



Contents lists available at ScienceDirect

## Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: [www.cancerepidemiology.net](http://www.cancerepidemiology.net)



# An audit of cancer of unknown primary notifications: A cautionary tale for population health research using cancer registry data

Claire M. Vajdic<sup>a,\*</sup>, Chuang Ching Er<sup>a</sup>, Andrea Schaffer<sup>b</sup>, Timothy Dobbins<sup>c</sup>, Lucy Wyld<sup>a</sup>, Nicola S. Meagher<sup>a</sup>, Jane Barrett<sup>d</sup>, Robyn L. Ward<sup>a</sup>, Sallie-Anne Pearson<sup>b,c</sup>

<sup>a</sup>Adult Cancer Program, Prince of Wales Clinical School, University of New South Wales, Australia

<sup>b</sup>Faculty of Pharmacy, University of Sydney, Australia

<sup>c</sup>School of Public Health, University of Sydney, Australia

<sup>d</sup>CUP Action, Australia

### ARTICLE INFO

#### Article history:

Received 18 February 2014

Received in revised form 13 May 2014

Accepted 16 May 2014

Available online xxx

#### Keywords:

CUP

Audit

Cancer registry

Incidence

Legislation

Descriptive epidemiology

### ABSTRACT

**Background:** Cancer of unknown primary (CUP) is a common cancer yet little is known about the reliability of incidence data. **Methods:** We audited 574 CUP (C80.9) diagnoses (median age 81 years) registered by the New South Wales (NSW) Central Cancer Registry (2004–2007) in a cohort of Australian Government Department of Veterans' Affairs clients. The registry did not clarify diagnoses with notifiers during this period due to interpretation of privacy legislation. For the audit, current registry practice was applied by seeking additional information from CUP notifiers and reclassifying diagnoses as necessary. In addition, clinicopathological characteristics were extracted from notifications. Fisher's exact test and Student's *t*-test were used to compare the demographic and clinicopathological characteristics of the CUP subgroups. Age/sex-standardised CUP incidence rates and 95% confidence intervals were calculated, standardised to the 2001 Australian population. **Results:** 172 (30.0%) cases were reclassified to a known primary site, mostly cutaneous, and nine (1.6%) were found to be non-malignant diagnoses. After the audit the age/sex-standardised CUP incidence rates decreased from 26.0 (95% CI 21.2–30.8) to 15.9 (95% CI 12.5–19.3) per 100,000 person-years. Of the 393 remaining CUP cases, 202 (51%) were registered on the basis of a clinical diagnosis (46 by death certificate only) and 191 (49%) by pathological diagnosis (79 by cytology alone). Compared to cases with a pathological diagnosis, cases with a clinical diagnosis were older (85.6 vs. 82.0 years,  $p < 0.001$ ), and the reported number and location of metastases differed ( $p < 0.001$ ); metastatic sites were more likely to be unspecified for clinical diagnoses (36.1% vs. 4.2%). **Conclusions:** Cancer registry processes can markedly influence CUP incidence. Future population-based CUP research should take this into account, and consider stratification by basis of diagnosis due to differences in patient and tumour characteristics.

© 2014 Elsevier Ltd. All rights reserved.

## 1. Introduction

Cancer of unknown primary (CUP) is most commonly defined as metastatic cancer with no known primary site, despite comprehensive clinical and pathological investigations [1]. In contrast, the

UK National Institute for Health and Clinical Excellence (NICE) [2], defines three types of CUP on the basis of increasing levels of confidence in the diagnosis of cancer. These subtypes are clinically diagnosed metastatic cancer without histopathological confirmation (malignancy of undefined primary, MUO); cytologically or histologically confirmed metastatic malignancy following initial investigations (provisional CUP, pCUP); and histopathologically confirmed metastatic malignancy after appropriate specialised investigations (confirmed CUP, cCUP), which corresponds to the common definition. CUP incidence data reported by population-based cancer registries encompasses but does not distinguish these three subtypes. As a result, it is not possible to reconcile the common definition for CUP with population-level statistics for the disease. This creates confusion and limits population-based

**Abbreviations:** CI, confidence interval; CUP, cancer of unknown primary; cCUP, confirmed CUP; DVA, Department of Veterans' Affairs; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; MUO, malignancy of undefined origin; NMSC, non-melanoma skin cancer; pCUP, provisional CUP.

