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Chapter 5

Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: A nationwide study and systematic review

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Abstract

Introduction: Recent years have seen major changes in clinical practice which may have affected the incidence rates of pheochromocytoma (PCC)/sympathetic paraganglioma (sPGL). There is, however, a lack of up-to-date information describing trends in these incidence rates.

Methods: We searched the Dutch pathology registry to identify all histopathologically confirmed cases of PCC/ sPGL diagnosed between 1995 and 2015. We calculated incidence rates according to age category as well as age-standardized incidence rates (ASR). We also searched Medline and Embase to find data on nationwide incidence rates of PCC/sPGL.

Results: The nationwide pathology study revealed a total of 1493 patients with either PCC or sPGL. The ASR for PCC increased from 0.29 (95% CI: 0.24–0.33) to 0.46 (95% CI: 0.39–0.53) per 100,000 person-years in the periods 1995–1999 and 2011–2015, respectively. For sPGL the ASR in these same periods were 0.08 (95% CI: 0.06–0.10) and 0.11 (95% CI: 0.09–0.13) per 100,000 person-years, respectively. Concomitantly, PCC size decreased (β −0.17; P < .001) and age at diagnosis increased (β 0.13; P = .001). Our systematic search yielded 3 papers reporting on a total of 530 PCC/sPGL cases, showing a combined annual incidence rate varying from 0.04 to 0.21 per 100,000 person-years.

Conclusion: Incidence rates of PCC/sPGL have increased significantly over the past two decades. This trend coincides with a higher age and a smaller tumor size at diagnosis. Most likely these observations are at least in part the result of changes in clinical practice during the study period, with a more intensified use of both imaging studies and biochemical tests for detecting PCC/sPGL.
Introduction

Pheochromocytomas (PCC) and sympathetic paragangliomas (sPGL) are rare neuroendocrine tumors derived from chromaffin tissue of the adrenal medulla and the extra-adrenal sympathetic paraganglia, respectively. Histologically these tumors are identical and they share the capacity to synthesize and release catecholamines (dopamine, norepinephrine and epinephrine) (1–3). Uncontrolled hypersecretion of catecholamines by these tumors may evoke typical signs and symptoms such as paroxysmal hypertension, sweating and tachycardia, and can result in severe cardiovascular morbidity and mortality (4). Surgical resection is the treatment of choice, as it represents the only option for cure (5).

In the past, a substantial proportion of PCC/sPGL was not diagnosed during life but discovered post mortem during autopsy (6). Recent years have seen a tremendous rise in the number of imaging studies being ordered in clinical practice (7, 8), as well as more frequent assessment of metanephrines in plasma or urine (9). The sensitivity of biochemical testing and imaging techniques for detecting PCC/sPGL has also improved substantially over the past two decades (10–12). It is conceivable that these changes in diagnostic procedures have influenced the detection rate of PCC/sPGL during life in recent years. However, epidemiological data on PCC/sPGL, and particularly on its incidence rate, are surprisingly scarce.

Our objective was to determine the annual incidence rate of PCC/sPGL during the past two decades in the Netherlands. To this end we conducted a retrospective nationwide pathology study. We hypothesized that the annual incidence rate has increased during the past two decades. For comparison of our data, we performed a systematic review of the literature on previously reported nationwide incidence rates of PCC/sPGL.

Methods

Systematic review

In order to identify articles published in peer-reviewed medical journals we conducted a systematic search of PubMed/MEDLINE and Embase, in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (13). We used the following search terms: pheochromocytoma, paraganglioma, epidemiology, incidence, prevalence, autopsy, and post mortem examination (see Supplemental data for detailed information). The search was
carried out on November 10, 2016. We considered articles to be eligible for inclusion if they reported original research data on nationwide annual incidence rates of PCC and sPGL, or both, and were published in the English, German, French, Spanish or Dutch language. To avoid the risk of referral and migration bias we excluded papers reporting incidence rates derived from cases collected in one or more centers or only in a certain geographical region. We likewise excluded papers that exclusively described autopsy series without reporting estimates of nationwide incidence rates.

