

Systematic Review: Incidence of Pheochromocytoma and Paraganglioma Over 70 Years

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Abstract

Context: Pheochromocytomas and paragangliomas (PPGLs) are known to be rare. However, there is scant literature reporting their epidemiology, particularly whether the diagnosis of PPGL has increased with advances in medical imaging and biochemical and genetic testing.

Objective: The primary objective of this systematic review was to determine the annual incidence of PPGLs and change over time.

Design: A systematic review was performed. Medline, Embase, PubMed, and Web of Science Core Collection databases were searched to identify studies reporting PPGL incidence. Studies were eligible for inclusion from the database's inception until August 30, 2021.

Results: A total of 6109 manuscripts were identified; 2282 duplicates were excluded, and a further 3815 papers were excluded after abstract and/or full text review. Twelve studies were included in the final review. The incidence of PPGL ranged from 0.04 to 0.95 cases per 100 000 per year. Incidence increased over time, from approximately 0.2/100,000 individuals in studies performed before 2000, to approximately 0.6/100,000 in studies undertaken after 2010. The mode of diagnosis changed over the same time period, with more patients diagnosed from incidental imaging findings, and fewer at autopsy or from symptoms.

Conclusion: The annual incidence of PPGL has increased over time. Much of this increase is likely from incidental identification of tumors on imaging. However, the epidemiology of PPGL remains understudied, in particular, in associations with altitude, ethnicity, and genetics. To improve early detection and management guidelines, these gaps should be addressed.

Key Words: pheochromocytoma, incidence, paraganglioma, epidemiology

Abbreviations: HNPGL, head and neck paraganglioma; PCC, pheochromocytoma; PGL, paraganglioma; PPGL, pheochromocytomas and paragangliomas

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors originating from the chromaffin cells of the autonomic nervous system [1]. Pheochromocytomas (PCCs) originate from the adrenal medulla, whereas paragangliomas (PGLs) arise from extra-adrenal paraganglia [2]. Paragangliomas are divided into 2 subtypes: sympathetic paragangliomas, occurring along the sympathetic trunk, and head and neck paragangliomas (HNPGL); the latter named because the majority of parasympathetic paragangliomas arise in the head and neck region [2].

Detailed epidemiological studies on PPGLs are scarce, with most conducted before the era of modern imaging and improvements in biochemical analysis. One of the oldest and most frequently cited studies, by Beard et al of patients from Rochester, Minnesota, with PPGL identified from 1950 to 1979, reported an annual PPGL incidence of 0.95/100,000 [3]. In comparison, incidence rates reported in other studies from a similar time period were far lower, between 0.04 and 0.21/100,000 [4–7], suggesting that either Rochester had an unusually high incidence of PPGL or that PPGLs may be underdiagnosed in other centers.

Over the past 5 decades, there have been significant advances in clinical medicine. For example, there is now widespread availability of high-resolution anatomical imaging and a variety of functional imaging options including longstanding

techniques such as I-123 metaiodobenzylguanidine scintigraphy, and more recent positron emission tomography scanning options including 18F-fluoro-2 deoxy-D-glucose, 18-F-fluorodihydroxyphenylalanine, and gallium-68 Dotatate [8, 9]. The sensitivity of biochemical detection has also improved with the development of assays for the detection of catecholamine metabolites [10]. With these advances, improved detection of PPGL is expected, and therefore higher incidence rates compared with those reported in the past century [11].

Particularly over the past 2 decades there have been marked advances in our knowledge of the genetics of PPGL [12, 13]. An increased number of germline susceptibility genes have been identified, genetic testing is more widely available, and there is an increased awareness of the importance of screening those with a known PPGL susceptibility gene. Nearly one-half of patients with PPGL harbor a germline mutation in 1 of the PPGL susceptibility genes [13, 14]. Patients with a genetic predisposition often present younger and, particularly if identified from surveillance because of a known familial germline mutation, are more likely to be asymptomatic compared with those with sporadic tumors [9]. However, geographical differences in availability and uptake of screening and the presence of founder mutations in certain regions, such as the “Black Forest” VHL mutation [15], the SDHx Dutch founder

mutations [16], and the Trentino SDHD mutation [17], may result in different epidemiological patterns.