\* Corresponding author at: Adult Cancer Program, Lowy Cancer Research Centre, University of New South Wales, NSW 2052, Australia. Tel.: +61 2 9385 1424; fax: +61 2 9385 1430.

E-mail address: [claire.vajdic@unsw.edu.au](mailto:claire.vajdic@unsw.edu.au) (C.M. Vajdic).

<http://dx.doi.org/10.1016/j.canep.2014.05.004>

1877-7821/© 2014 Elsevier Ltd. All rights reserved.

research into the causes and prevention of CUP, a cancer with a poor prognosis [3,4].

In 2010, CUP was the 7th most common cancer and the 6th most common cause of cancer death in Australia [5]. The incidence of CUP was 10.7–12.7 per 100,000, higher in men than women, and the mean age at diagnosis 73 years. Both incidence and mortality rates have declined over the last two decades [5], a pattern observed internationally and ascribed to advances in diagnostic technology and cancer registration practices. Nevertheless, Australian and international data shows a median survival of 9–12 weeks, with no apparent increases over time [4,6–9]. Clinically, the presentation of CUP is heterogeneous, most displaying aggressive metastatic spread and a poor treatment response [10]. The causes of CUP are unknown, and the sparse observational evidence indicates an increased risk of pathologically verified CUP in association with a genetic predisposition or family history of cancer [11], tobacco smoking, and high waist circumference [12].

In a cohort of Australian veterans and their dependants, we undertook an audit of CUP diagnoses registered by a population-based Australian cancer registry during a period when the registry did not write to notifiers to request clarification about cancer diagnoses. Our aim was to assess the impact of registry processes on CUP incidence. We also describe the relative burden of CUP subtypes and the characteristics of the newly audited cases.

## 2. Methods

We wanted to assess the impact of population-based cancer registry processes on CUP incidence estimates. Between 2002 and 2007, state and federal privacy legislation was interpreted as preventing the New South Wales Central Cancer Registry (NSW CCR) from writing to notifiers to request more information about ambiguous notifications prior to cancer registration. For this study, CUP notifications to the NSW CCR during this period were audited and notifiers were followed up according to current registry practices.

### 2.1. Study population

The study population was 143,956 Australian Government Department of Veterans' Affairs (DVA) clients residing in NSW between July 1 2004 and December 31 2007. The DVA assists veteran and defence force communities and their families. This includes a predominantly elderly population of veterans, war widows/widowers, serving and former Australian Defence Force members and certain Australian Federal Police officers with overseas service [13]. Eligible members of the veteran community receive subsidised health care services under DVA arrangements and this may include consultations, diagnostic tests, treatments, and pharmaceuticals. Seventy percent of the study cohort was entitled to fully subsidised medical care under DVA arrangements. It is an elderly cohort, with 88% aged 65 years or older; this age group corresponds to the population at greatest risk of a CUP diagnosis in NSW and internationally.

### 2.2. Data collection

Records for the NSW DVA population were linked with the NSW CCR to identify CUP diagnoses (ICD-0-3 C80.9). The NSW Centre for Health Record Linkage performed probabilistic linkage between the datasets on the basis of client name, sex, date of birth, and date of death. For each CUP diagnosis, the date and basis of diagnosis, topography, and morphology were ascertained. The NSW CCR is a register of incident primary invasive cancers diagnosed in NSW since 1972. Notification of malignant neoplasms, other than cutaneous basal and squamous cell carcinoma, is a statutory requirement for NSW public and private hospitals, outpatient

radiotherapy and chemotherapy departments, pathology laboratories, nursing homes, and day procedure centres. The registry operates in accordance with International Association of the Cancer Registries regulations [14], and cancers are classified according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3). Routine indices of data quality and completeness show that registry performance meets international standards [15].

