)
Females	0.12 (0.06–0.18)	0.11 (0.06–0.16)	0.18 (0.13–0.24)	0.15 (0.11–0.18)
Persons	0.09 (0.05–0.12)	0.10 (0.07–0.13)	0.13 (0.10–0.17)	0.11 (0.09–0.13)
Unknown primary site				
Males	0.13 (0.06–0.19)	0.13 (0.08–0.19)	0.19 (0.13–0.25)	0.16 (0.12–0.19)
Females	0.17 (0.10–0.24)	0.15 (0.09–0.20)	0.16 (0.11–0.21)	0.16 (0.12–0.19)
Persons	0.15 (0.10–0.20)	0.14 (0.10–0.18)	0.17 (0.13–0.21)	0.16 (0.13–0.18)

Table 5
: Site distribution according to sociodemographic characteristics for 4580 NETS diagnosed from 1986 to 2015.

	Appendix N = 1142 (%)	Small Intestine N = 892 (%)	Colon N = 272 (%)	Rectum N = 670 (%)	Stomach N = 198 (%)	Pancreas N = 250 (%)	Lung N = 872 (%)	Other known N = 119 (%)	Unknown primary N = 165 (%)	P-value
Sex										
Male (n = 2107)	35.0%	58.4%	48.5%	53.6%	38.4%	50.8%	42.9%	33.6%	47.3%	< 0.001
Female (n = 2473)	65.0%	41.6%	51.5%	46.4%	61.6%	49.2%	57.1%	66.4%	52.7%	
Age group										
< 40 (n = 977)	58.9%	3.9%	6.3%	12.8%	6.6%	11.6%	11.7%	13.4%	3.6%	< 0.001
40-49 (n = 615)	13.7%	10.5%	11.0%	21.8%	14.7%	11.2%	11.2%	16.0%	9.1%	
50-59 (n = 949)	9.9%	23.7%	27.6%	30.3%	17.7%	24.0%	23.6%	17.7%	15.1%	
60-69 (n = 989)	8.8%	28.4%	23.9%	19.2%	31.3%	28.0%	27.3%	21.0%	28.5%	
70+ (n = 1050)	8.8%	33.5%	31.3%	15.8%	29.8%	25.2%	26.2%	31.9%	31.9%	
Socioeconomic status										
Affluent (n = 753)	15.6%	16.7%	12.9%	16.6%	22.7%	18.4%	17.8%	19.3%	6.7%	0.004
Middle (n = 2913)	64.1%	64.7%	63.2%	66.1%	59.1%	64.0%	60.7%	63.9%	65.4%	
Disadvantaged (n = 912)	20.3%	18.6%	23.9%	17.3%	18.2%	17.6%	21.6%	16.8%	27.9%	
Residence										
Urban (n = 3150)	68.2%	70.6%	61.4%	70.2%	71.7%	70.0%	69.8%	70.6%	57.0%	0.006
Rural (n = 1430)	31.8%	29.4%	38.6%	29.4%	28.3%	30.0%	30.2%	29.4 %	43.0%	
Diagnosis year										
1986-1995	14.4%	10.1%	19.9%	9.0%	7.6%	12.4%	31.2%	19.3%	23.0%	< 0.001
1996-2005	28.3%	29.5%	29.4%	31.9%	28.3%	20.8%	24.9%	28.6%	28.5%	
2006-2015	57.3%	60.4%	60.4%	59.1%	64.1%	66.8%	43.9%	52.1%	48.5%	