A clear understanding of the epidemiology of PPGLs is needed, especially with the recent advances in screening and investigation methods. Additionally, studying the epidemiology of the disease can help determine whether changes to the current guidelines are needed. The primary objective of this systematic review was to determine the annual incidence of PPGLs and determine any change in incidence over time.

Methods

This systematic review was performed following the PRISMA guideline [18]. Medline, Embase, PubMed, and Web of Science Core Collection databases were searched to identify manuscripts and conference abstracts using the following terms: pheochromocytoma, phaeochromocytoma, chromaffin cell, adrenal medulla, paraganglioma, chemodectoma, carotid body tumor, carotid body tumour, glomus cell tumor, glomus cell tumour, epidemiology, and incidence (see Table 1 for details). There was no specific timeframe set; studies were eligible for inclusion from the database's inception until the August 30, 2021. Descriptive, observational studies published in English reporting original data on the annual incidence of PPGL within a defined population were eligible for inclusion. Studies that did not report the incidence rates of PPGL were excluded. Studies were excluded if they only reported malignant/metastatic PPGLs or only patients identified at autopsy. Single-center surgical series without a defined catchment area were excluded.

Three authors (A.A., V.B., and M.S.E.) independently assessed the eligibility of all papers at each step. Following independent review, consensus was reached through discussion. Titles and abstracts were screened first followed by assessment of the complete text, and relevant articles included.

References of included articles were searched for relevant papers, and those identified were evaluated for eligibility based on the same criteria. A.A. extracted data, using Microsoft Excel for Mac (version 16.56) on the following categories: study design, timeline, data source, country, postmortem cases, primary tumor, disease stage, number of cases, demographics of study participants (age and sex), tumor size, and annual incidence rates. M.S.E. and V.B. reviewed the accuracy of the extracted data. To assess the risk of bias in the included studies, we used a tool developed to appraise prevalence and incidence studies [19].

Results

The literature review yielded 6109 titles; 2282 duplicates were removed. Upon systematic screening of the remaining titles, abstracts, and full texts, an additional 3815 papers were excluded (Fig. 1). The full text of 1 article was unable to be located despite extensive efforts, including contacting the study authors. The remaining 12 studies were included in this review [3-7, 11, 20-25].

The data collection period ranged from 1949 to 2019. Eight studies collected information from 1 or more registry-based systems [3, 5, 6, 11, 21-24] and 1 study did not state how patients were identified [20]. In 5 of the 8 registry-based systems, patients were identified from national registries. One group used 3 registries (Danish National Patient Registry, Danish National Pathology Registry, and Danish National Registry of Causes of Death) [21], whereas the remaining studies used a single registry [5, 6, 11, 24]. Of these, 1 was a national cancer registry [5], 1 was a pathology registry [11], 1 a national registry of hospital patients [6], and 1 a national insurance registry [24]. Of the registry-based studies, 2 sent additional questionnaires to departments to obtain additional cases and information and confirm the diagnosis [5, 6]. The remaining 3

Table 1. Search terms used for systematic review

Database	Search term	Filters	Date of search	Results
Web of Science	((ALL = (Pheochromocytoma OR phaeochromocytoma OR chromaffin cell OR adrenal medulla)) OR ((ALL = (paraganglioma OR chemodectoma OR carotid body tumour OR carotid body tumor OR glomus cell tumour OR glomus cell tumor)) AND ALL = (epidemiology OR incidence OR prevalence))	English, human only	August 30, 2021	223
PubMed	((Pheochromocytoma OR phaeochromocytoma OR adrenal medulla* OR chromaffin cell) OR (Paraganglioma OR chemodectoma OR Carotid body tumo* OR glomus cell tumo*)) AND (Epidemiology OR incidence OR prevalence)	Human, English	August 30, 2021	1831
Ovid (Medline and Embase)	1. (pheochromocytoma or phaeochromocytoma or Adrenal medulla* or chromaffin cell).mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui,sy] 2. (paraganglioma or chemodectoma or Glomus cell tumour or Glomus cell tumor or carotid body tumo*).mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui,sy] 3. (Epidemiology or incidence or prevalence).mp. [mp = ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui,sy] 4. 1 or 2 5. 3 and 4 6. Remove duplicates from 5 7. Limit 6 to English language 8. Limit 7 to human		August 30, 2021	76 710 22 996 5 955 315 92 794 4770 3625 3202 2794