A senior NSW CCR coder or pathologist reviewed the notifications for each linked registered diagnosis of CUP in the cohort, including pathology and cytology reports, cancer notification forms, inpatient and outpatient electronic records, and death certificates. Where necessary, a letter was sent to the notifying doctor or institution requesting additional information about the diagnosis. On the basis of new information, the diagnosis of CUP was retained or reclassified. For cases retained as CUP, the reported tumour morphology, grade and the site(s) of nodal and extranodal metastases were extracted from the registry notifications.

### 2.3. Statistical analyses

Before and after the audit, crude and age/sex-standardised CUP incidence rates, standardised to the 2001 Australian population, and 95% confidence intervals (CIs; based on the Poisson distribution) were calculated. Person-years of follow-up accrued from the date of issue of the DVA health care entitlements or July 1 2004 (whichever occurred last) until the date of CUP diagnosis, death, or December 1 2007 (whichever occurred first), corresponding to the dates of overlap of the administrative health datasets.

Fisher's exact test and Student's *t*-test were used to compare the demographic and clinicopathologic characteristics of the population subgroups. After the audit, CUP cases diagnosed by cytology or histology were classified as pathological diagnoses (i.e. pCUP/cCUP), and those diagnosed solely on clinical grounds e.g. radiological findings or notified by death certificate alone were classified as clinical diagnoses (i.e. MUO).

The study was approved by the NSW Population and Health Services (2008/02/060) and DVA Human Research Ethics Committees (E008/03) and the requirement for informed consent was waived because the researchers received only coded data.