Two authors (A.B. and E.B.) independently and in duplicate assessed the eligibility of all papers. Titles and abstracts were screened first. Next, full-text articles were retrieved of potential relevant articles and these were thoroughly assessed. Articles were also searched for relevant references. If titles and abstract screening were inconclusive the full-text article was evaluated for eligibility. One reviewer extracted data including study design, national annual incidence rates of PCC/sPGL, and demographics of the study participants. The second reviewer checked the accuracy of the extracted data. The primary endpoint of this systematic review was the nationwide annual incidence rate of PCC/sPGL.

For each study we considered the following risks of bias: completeness and reliability of data acquisition and reporting of the primary endpoint, duration of the study period, and selection of the population. We graded the quality of the reported data according to the Oxford Centre for Evidence-Based Medicine levels of evidence (14).

Nationwide pathology study
We searched the Dutch Pathology Registry (PALGA) to identify all histologically proven PCC and sPGL diagnosed in the Netherlands between January 1, 1995 and December 31, 2015. The PALGA registry is a nationwide network and registry of histo- and cytopathology in the Netherlands, with coverage dating back to 1991 (15). We conducted a systematic analysis of the PALGA registry, using the following search terms: adrenal, adrenal medulla, pheochromocytoma(s) and paraganglioma(s). This search yielded a list of excerpts, i.e. summaries of the original pathology reports, including a limited amount of anonymized patient data. We labeled each excerpt with a unique patient identification number. It is worth noting that if the pathology material was obtained from different anatomical locations or at separate dates a single patient could have more than one excerpt in the PALGA registry. Two reviewers (A.B. and E.B.) independently evaluated all excerpts and included those describing a
Incidence of PCC and sPGL. Excerpts reporting on pathology material offered for revision were excluded. We also excluded excerpts describing residual or recurrent disease, defined as a tumor resected from the same anatomical location as the first PCC/sPGL within or after 6 months of the initial resection, respectively. We also excluded metastatic lesions. A lesion was considered metastatic when PCC/sPGL tissue was reported to be present in nonchromaffin tissues such as lymph nodes, liver, lung or bones (3, 16). Furthermore, we excluded excerpts describing only cytology specimens and material offered for either additional immunohistochemistry staining or research purposes. Excerpts reporting a sPGL located in the aortopulmonary window were excluded as differentiation between sPGL and parasympathetic PGL was not feasible in the absence of clinical information (3). If the information provided in the excerpt was not sufficient, the original histopathology report was requested for further study. If the original histopathology report did not permit a definite diagnosis, an experienced pathologist (R.K.) re-examined the original pathology specimens.

Demographic data and tumor specifications were extracted from the excerpts. sPGL were further subdivided by localization according to the World Health Organization (WHO) classification of endocrine tumors (3). A spinal localization was defined as a well-demarcated intradural or extradural mass without infiltration of spinal cord, soft tissues or bone (17). Bilateral PCC was subdivided into synchronous and metachronous presentation, defined as resection of the second PCC less or > 6 months after the preceding contralateral adrenalectomy, respectively. In accordance with the Dutch Medical Research Involving Human Subjects Act, this study has been exempted from approval by the medical ethics committee.

For each study year we calculated age-specific incidence rates for PCC, sPGL, and PCC/sPGL combined. We subsequently determined an age-standardized incidence rate (ASR) for each year by calculating a weighted mean of the age-specific incidence rates, according to the standardized European population, in order to correct for changes in age distribution over time (18). In order to comprehensively delineate age-specific changes, we defined larger age categories as follows: 0–24, 25–49, 50–74, and 75 years or older. Age group specific incidence rates and their ratios were determined. We also calculated ASR and age-group specific incidence rates over the first and last 5 years of the study period. We obtained the required demographic data for these calculations from Statistics Netherlands.

In order to investigate a possible shift from post mortem towards ante mortem diagnosis, we calculated the incidence rate of post mortem diagnosed PCC/sPGL
per annum. Annual autopsy rates were calculated as the percentage of deceased individuals per annum in the Dutch population in whom an autopsy had been performed. We derived the number of clinical autopsies performed for each year from PALGA, in collaboration with the Dutch Society for Pathology.