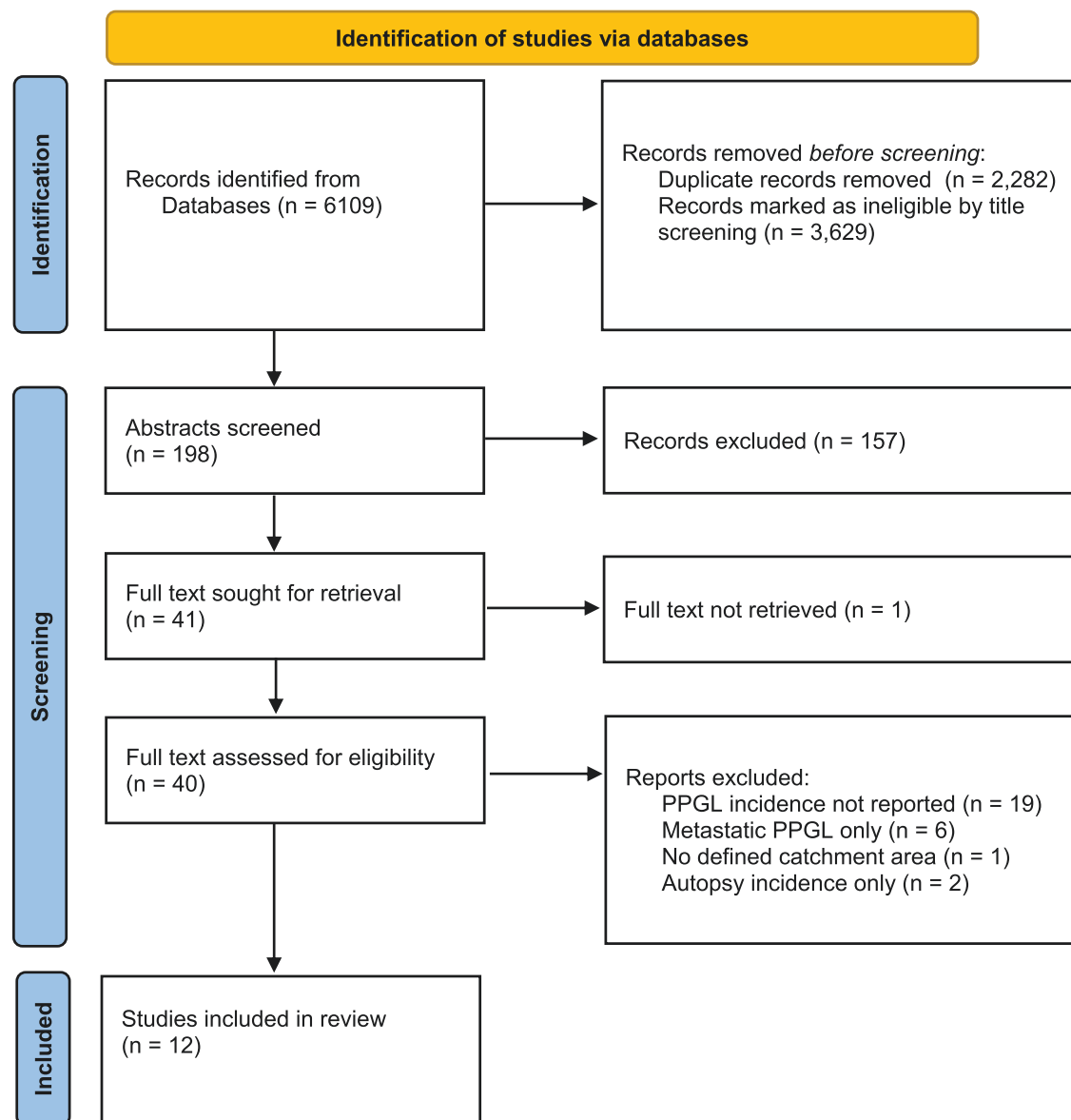


Figure 1. PRISMA flow chart.