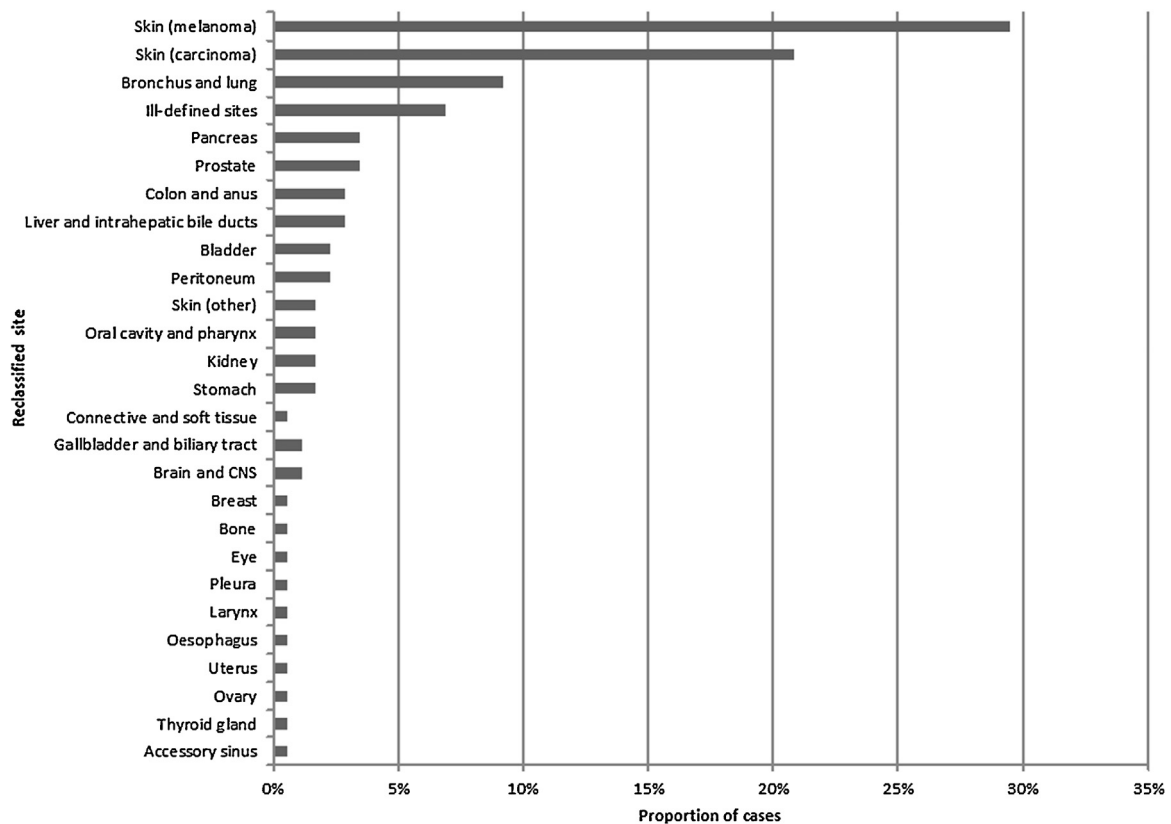
## 3. Results

The median age of the DVA clients at the start of follow-up was 81 years (interquartile range, IQR 76–85) and 51% were male. Over 310,146 person-years, 574 clients were originally registered with CUP (ICD-0-3 C80.9) by the NSW CCR. Compared to DVA clients without a CUP diagnosis, those with CUP were 1.2 (95% CI 1.1–1.3) times more likely to be male than female ( $p < 0.0001$ ), and a mean of 5 years older at the start of follow-up ( $p < 0.0001$ ). The crude incidence of CUP was 185.1 per 100,000 person-years and the age/sex-standardised rate 26.0 (95% CI 21.2–30.8) per 100,000 person-years.

### 3.1. Audit of registered CUP cases

The audit processes led to reclassification of 181 (31.5%) of the 574 registered CUP cases; 9 (1.6%) were non-cancer diagnoses and 172 (30.0%) were reclassified to another malignancy. Of those reclassified to a more specific cancer, 27 different malignancies were identified (Fig. 1). Cutaneous melanoma (29.5%), squamous cell skin cancer (20.8%), and bronchus/lung cancer (9.2%) were the most common reclassified cancers.

After the audit, the crude and age/sex-standardised CUP incidence rates decreased to 126.7 per 100,000 person-years and 15.9 (95% CI 12.5–19.3) per 100,000 person-years respectively. Based solely on whether the diagnosis was made on clinical or



**Fig. 1.** Distribution of reclassified CUP cases by new topography. Ill-defined sites: C26 ( $n = 4$ ) malignant neoplasm of other and ill-defined digestive organs; C57 ( $n = 5$ ) malignant neoplasm of female genital organ, unspecified; C763 ( $n = 2$ ) malignant neoplasm of other and ill-defined sites; C779 ( $n = 1$ ) secondary and unspecified neoplasm of lymph node, unspecified. Skin (other): Merkel cell carcinoma ( $n = 2$ ), giant cell cancer not otherwise specified ( $n = 1$ ).

pathological grounds, the age-standardised incidence of MUO and pCUP/cCUP in this elderly cohort is estimated to be 6.3 (95% CI 5.1–7.5) and 9.6 (95% CI 6.5–12.8) per 100,000 person-years respectively. It is not possible to distinguish pCUP and cCUP without information on specialised diagnostic investigations.

### 3.2. Characteristics of post-audit CUP cases

#### 3.2.1. Demographic characteristics

Of the 393 CUP cases, the median age at diagnosis was 84 years (IQR 81–88; Table 1). Males were 1.2 (95% CI 1.1–1.3) times more likely to have a CUP diagnosis than females ( $p < 0.0001$ ). Forty-six cases (11.7%) were registered on the basis of a death certificate

alone, 156 (39.7%) a clinical diagnosis, 79 (20.1%) cytology, and 112 (28.5%) histology. Thus, similar proportions of cases were diagnosed on a clinical basis without pathological confirmation of cancer (51.4%) than with pathology (48.6%). The gender distribution did not differ between these two diagnostic groups ( $p = 0.27$ ), but the mean age of the clinical subgroup was slightly older than the pathological subgroup (85.6 vs. 82.0 years,  $p < 0.0001$ ).