Data are expressed as mean with 95% confidence interval (CI) or median with interquartile ranges [IQR], where appropriate. Distributions were analyzed using the Chi-square test. Univariate relationships were determined using Pearson’s or Spearman’s correlation coefficients, where appropriate. Multivariate linear regression analyses were carried out to disclose the relationship between year of diagnosis, post mortem incidence rate, and autopsy rate. Statistical analyses were performed using SPSS version 23.0 for Windows (IBM Corporation, Chicago, IL, USA). A two-sided P-value < .05 was considered significant.

Results

Systematic review

After removal of duplicates, the literature search yielded 2095 papers. After reading titles and abstracts we excluded 2025 articles. We excluded an additional 67 papers after reading the full texts (Supplemental Fig. 1). We finally included three papers in the present systematic review (19–21).

The three publications included in this systematic review were published between 1964 and 1988. Two of the three used a national disease registry for data extraction. One study used a questionnaire to identify cases retrospectively and probably suffered from recall bias. Nevertheless, we considered the risk of publication bias and selective reporting to be low.

Collectively, these three studies comprised a total of 530 PCC/sPGL cases, with a mean observation period of 13 years. The reported crude incidence rates of PCC/sPGL in these studies varied between 0.04 per 100,000 and 0.21 per 100,000 person-years. Mean age at time of diagnosis varied between 43 ± 17 and 56 ± 18 years. The majority of the described tumors were PCC (80–100%). Reported localizations of sPGL were intra-abdominal/retroperitoneal (40–64%), intra-thoracic (3.5–60%) and in the urinary bladder (3.5%). In 17–42% of cases, the PCC/sPGL had remained undetected until autopsy (Table 1). The annual incidence rate of PCC/sPGL reported in these three papers and in the present study is depicted in Fig. 1.
Table 1: Overview of previous nationwide patient series with PCC/sPGL.

<table>
<thead>
<tr>
<th>Study description</th>
<th>Population studied</th>
<th>Study outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author/year</strong></td>
<td><strong>Country</strong></td>
<td><strong>M:F</strong></td>
</tr>
<tr>
<td>Stenström, 1986</td>
<td>Sweden</td>
<td>1:1.4</td>
</tr>
<tr>
<td></td>
<td>1958–1981</td>
<td>National disease registry</td>
</tr>
<tr>
<td></td>
<td>Retrospective (multicenter)</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Andersen, 1988</td>
<td>Denmark</td>
<td>1.4:1 M: 45 [15–73]²</td>
</tr>
<tr>
<td></td>
<td>1977–1981</td>
<td>National disease registry</td>
</tr>
<tr>
<td></td>
<td>Retrospective (multicenter)</td>
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<td></td>
<td></td>
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<tr>
<td>Graeff, 1964</td>
<td>The Netherlands</td>
<td>1:1.2</td>
</tr>
<tr>
<td></td>
<td>1949–1959</td>
<td>National questionnaire</td>
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<tr>
<td></td>
<td>Retrospective (multicenter)</td>
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</table>

Abbreviations: M, male; F, female; yrs., years; PCC, pheochromocytoma; sPGL, sympathetic paraganglioma. Age is described as mean (± SD)² or median [range]². Mean annual incidence rates are presented per 100,000 person-years.
Figure 1: Nationwide incidence rates from literature and present study. Incidence rate presented per 100,000 person-years.

Year of study presented as median year of data collection period for the three earlier reports. For the present study, incidence rates are shown at start and end of data collection period (1995 and 2015, respectively).

Nationwide pathology study

The search through the PALGA registry yielded a total of 2871 excerpts. After processing, we included 1899 excerpts, corresponding to 1493 unique patients (Supplemental Fig. 2). The distribution of pathology diagnoses was as follows: PCC (n = 1210), sPGL (n = 274), synchronous presentation of PCC and sPGL (n = 9). Mean age at presentation was 51 ± 16 years with a wide range varying from 0 to 88 years (Fig. 2).

PCC/sPGL occurred more frequently in females than in males (55% vs. 45%, P < .001). Among the 1210 patients with PCC, 1114 (92%) had a unilateral localization originating in the right (53%) or left (47%) adrenal gland (P = .026). The median diameter of PCC was 4.0 [2.5–6.5] cm. Thirty-eight patients (3.1%) with a PCC developed an additional PCC in the contralateral adrenal gland at least 6 months after the primary diagnosis (Table 2). Localizations of sPGL were intra-abdominal/retroperitoneal (56%), spinal (22%), in the urinary bladder (10%), intra-thoracic (9%) or miscellaneous (3%) (Table 2). The miscellaneous group consisted of sPGL originating in the mesentery, uterus, ovary, testicle or spermatic cord.
Figure 2: Age at diagnosis pheochromocytoma (PCC).