registry-based studies were single center and used either hospital medical records system [3, 22] or a mixed approach of surgical pathology and surgical adrenalectomy lists and diagnostic codes [23]. Two studies were questionnaire-based [4, 7]. De Graeff and Horak sent a questionnaire to 28 pathology institutes, of which 23 responded [4]. Similarly, Hartley and Perry-Keene sent letters to Endocrine Society colleagues and pathology centers throughout Queensland, Australia [7]. Leung et al collected information using a combination of administrative health data, chart reviews, diagnostic imaging, anatomical pathology, and autopsy records [25]. Four studies were conducted in single centers (Rochester, Minnesota, USA [3]; South Galicia, Spain [22]; Newfoundland, Canada [23]; and Northern Ireland [20]). Overall, using the bias assessment tool, studies were deemed likely to have a low risk of bias with the exception being that of Kim et al [24], who obtained anonymous data; therefore, accuracy of the data was unable to be confirmed.

Included studies were divided into 2 groups based on the last year of data collection (Table 2). Six studies completed data collection between 1959 and 1992 [3-7, 22], whereas a further 6 studies completed data collection between 2010 and 2019 [11, 20, 21, 23-25]. Annual incidence rates (per 100,000 individuals per annum) were available for 9 studies [4, 5, 7, 11, 20-22, 24, 25]. For the other 3 studies, 5-year data were available for 1 [6] and 10-year data periods for 2 studies [3, 23]. For these 3 studies, a mean incidence was calculated for the midpoint of the study period. PPGL incidence rates over time for the 12 studies are shown in Fig. 2.

From the 12 studies, a total of 4060 cases were included. Of these cases, 2047 (50.4%) were female. Age was variably reported with the mean or median age ranging from 43 to 56.2 years. Berends et al reported a linear increase in age at presentation with PCC from approximately age 45 years in 1995 to almost age 55 years by 2015 [11]. Ebbehøj et al reported a younger median age for those diagnosed because of

Table 2. Characteristics of 12 included studies reporting the incidence of pheochromocytoma and paraganglioma

First author	Study design	Period of data collection	Country (place)	Number of cases			Demographics of study participants			PPGL incidence per 100,000 per annum			
				PCC	PGL total	HNPGL	Total	Male (n)	Female (n)		Age range	Median age	Mean age
De Graeff [4]	Retrospective (nationwide)	1949-1959	Netherlands	35	5	0	44	20	24	8-74	44	42.48	0.042
Ebbelohj ^a [21]	Retrospective (nationwide)	1977-2006	Denmark	NS	NS	NS	339 ^b	153	186	<25-75+	56.2		0.14 ^c
Beard [3]	Retrospective (single center)	1950-1979	Rochester, Minnesota, USA	NS	NS	NS	13	7	6	21-77	54	53.1	0.95
Stenstrom [5]	Retrospective (nationwide)	1958-1981	Sweden	344	95	NS ^d	439	184	255	20-90+		55.8	0.21
Andersen [6]	Retrospective (nationwide)	1977-1981	Denmark	45	2	NS	47	27	20	15-81	45 F 50 M		0.19
Hartley [7]	Retrospective (multicenter)	1970-1983	Queensland, Australia	41	5	0	46	25	21	9-80+		44.95	0.155
Fernandez-Calvet [22]	Prospective (single center)	1980-1992	South Galicia, Spain	13	1	NS	14	6	8	21-65		43	0.206
Berends ^e [11]	Retrospective (nationwide)	1995-1999	Netherlands	1210	274	0	1493 ^f	821	672	0-88		51	0.37 ^c
Holland [23]	Retrospective single center	2001-2010	Canada	23	1	NS	24	13	11	13-76		55.6	0.47
Kim [24]	Retrospective (nationwide)	2003-2014	Korea	NS	NS	NS	1048	517	528	0-80		47.6	0.18 ^c
Berends ^e [11]	Retrospective (nationwide)	2011-2015	Netherlands	1210	274	0	1493 ^f	821	672	0-88		51	0.57 ^c
Ebbelohj ^a [21]	Retrospective (nationwide)	2007-2015	Denmark	NS	NS	NS	228	99	129	<25-75+	56.2		0.66 ^c
Cvasciuc [20]	Retrospective (single center)	2010-2019	Northern Ireland	73	13	NS	86	41	45	28-83		54.5	0.53
Leung [25]	Retrospective (multicentre)	2012-2019	Alberta, Canada	118	121	93	239	97	142	0-80+		55	0.66

Abbreviations: F, female; M, male; NS, not stated; PCC, pheochromocytoma; PGL, paraganglioma; PPGL, pheochromocytoma and paraganglioma.