#### 3.2.2. Tumour morphology and grade

Of the tumours with cytology or histology performed and notified to the registry, the most common morphologies were adenocarcinoma ( $n = 72$ , 37.7%), squamous cell carcinoma ( $n = 37$ ,

**Table 1**  
Post-audit demographic characteristics of Department of Veterans' Affairs clients with CUP, by basis of diagnosis.

Characteristic	Basis of diagnosis, $n$ (%)				Total ( $n = 393$ )
	Pathological ( $n = 191$ )		Clinical ( $n = 202$ )		
	Histological	Cytological	Clinical	Death certificate only	
Gender					
Female	33 (29.5)	37 (46.8)	69 (44.2)	16 (34.8)	155 (39.4)
Male	79 (70.5)	42 (53.2)	87 (55.8)	30 (65.2)	238 (60.6)
Age at diagnosis (years)					
Mean (SD) <sup>a</sup>	81.9 (7.9)	82.1 (6.7)	85.0 (4.7)	87.6 (4.2)	83.9 (6.4)
Median (IQR) <sup>b</sup>	83 (81–86)	83 (79–86)	85 (82–88)	87 (84–90)	84 (81–88)
<65	8 (7.1)	2 (2.5)	0 (0.0)	0 (0.0)	10 (2.5)
65–74	2 (1.8)	6 (7.6)	2 (1.3)	0 (0.0)	10 (2.5)
75–84	61 (54.5)	40 (50.6)	71 (45.5)	13 (28.3)	185 (47.1)
85+	41 (36.6)	31 (39.2)	83 (53.2)	33 (71.7)	188 (47.8)
Total	112	79	156	46	393

<sup>a</sup> SD: standard deviation.

<sup>b</sup> IQR: interquartile range.

**Table 2**  
Cancer registry-notified metastatic site(s) in post-audit CUP, by the basis of diagnosis.

Notified metastatic site(s)	Basis of diagnosis, n (%)		Total, n (%)
	Pathological	Clinical	
Single lymph node			
Axillary	13 (6.8)	0 (0.0)	13 (3.3)
Cervical	9 (4.7)	1 (0.5)	10 (2.5)
Inguinal	6 (3.1)	0 (0.0)	6 (1.5)
Other <sup>a</sup>	3 (1.6)	1 (0.5)	4 (1.0)
Sub-total	31	2	33
Single extranodal			
Liver	42 (22.0)	42 (20.8)	84 (21.4)
Bone	14 (7.3)	13 (6.4)	27 (6.9)
Lung	16 (8.4)	8 (4.0)	24 (6.1)
Brain	1 (0.5)	17 (8.4)	18 (4.6)
Other <sup>b</sup>	16 (8.4)	0 (0.0)	16 (4.1)
Sub-total	89	80	169
Multiple			
Nodal <sup>c</sup>	11 (5.8)	1 (0.5)	12 (3.1)
Extranodal	23 (12.0)	23 (11.4)	46 (11.7)
Nodal and extranodal/disseminated	21 (11.0)	14 (6.9)	35 (8.9)
Sub-total	55	38	93
Ascites/abdominal	8 (4.2)	9 (4.5)	17 (4.3)
Unspecified	8 (4.2)	73 (36.1)	81 (20.6)
Total	191	202	393

<sup>a</sup> Epigastric ( $n=1$ ), intraparotid ( $n=1$ ), brachial plexus ( $n=1$ ), and not specified ( $n=1$ ).

<sup>b</sup> Bowel ( $n=3$ ), skin ( $n=3$ ), chest ( $n=2$ ), peritoneum ( $n=2$ ), periscapular soft tissue ( $n=1$ ), parotid gland ( $n=1$ ), adrenal gland ( $n=1$ ), paraspinal ( $n=1$ ), breast ( $n=1$ ), and paracervical soft tissue ( $n=1$ ).

<sup>c</sup> At least 2 nodes or nodal sites involved.

19.4%), carcinoma not otherwise specified ( $n=29$ , 15.2%), and other specified carcinomas ( $n=29$ , 15.3%). There was one case of leiomyosarcoma, five neuroendocrine carcinomas, seven carcinoid tumours, and 11 with no specified morphology. Of the tumours with a histological diagnosis, the most common grade was poorly differentiated (30.4%), but grade was not reported in 36.6%.