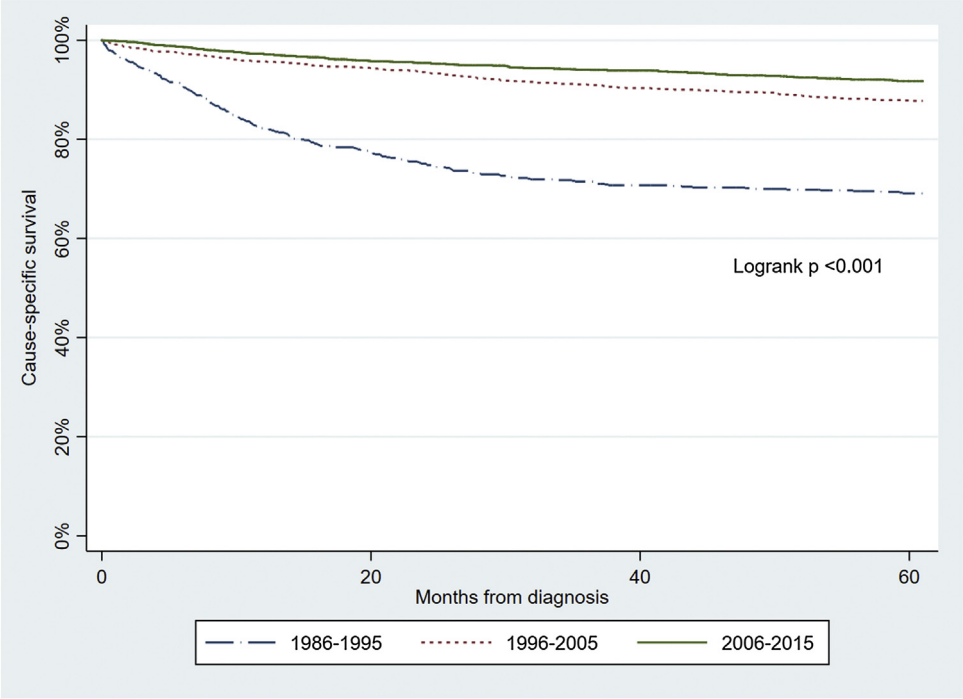

Fig. 2. Five-year cause-specific survival over three decades.

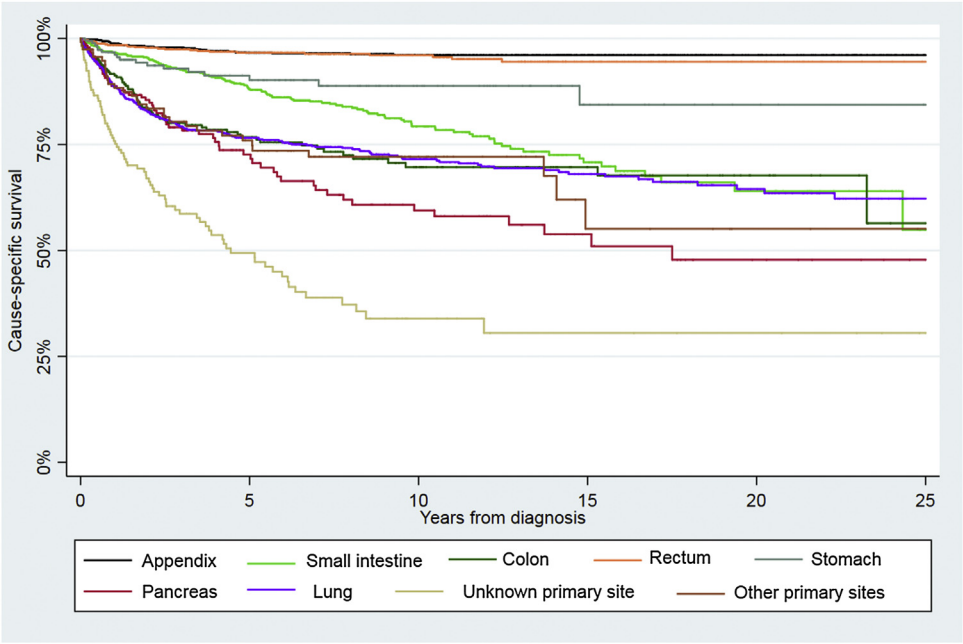

Fig. 3. Cause-specific 25-year survival rates according to primary site.

In the 2010 WHO classification some morphologies with "uncertain tumour behaviour status" were changed to malignant tumour status. This resulted in appendiceal carcinoid tumours previously recorded as uncertain tumour behavior, being classified as malignant. In Queensland, the QCR (the primary source of data for this study), has received all uncertain behaviour cancer notifications since its establishment in 1982. Thus, unlike other registries we were able to re-code all uncertain behaviour tumours to malignant for notifications prior to 2010, thus providing us with a complete dataset of NETs, unlike other Australian studies. [11]

4.2. Site-specific incidence

Our study found appendix, small intestine and lung were the most common NET sites. Several other studies have reported most common sites are lung, small intestine and large bowel. [5,8,11,22] While for the most part these studies have included NECs, a Norwegian study found appendix and small intestine were the most common sites for grade 1 and grade 2 tumours [10]. Further, the high incidence of appendiceal NETs we observed is likely a result of the inclusion of tumours of uncertain behaviour, whereas most other studies have not been able to include these tumours. Some studies have reported a higher incidence of large bowel NETs compared to ours, however those studies included

Table 6
: Cox proportional hazards model of risk of death.