^aSame study but incidence reported for 1977 and 2015.^bOnly 192 of 367 had clinical data available, so separation into PCC and PGL (including head and neck PGL) not available.^cAge-specific incidence rate.^dBreakdown by site: 61 abdominal, 22 peripheral nerve, 3 intrathoracic, 3 urinary bladder, and 6 miscellaneous.^eSame study but incidence reported over 2 time periods.^f9 patients had both.^gMean age for familial cases.

genetic causes at 34.3 years compared with 63 years for those diagnosed from imaging for cancer [21], with similar findings reported by other groups when familial cases were compared to either symptomatic apparently sporadic or incidentally identified tumors [20, 23].

Of the studies that clearly detailed the numbers of PCC and PGL, the majority of tumors arose in the adrenals (2105 vs 553 extra-adrenal). In most studies, the incidence of PCCs were higher than that of PGLs. For example, in 8 studies, PCCs made up 78.4% to 95.8% of the total PPGLs [4-7, 11, 20, 22, 23]. In only 1 study was the proportion of PGLs higher than that of PCCs at 50.6% [25]. For most studies, the number of HNPGLs was not clearly documented (Table 2).

Patients diagnosed at autopsy were included in 9 of the 12 studies [3-7, 11, 21, 22, 25]. Autopsy rates were highly variable, ranging from > 50% of deaths in the Rochester

study [3] to less than 10% of deaths in a recent Canadian study [25]. Table 3 reports the proportion of PPGL diagnosed at autopsy (Table 3), with the proportion of cases diagnosed by autopsy ranging from 42% in earlier studies [5] to < 1% in more recent times [21, 25]. For all studies apart from that of Ebbehof et al [21], it was unclear whether the mode of discovery for any of the PPGLs was due to familial screening. Because of the time periods included, genetic testing was variably reported, but some studies in the pregenetic testing era had high rates of apparent clinically familial disease [22]. Ebbehof et al reported that almost one-half of all PPGL patients (46.8%) had not undergone genetic testing, although this improved over the course of the period studied [21]. Of the 86 patients identified by Cvasciuc et al, 46 underwent genetic testing, with 52% of these being identified as having an underlying germline mutation [20].

Tumor size was only clearly documented in 4 studies [11, 21, 23, 25]. Berends et al reported a median PCC diameter of 4 cm and demonstrated a linear decrease of median PCC diameter between 1995 and 2015 [11]. Leung et al reported a median diameter of PPGLs as 3.2 cm [25]. Holland et al reported a mean tumor size of 4.5 cm for sporadic tumors compared with 3.2 cm for familial tumors with a wide overlap between both groups [23]. Ebbehof et al reported a median tumor size of 4.5 cm for the cohort with clinical data available and an increased proportion of patients over time being diagnosed with smaller tumors (ie, <4 cm) [21].

Six of the 12 studies [4, 6, 7, 22-24] reported the number of metastatic PPGL cases with the proportion of patients with metastatic disease ranging from 4.2% (Holland et al) to 17.7% (Kim et al) of total cases.

Three additional studies had a robust design and reported useful information on the incidence of PPGLs but did not meet the inclusion criteria (Table 4). Dua et al reported an

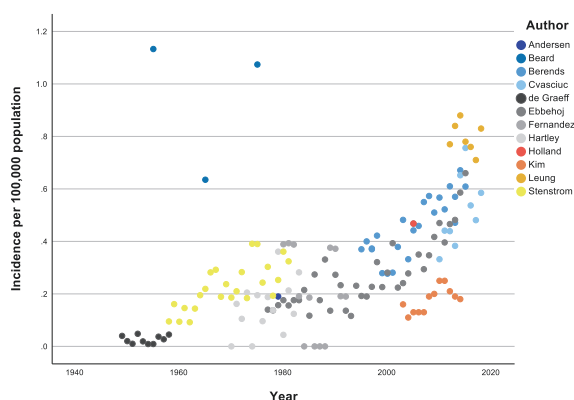


Figure 2. Annual incidence of PPGL 1949 to 2018.