Figure 3: Annual age-standardized incidence rates (ASR) per 100,000 person-years of pheochromocytoma (PCC)/sympathetic paraganglioma (sPGL).

Combined PCC + sPGL ($\beta$ 0.80, $P < .001$), PCC ($\beta$ 0.82, $P < .001$) and sPGL ($\beta$ 0.45, $P = .04$) in the Netherlands during 1995–2015.

The overall ASRs of PCC/sPGL were 0.37 (95% CI: 0.31–0.43) and 0.57 (95% CI: 0.49–0.66) per 100,000 person-years in the period 1995–1999 and 2011–2015, respectively. The annual ASR of PCC/sPGL increased significantly during the study period ($\beta$ 0.80, $P < .001$).
The overall ASRs of PCC were 0.29 (95% CI: 0.24–0.33) and 0.46 (95% CI: 0.39–0.53) per 100,000 person-years in the periods 1995–1999 and 2011–2015, respectively. For sPGL, the overall ASRs were 0.08 (95% CI: 0.06–0.10) and 0.11 (95% CI: 0.09–0.13) per 100,000 person-years, respectively. The annual ASR of PCC increased during the whole study period (β 0.82, P < .001), whereas the annual ASR of sPGL increased (β 0.45, P = .04) to a lesser extent (Fig. 3). We observed the largest relative increase in age-specific incidence rates of PCC/sPGL in patients ≥75 years with a ratio of 2.2 in the last 5 years, compared to the first 5 years of the study period. During the entire observation period, the incidence rate was greatest among subjects in the age group 50–74 years (Fig. 4).

Age at diagnosis increased, (β 0.12; P < .001) while PCC tumor size decreased significantly (β −0.17; P < .001) during the study period (Figs. 5 and 6, respectively). In a multivariable linear regression model with study year as dependent variable, these correlations remained significant (PCC size: β −0.17; P < .001, age: β 0.13; P = .001).

A total of 72 (4.8%) PCC/sPGL were diagnosed during post mortem examination. The mean annual incidence rate of post mortem diagnosed PCC/sPGL was 0.02 (95% CI: 0.016–0.027) per 100,000 person-years. Information on the number of autopsies performed in the Netherlands was available for the years 1995 through 2013. There was a strong decline in autopsy rate during this period (β −0.99; P < .001). Post mortem incidence of PCC/sPGL did not change during the study period (β −0.02; P = .612) after correction for the decrease in annual autopsy rate.

**Figure 4:** Absolute increase of age specific incidence rate (left) and relative increase of age specific incidence rate (right) stratified according to age group during the first, middle, and last 5 years of study period

Incidence rate per 100,000 person-years.
**Figure 5:** Median age at diagnosis of pheochromocytoma.

Significant increase of age during whole study period ($\beta 0.12; P < .001$).

**Figure 6:** Median size of pheochromocytoma (PCC) at diagnosis.

Significant decrease of PCC tumor size during whole study period ($\beta -0.17; P < .001$).
<table>
<thead>
<tr>
<th></th>
<th>PCC ((n = 1210))</th>
<th>sPGL ((n = 274))</th>
<th>Synchronous PCC and sPGL ((n = 9))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (M:F %)</strong></td>
<td>43:57</td>
<td>53:47</td>
<td>44:56</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>51 ± 16</td>
<td>51 ± 16</td>
<td>37 ± 16</td>
</tr>
<tr>
<td><strong>Localization</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Right</td>
<td>43%</td>
<td>Abdominal-retroperitoneal 56%</td>
<td>Adrenal/abdominal 66%</td>
</tr>
<tr>
<td>Left</td>
<td>49%</td>
<td>Spinal</td>
<td>Adrenal/thoracic 22%</td>
</tr>
<tr>
<td>Bilateral synchronous</td>
<td>5%</td>
<td>Urinary bladder 10%</td>
<td>Adrenal/abdominal/thoracic 11%</td>
</tr>
<tr>
<td>Bilateral metachronous</td>
<td>3%</td>
<td>Thoracic</td>
<td>Bilateral adrenal/abdominal 11%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>Miscellaneous 3%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: M, male; F, female; yrs., years; PCC, pheochromocytoma; sPGL, sympathetic paraganglioma.
Incidence of PCC and sPGL

Discussion

We here describe the epidemiology of PCC/sPGL in the Netherlands during two decades, i.e. from 1995 to 2015. We found a significant increase of the ASR of PCC/sPGL, which coincided with a reduction in tumor size and a higher age at the time of initial diagnosis.