### 3.2.3. Metastatic site

The site(s) of metastatic disease were not specified in 20.6% of cases (Table 2). In the majority of cases a single extranodal site (43.0%), typically the liver, was reportedly involved. Multiple metastases were reported in 23.7% of cases, and ascites or 'abdomen' in 4.3%. Of those reporting multiple extranodal metastases ( $n=46$ ), the most common involved organs were the lung ( $n=25$ ) and the liver ( $n=23$ ). In 8.4% of cases a solitary lymph node metastasis was reported, most commonly axillary. The reported site of metastatic disease was associated with the basis of diagnosis ( $p < 0.0001$ ; Table 2). Compared to cases registered on the basis of pathology, cases with a clinical diagnosis were less likely to have a metastatic site specified and less likely to have a solitary involved lymph node or multiple metastatic sites.

Most (58.1%) pathologically confirmed solitary lymph node metastases ( $n=31$ ) were squamous cell carcinoma, specifically 4 of 9 cervical, 9 of 13 of axillary, and 3 of 6 inguinal nodes. Single reported extranodal metastases were most commonly of adenocarcinoma lineage (43.8%).

## 4. Discussion

Our audit demonstrated the marked impact of the quality of notifications to cancer registries and cancer registration practices on the population-based incidence of CUP. When notifiers were asked to clarify ambiguous CUP notifications the number of CUP cases reduced by one third. In this elderly cohort of Australian veterans with subsidised health care, clinically diagnosed, or non-pathologically confirmed CUP, constituted one half of all CUP

registrations. Furthermore, clinical and pathologically confirmed CUP exhibited different demographic and clinicopathological features, showing the importance of taking into account basis of diagnosis when working with and reporting CUP data. These findings support further investigations of cancer registry and other data sources to better understand the true burden for this common yet highly heterogeneous group of malignancies.

Historically, CUP incidence rates have been viewed as a measure of population-based cancer registration quality [16], with high rates reflecting inadequate diagnostic services, low utilisation of diagnostic services, poor documentation and notification of diagnostic results, or inadequate cancer registry practices [17]. In this audit, we quantified the potential impact of cancer registry practices on the population-level incidence of CUP. Registered CUP diagnoses were reclassified on the basis of additional information obtained from notifiers, information that would have been sought had the privacy legislation been interpreted differently. Indeed, the Public Health Act 1991 was amended and the registry resumed writing to doctors in 2008. Half of the reclassifications were to malignancies of cutaneous origin, including primary cutaneous squamous cell carcinomas not mandated to be notified to, or registered by, the NSW population-based cancer registry. The extent of over-estimation of CUP incidence is therefore likely to vary depending on the population-level incidence of skin cancers and whether they are notifiable malignancies as this will influence the number and completeness of registry notifications. There are no prior similar studies with which to compare our findings, but they highlight the need for cautious interpretation of CUP incidence rates and comparison of rates between countries.

Over the last thirty years, CUP has been increasingly recognised as a clinical entity [1,2,18,19], but the incidence of the CUP subtypes, MUO, pCUP and cCUP, is not known. Differentiation of these subtypes at the population-level would help clarify the public health burden of this disease. Sub-classification would also aid research into the risk factors and health service utilisation associated with these diagnoses. Around half of the retained CUP cases were registered without pathological investigation, thereby meeting the criteria for MUO. This finding is consistent with a recent UK hospital-based study (45%) [20], but is higher than observed in population-based cancer registry studies in Europe between 1984 and 1992 (20%, 22%) [7,8] and the United States between 1973 and 1987 (35%) [18] and between 1973 and 2008 (22%) [4]. These differences may be explained by our predominantly elderly cohort, who may be less fit to undergo biopsy compared to the general population.