Table 3. Studies including autopsy-identified pheochromocytoma and paraganglioma

First author	Period of data collection	Total cases	Autopsy-diagnosed cases N (% of total cases)	Symptomatic N (% of total cases)	Incidental N (% of total cases)	Familial screening
De Graeff [4]	1949-1959	44	16 (36.4%)	27 (61%)	1 (2.3%) ^a	-. ^b
Beard [3]	1950-1979	13	5 (38.5%)	2 (15%)	4 (31%) ^a	2 ^c
Stenstrom [5]	1958-1981	439	184 (41.9%)	NS	NS	NS
Andersen [6]	1977-1981	47	8 (17.0%)	36 (77%)	3 (6.4%) ^a	5 ^c
Hartley [7]	1970-1983	46	7 (15.2%)	NS	NS	NS
Ebbehof [21] ^h	1977-1986	42*	10 (24.4%)	21 (50%) ^d	5 (11.9%)	3
Fernandez-Calvet [22]	1980-1992	14	1 (7.1%)	11 (78.6%)	2 (14%) ^a	5 ^c
Ebbehof [21] ^h	1987-1996	27*	7 (25.9%)	13 (48.1%) ^e	2 (7.4%)	1
	1997-2006	44*	7 (15.9%)	20 (45.5%)	12 (27.3%) ^e	2
Berends [11]	1995-2015	1493	72 (4.8%)	NS	NS	NS
Ebbehof [21] ^h	2007-2015	79 ^f	0 (0%)	19 (24.1%)	44 (55.7%) ^g	10
Leung [25]	2012-2019	239	1 (0.4%)	NS	NS	NS

Abbreviation: NS, not stated.

^aIncidental diagnosis during surgery for another reason.

^bNo apparent family screening but 7 cases appear to be likely familial including 3 with neurofibromatosis.

^cFamilial cases reported but method of diagnosis unclear.

^dIncluded cases with paroxysmal symptoms and hypertension, an additional 2 patients were reported to have "other" as mode of discovery.

^eIncluded cases with paroxysmal symptoms and hypertension, an additional 3 patients were reported to have "other" as mode of discovery.

^fOnly 192 of the entire 567 case cohort had clinical information available (42/87 for 1977-1986, 27/104 for 1987-1996, 44/148 for 1997-2006, and 79/228 for 2007-2015 time periods, respectively).

^gIncluded cases with paroxysmal symptoms and hypertension, an additional 6 patients were reported to have "other" as mode of discovery.

^hSame study but different timepoints.

Table 4. Well-conducted studies that did not meet the inclusion criteria

First author	Reason for exclusion	Study design	Period of data collection	Country (Place)	Number of cases			Demographics of study participants				PPGL incidence per 100,000/annum	PGL incidence per 100,000/annum	PCC incidence per 100,000/annum
					PCC	PGL	Total	M (n)	F (n)	Age range	Median age			
Dua [26]	Carotid body PGLs only	Retrospective (nationwide)	1998-2011	US	684	684	684	271	413			53.8	1998 0.07 2011 0.1	-
Ebbehoj [27]	PCCs only	Retrospective (multicentre)	1995-2017	Olmsted County, MN, USA	14	-	14	5	9	26-70	46		-	0.4
Takayanagi [28]	Survey	Nationwide	1997	Japan	1030 ^a	NR	1030 ^a						-	-

Abbreviations: M, male; F, female; PCC, pheochromocytoma; PGL, paraganglioma; PPGL, pheochromocytoma and paraganglioma.

^aEstimated number.

increase of 37% in PGL incidence from 1998-2000 to 2009-2011 [26]. This study was excluded because only carotid body PGLs were included. Ebbehoj et al comprehensively reported the incidence of adrenal tumors, including PCC, in Olmsted county, Minnesota; however, it was excluded because PGLs were not included [27]. Of note, this study was performed in the same region as that of Beard et al, but showed a lower incidence (0.4/100,000 compared with 0.95/100,000, respectively) [3, 27]. Takayanagi et al reported the epidemiology of adrenal disorders in Japan but undertook a survey-based method with the results extrapolated to estimate the total number of patients with PCC but did not give an estimate of the incidence [28].