Covariate	HR[a] (95%CI)	P value
Sex		
Female	Ref	< 0.001
Male	1.41 (1.20–1.65)	
Age at diagnosis		
< 40	Ref	< 0.001
40–49	3.51 (2.00–6.14)	
50–59	6.78 (4.07–11.29)	
60–69	9.90 (5.99–16.37)	
70+	14.38 (6.70–23.77)	
Period of diagnosis		
1986–1995	Ref	< 0.001
1996–2005	0.48 (0.39–0.58)	
2006–2015	0.25 (0.21–0.30)	
Socioeconomic status		
Affluent	Ref	0.45
Middle	1.15 (0.73–2.49)	
Disadvantaged	1.14 (0.86–1.50)	
Residence at diagnosis		
Urban	Ref	0.87
Rural	0.99 (0.83–1.18)	
Primary site		
Lung	Ref	< 0.001
Appendix	0.27 (0.19–0.40)	
Small intestine	0.58 (0.47–0.73)	
Colon	0.91 (0.69–1.20)	
Rectum	0.18 (0.11–0.27)	
Stomach	0.44 (0.27–0.82)	
Pancreas	1.62 (1.23–2.15)	
Other known sites	1.25 (0.86–1.83)	
Unknown primary	2.44 (1.88–3.16)	

[a] Hazard rate.

either appendiceal or rectal NETs (or both) in calculating large bowel incidence, while we have reported rates separately [5,11]. The only primary site where we observed decreasing rates was for male lung NETs. While these decreasing rates may reflect reductions in smoking, smoking has also been shown to be a risk factor for NETs of the pancreas and small intestine, sites where incidence increased [27]. In the most recent time period (2006-15), the most common site was small intestine in males and appendix in females. The reasons for these differences are not clear but it has been suggested that the higher rates of appendiceal NETs may be due to a higher rate of surgical interventions in females and potentially a higher rate of incidentally detected tumours [29].

4.3. Survival

The low mortality rates despite increased incidence we, and others have found supports the hypothesis of increased detection of early stage lesions. We observed significant improvements in 5-year survival over time, from 69% in 1986–1995 to 92% in the period 2005-2015. In multivariate analysis we observed a 75% lower risk of death at five years for patients diagnosed in the most recent period (2006–2015) compared to 1986–1995, with the magnitude of risk similar when we examined all-cause survival. When we compared the time periods 2006–2015 and 1996–2005, the reduction in risk of death was similar to a large SEER-based study of cases diagnosed between 1995–2014. [22] We additionally found long-term (25-year) survival was lowest for patients with pancreatic and unknown primary NETs.

Several factors were associated with significantly poorer survival including, male sex, older age and pancreatic or unknown primary NET site. Again, these findings are similar to those observed elsewhere, where survival for NETs and NECs have been reported separately. [8,22,30] Interestingly, in our study survival was similar for urban and rural patients. A Canadian study of over 6000 NET patients, (13% were from a rural location), found 10-year overall survival was worse for rural versus urban patients [31]. Difficulties in accessing specialized services, delays in diagnosis and lack of awareness of symptoms were suggested as potential reasons for the poorer survival. In Queensland, more uniform access to diagnostic services as well as the establishment of regional cancer centres (providing cancer services to regional and rural patients), may explain in some part why we did not find a survival disadvantage for rural patients

Factors contributing to the increase in survival likely include early detection along with the development of new treatments and therapies. While we were unable to include stage in our study, a Canadian study found the proportion of patients presenting with metastatic disease decreased by about 55% from 1995 to 2009. [5] Management advances have included improvement in surgical techniques, endoscopic management of Gastrointestinal mucosal NETs, effective systemic therapies for specific subcategories of NETs (chemotherapy, sunitinib, everolimus), and Peptide Receptor Radioisotope therapy [32]. One important advance has been the development of somatostatin analogues. Sandostatin is a somatostatin analogue and its widespread use has been linked with dramatic increase in survival rates as reported by Yao et al. [30].

4.4. Limitations

While this was a population-based study including 30 consecutive years of data, there are some limitations. We were unable to include other prognostic indictors such as stage. These variables are not routinely collected in Australia. Further, we did not include data on surgical approach and the use of other treatment modalities. While these are limitations, they only relate to the survival analysis and not the analysis of incidence where our findings are in keeping with others.

5. Conclusions

This study, including 30 years of data, found significantly increasing rates of NETs in our population and confirms results from other countries. Survival had improved significantly over time, likely a result of early detection, improvements in diagnostic and surgical procedures, and the development of new therapies.

Author contributions

The study was conceived by DW. JM extracted the data from the QCR. DW, ND, PY designed the statistical approach and conducted the analyses. DW, MT, JM, PY drafted the manuscript, which was reviewed and modified with input from all authors. All authors saw and approved the final version of the paper and JM had the final responsibility to submit the paper.

Declaration of Competing Interest

The authors have no conflicts of interest to declare

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