The incidence rates in the present study are derived from the largest series of patients with PCC/sPGL published so far, and are considerably higher than previously reported. There is, however, a lack of good quality estimates with respect to the epidemiology of PCC/sPGL. Despite a comprehensive review of the literature, we were able to retrieve only three papers reporting on nationwide incidence rates of PCC/sPGL (19–21). These previous studies were much smaller in size and difficult to compare with the present study because of differences in study design and population composition. Moreover, the reported incidence rates were not standardized for age distribution, thereby precluding reliable comparisons with contemporary populations. Nevertheless, the collective data from those earlier publications and the present study clearly suggest an increase in the annual incidence rate of PCC/sPGL over the past 60 years, as shown in Fig. 1.

Theoretically, the increased incidence rate of PCC/sPGL could reflect a true increase in the number of patients affected by this disease, a change in diagnostic practices resulting in earlier detection, or a combination of these. The observed increase in the incidence rate diagnosed during life combined with an unaffected post mortem incidence rate might support the contention that the number of patients developing a PCC/sPGL has actually increased.

Changes in tumorigenesis could be responsible for such an increased occurrence. For example, the rising incidence of papillary thyroid carcinoma has been linked to an increase in the frequency of somatic mutations in BRAF and RAS proto-oncogenes (22, 23). Recent genetic analysis in PCC/sPGL also identified somatic BRAF and RAS mutations as pathogenic, but it is currently unknown whether the occurrence of these mutations in PCC/sPGL has changed over the course of time (24). It can be questioned, however, whether the post mortem incidence rate of PCC/sPGL has indeed been stable over the years, as the number of autopsies fell dramatically in the Netherlands during the study period. A similar trend has also been reported in several other countries (25–28). This means that the selection of deceased individuals who are ultimately subjected to an autopsy procedure has
changed considerably over time, which will inevitably confound any attempt to extrapolate results from post mortem incidence rates to the general population (28, 29).

Diagnostic practices have changed profoundly in recent years and it seems plausible that these changes have largely contributed to the observed increase in the incidence rates of PCC/sPGL. The concomitant decrease in tumor size is also in support of a shift to an earlier diagnosis of PCC/sPGL. These trends correspond with recent studies describing increasing incidence rates of neuroendocrine tumors, in particular of localized disease, most likely as a result of earlier detection (30–32). The exponential growth in the use of various imaging studies (e.g. ultrasound, computed tomography, magnetic resonance imaging, positron emission tomography scanning) obviously increases the chance of visualizing an unexpected lesion such as an adrenal gland tumor (7,8,33). It has been demonstrated that a substantial number of these so called adrenal incidentalomas harbor a PCC (34–36). We found that both the absolute incidence rates and the relative increase in incidence rates were greatest among subjects older than 50 years, which is in agreement with the fact that most imaging studies are performed in this age group (7). Diagnostic practices during the study period were also altered by the introduction of a routine laboratory assay to determine metanephrines in either plasma or urine (9). This assay has significantly improved the accuracy of the biochemical diagnosis of PCC/sPGL and has become the recommended first line test (5). In addition, DNA mutation screening programs have become standard practice as a direct consequence of the expanding number of identified mutations in PCC/sPGL susceptibility genes. Currently, about 30–40% of all PCC/sPGL are considered to be hereditary, and annual biochemical screening with measurement of metanephrines in germline mutation carriers is now considered standard clinical practice (5,37,38).