Discussion

The purpose of this systematic review was to compare studies of PPGL incidence and identify trends over time. The main finding from this systematic review is the increase in PPGL incidence over time, with the mean incidence increasing from 0.19/100,000 per annum in studies after excluding 1 outlier [3] performed before 2000 [4-6] to 0.58/100,000 per annum after excluding 1 outlier [24] in the studies after 2010 [11, 20, 21, 23, 25]. Outlying studies are discussed in the following section.

There are several potential reasons for this increase. First, there has been a substantial rise in adrenal incidentaloma detection over the years because of increasing utilization of noninvasive imaging modalities in clinical practice. For example, in the United States, computed tomography scans increased from approximately 14.4 scans per 1000 population in 1980-1982 to approximately 225 per 1000 population in 2006 [29]. Similarly, magnetic resonance imaging scanning in the United States increased from 34.3 scans per 1000 population in 1995 to 128 per 1000 population in 2019 [30]. As such, incidental lesions (adrenal or extra-adrenal) may contribute to the increase in incidence of PPGL, despite incidentally identified adrenal lesions often are not assessed according to recommended guidelines [31]. This is supported by the finding of Ebbehoj et al, in which more than one-half of the PPGLs between 2007 and 2015 were identified from imaging (adrenal incidentalomas or cancer imaging) with only 15.2% being diagnosed from paroxysmal symptoms and none at autopsy [21]. In comparison, those diagnosed before 1986 were diagnosed because of symptoms in approximately 50% of cases (including as a consequence of investigating possible secondary hypertension) and one-quarter of patients were diagnosed at autopsy [21]. Also of note, Ebbehoj et al reported that the standardized incidence rate of adrenal tumors (all subtypes combined) in Olmsted County, Minnesota, USA, increased from 4.4/100,000 person-years in 1995 to 47.8/100,000 person-years in 2017, predominantly from the increase in incidentally detected adrenal lesions [27]. Although the rise in PPGL incidence over time shown here is less marked than the 10-fold increase in adrenal tumour demonstrated by Ebbehoj et al [27], this is likely influenced by the lower autopsy rates in more recent times offsetting the increase in PPGL identified by imaging. This is important because, historically, many patients with PPGL were only diagnosed postmortem. For example, Stenstrom et al reported that 42% of patients were diagnosed at autopsy [5]. The very high rates of autopsy (>50%) also likely contributes to the very

high PPGL incidence of 0.95/100,000 in the study published in 1983 by Beard et al, where 5/11 cases were diagnosed at autopsy [3]. There has been a marked reduction in autopsy rates from > 70% in some centers before 1970 to < 1% in some centers in 2013 [32]. The reasons for this are likely to be multifactorial and complex including social, cultural, legal, and financial.

In addition to advances in medical imaging, there have also been improvements in biochemical testing. Plasma-free metanephrine measurements are now widely available. They have a very high sensitivity for the diagnosis of functioning PPGL [33], making biochemical diagnosis of these tumors less challenging than previously because of the stability of these metabolites compared with plasma catecholamines. A further potential explanation for the increase in diagnosis of PPGL is the advances in knowledge of the high rates of underlying germline mutations in patients with PPGL, an increase of genetic testing, and surveillance of at-risk family members, particularly over the past decade [34]. However, it has been observed that screening and surveillance guidelines have not been widely implemented, and in some centers/countries may be limited by cost [34]. Even though PPGL genetics is being increasingly studied, most of the studies included in this review provide limited information on hereditary PPGLs.

There remain difficulties in the classification of malignant PPGL. In the absence of metastatic disease, there are no histological features that can confidently differentiate malignant from benign disease. As such, the term “malignant” was replaced with “metastatic” in 2017 [2]. Only 6 studies in this review reported the rates of metastatic disease [4, 6, 7, 22-24].

Data on tumor size was limited; therefore, it is difficult to interpret the data based on 4 studies with findings from Berends et al suggesting a possible decrease in size over time [11]. This could be again contributed to by advances in imaging, biochemical testing, and surveillance of patients known to harbor an underlying germline mutation. The possible increase in age at presentation reported by Berends et al [11] may also be explained in the context of increasing adrenal incidentaloma detection.

The results showed PCC preponderance in all but 1 of the studies [25]. This is likely because of Leung et al also including patients with HNPGLs, which make up to 20% of all PGLs [2], whereas the other 3 recent studies excluded this group of patients. This is, however, difficult to apply to the earlier 6 studies because those were published before the formal differentiation between PGLs and PCCs in 2004 [35], and it is unclear from those papers whether any patients with HNPGLs were included.

A recent meta-regression analysis reported the incidence of PPGLs but in the context of altitude and showed that increase in altitude is associated with PPGLs rather than time [36]. However, the findings of that study have been queried because of various limitations, including noninclusion of several seemingly relevant papers [37]. A limitation of our current review is the lack of information on not only altitude at the time of diagnosis but also altitude over the lifespan of the individual, the latter potentially being more relevant to tumorigenesis.

Race was rarely reported. There are very limited data on the association of race with PPGL incidence. Hartley et al reported a far higher incidence in Europeans compared with

Aborigines and Pacific Islanders in Queensland [7], but in that era, access to health care was likely to be vastly different between these groups, likely leading to underdiagnosis in the latter 2 groups. Additionally, all but 1 study [24] was done in countries where the majority of the population are of European ancestry. To gain a better understanding of the role of race and PPGL, we need more studies from non-European countries and careful documentation of either patient race or ethnicity.

Two studies from this review appear to be outliers. The first is the study by Kim et al, which showed a lower rate of PPGL than expected but a higher rate of malignant disease [24]. This was the only study of patients predominantly not of European ancestry, and so may reflect a real difference in this population. However, the methodology was different from other studies using health insurance database rather than the more commonly used hospital discharges or surgical/pathology databases. Further work in this and other ethnically diverse regions would be helpful to clarify if there are marked differences according to geography or race, as potentially suggested by the findings from this group.

The other outlier is that of Beard et al, demonstrating a much higher incidence of PPGL than others in the same era, but this is the smallest study included with only 13 cases (including 2 familial cases) over 30 years [3]. It is possible that there is a true higher rate of PPGL in this population but, if so, this is not confirmed by Ebbehoj et al in the recent study of adrenal tumors, although this study only included adrenal tumors rather than both PCC and PGL [27]. Alternatively, there may be a higher detection rate as suggested by a possible association between an increased incidence in areas with university hospitals [5]. This may be due to an increase in awareness of, or investigation for PPGL, in these centers. Another possible explanation is the population used by Beard et al for the denominator was that of Rochester City [3]. The authors did not appear to account for change in population over time and it is also possible that the catchment should have been that of Olmsted County, which would decrease the incidence from 0.95/100,000 to 0.6/100,000 over the same time period [38]. Although still higher than historically comparable studies, this seems potentially more in keeping with the expected incidence from such an academic unit with a high rate of autopsy examinations.

Limitations of this review include restriction of search criteria to English language only, which raises the possibility of bias. We excluded 1 conference abstract because we were not able to obtain it, despite contacting local libraries and the abstract authors. There are missing data points; for instance, we had limited information on tumor size and race or ethnicity from most studies. In addition, because of the nature of this review, we did not have information from all studies as to how patients presented, specifically, whether from symptoms, incidental findings, or family screening because of a known hereditary mutation. Although the incidence appeared to have increased over time, it is difficult to ascertain from the information included in the literature whether this pertains to both PCC and PGL or predominantly the former. Changes in detection from family screening is expected to be seen with increased genetic testing but limited information was available on this from most of the included studies. Four single-center studies were included in

the review [3, 20, 22, 23], threatening the external validity of the results and applicability to the general population. De Graeff et al and Hartley et al used questionnaires and letters to identify patients [4, 7], raising the possibility of response and recall biases. In addition, most studies identified patients from surgical or pathology databases potentially missing those patients who did not undergo surgery.

In conclusion, the incidence of PPGL appears to have increased over time, despite a marked decrease in autopsy rates, most likely from an increase in incidental PCC detection through increased rates of imaging and improved imaging technology. The epidemiology of PPGL remains understudied, and there are gaps in our knowledge, in particular, changes in detection of PGLs, including HNPGLs, the association with altitude, tumour size, geographical and racial differences and the background genetics of the populations being studied.

Disclosures

The authors have nothing to disclose.

Data Availability

Datasets generated during and/or analyzed during the current study are available from Mendeley Data [39].

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