It could be argued that earlier detection of PCC/sPGL would only lead to the diagnosis of indolent and therefore clinically irrelevant neuroendocrine tumors. However, there are several lines of evidence to support the clinical importance of a timely diagnosis of PCC/sPGL. The study by Sutton et al. reported that cardiovascular disease was the main cause of death in patients in whom PCC had been an unsuspected autopsy finding. Notably, 27% of these patients had died of hypertensive or hypotensive crises precipitated by surgery for unrelated conditions (6). In addition, Stolk et al. demonstrated a 14-fold higher rate of cardiovascular events among patients with a PCC compared to patients with...
Incidence of PCC and sPGL

essential hypertension (4). This elevated risk was most likely explained by exposure to the toxic effects of catecholamines, as no differences were found in blood pressure or other cardiovascular risk factors. Moreover, it has been shown that normotensive patients and hypertensive patients with a PCC had similar degrees of hemodynamic instability during adrenalectomy (39). Collectively, these data underscore the importance of timely diagnosis and treatment of PCC.

Our study has some limitations. Unfortunately, we did not have access to clinical information on the study subjects and were therefore unable to analyze directly the potential determinants of the observed changes in incidence rates or to describe any relationships with morbidity, mortality or survival. Multifocal sPGL might be underreported in our study, since histopathology has probably not always been obtained from all tumor localizations. Another limitation was that the distinction between PCC and sPGL was not always clearly defined before the consensus report issued in 2004, which sometimes posed difficulties in interpretation of the terminology applied in older publications on incidence rates (3).

The strength of our study is the fact that the present results are derived from a nationwide pathology register, which precludes the potential selection bias that might occur in case of reports from one or a few referral centers. In addition, we provide novel epidemiological data on the incidence rates of PCC/sPGL over the past 20 years in the largest series of PCC/sPGL published until today.

In conclusion, the ASR of PCC/sPGL has increased significantly during the past two decades, most likely as a result of changes in diagnostic practices leading to earlier detection of these tumors. A higher detection rate of PCC/sPGL is of potential clinical importance, as earlier treatment is expected to reduce the elevated cardiovascular risk in these patients.


## Chapter 5

### References

Incidence of PCC and sPGL

Supplemental data

Supplementary information 1. Search strategy, full search string

Full search string by database.
Date search: November 10, 2016.

Search PubMed/Medline:

Search Embase:
(pheochromocytoma/exp OR pheochromocytoma*:ab,ti OR phaeochromocytoma*:ab,ti OR phaeochromocytoma*:ab,ti OR paraganglioma*:ab,ti AND (incidence/exp OR prevalence/exp OR ‘autopsy’/exp OR incidence:ab,ti OR prevalence:ab,ti OR autops*:ab,ti OR ‘postmortem examination’:ab,ti) NOT (‘animal’/exp NOT ‘human’/exp)) NOT (pheochromocytoma/exp OR pheochromocytoma*:ab,ti OR phaeochromocytoma*:ab,ti OR phaeochromocytoma*:ab,ti OR paraganglioma*:ab,ti AND (incidence/exp OR prevalence/exp OR ‘autopsy’/exp OR incidence:ab,ti OR prevalence:ab,ti OR autops*:ab,ti OR ‘postmortem examination’:ab,ti) NOT (‘animal’/exp NOT ‘human’/exp))
Supplemental figures

Supplemental Figure 1: Flow chart of search results and study selection.

2,095 publications identified by systematic search of databases

2,025 publications excluded, based on title and abstract

70 publications selected for full assessment

67 publications excluded:
No nationwide incidence rate (n = 43)
Subgroup analysis only (n = 16)
Autopsy study only (n = 4)
Double publication/no original study (n = 4)

3 publications included
Supplemental Figure 2: Flowchart of excerpt selection and processing.

Excerpts after PALGA database search
n = 2871

Exclusion n = 956
- No PCC/sPGL or HNPGL  n = 683
- Only cytology available  n = 35
- Molecular/immune histochemical analysis  n = 8
- Material used for research purposes  n = 3
- Recurrent disease/residual tumor/metastatic lesions  n = 193
- Revision material  n = 34

PCC/sPGL  n = 1879

Original pathology report screening

Inconclusive  n = 36

PCC/sPGL  n = 16

Revision by expert pathologist

Inconclusive  n = 8

No PCC/sPGL  n = 12

PCC/sPGL  n = 8

No PCC/sPGL  n = 4

PCC/sPGL  n = 1899

in 1493 patients