For patients registered on the basis of a clinical diagnosis alone, it is possible the primary site would have been identified if tissue sampling and histopathological investigation was performed. On average, these patients were slightly but significantly older than those with a pathological diagnosis, a finding consistent with prior cancer registry studies [7,8,18]. A number of factors, including the prognosis and age and overall health of the patient, are taken into account when deciding whether a patient would benefit from undergoing a fine-needle aspiration, biopsy, or resection [2]. As only 28% of our CUP cases were registered on the basis of a histological diagnosis, a minority of the total incident cases could satisfy the criteria needed to be classified as cCUP.

Our CUP cases showed similar demographic and clinicopathologic characteristics to those in prior cancer registry studies. A CUP diagnosis was more likely in males than females, in keeping with the higher incidence of any type of cancer in males than females [5]. Extranodal metastases were more frequently reported than nodal metastases, and the most common reported sites were liver, bone, and lung [7,21]. Adenocarcinoma was the most commonly reported morphology [7,8,18], except for cases reporting solitary lymph



node metastases where squamous cell carcinoma was more prevalent [21,22]. Furthermore, patients reported as having solitary lymph node involvement were more likely to be pathologically confirmed than clinically diagnosed [7]. Biopsy may be more likely in these patients due to their generally better health and prognosis at diagnosis compared to those with more extensive disease.

Overall, multiple metastatic sites were reported in only 24% of our CUP cases. This estimate is markedly lower than hospital-based CUP case series where 60% of patients present with metastases at multiple sites [23,24]. This discrepancy is most likely to be an artefact of the local population-level cancer registration process because this information is not always conveyed to reporting pathologists and registry notifications are not required to include the full extent of metastatic disease. In support of this explanation, the metastatic site(s) were not specified in 21% of our cases.

This is the first assessment of the impact of a cancer registry process on CUP incidence, and the first study to quantify incidence by CUP subtype. As the registry audit processes and cancer reclassification occurred independently of patient characteristics, they are not unique to the DVA population. However, the proportion of CUP cases with pathological verification may not be generalisable. Compared to the general Australian population of the same age, DVA clients with fully subsidised health care have significantly higher utilisation of general practitioner services (+17%) and rates of hospital separations (+21%) [25]. The impact of higher rates of health service use on diagnostic investigations for cancer is unknown. In addition, the metastatic sites reported in this study may not reflect the entire clinical picture and may be biased towards biopsy-accessible sites and the organ disease that precipitated the cancer diagnosis.

In summary, this study highlights some of the complexities in interpreting CUP incidence data and demonstrates that cancer registry processes may lead to overestimating incidence. Not only will such error inflate the reported burden of CUP and its subtypes, but also it will unpredictably impact CUP survival estimates, treatment profiles, and risk factors. Researchers using data of this kind should seek to understand the underlying registry processes and how these might influence case ascertainment and classification. Moreover, our results underscore the importance of stratification by basis of diagnosis when describing, comparing, and interpreting CUP incidence data. These findings support further studies of notifier and registry processes on CUP incidence and clinicopathological characteristics.

### Competing interests

None of the authors have any relevant conflicts of interest to declare in relation to this manuscript.

### Authors' contributions

Conceived and designed the study: CMV, AS, NM, TD, SAP. Analysed the data: CMV, TD, CCE. Wrote the manuscript: CMV, TD, LW, RLW, SAP. All authors read and approved the final manuscript.

### Acknowledgements

This work was supported by an Epidemiology Linkage Programme Grant from the Cancer Institute New South Wales (10/EPI/2-06), a project grant from Cancer Australia (568773), an IPRS scholarship and TCRN Top-up scholarship (to Lawrence Er), an NHMRC Career Development Fellowship (1023159 to CMV), a Cancer Institute New South Wales Career Development Fellowship (10/CDF/2-42 to CMV; 09/CDF/2-37 to SAP). Lucy Wyld is supported by the Translational Cancer Research Network funded

by the Cancer Institute NSW. The funding bodies played no role in the study design or conduct, data collection, analysis or interpretation of data, in the writing of the article or the decision to submit the article for publication.

We thank the Australian Department of Veterans' Affairs and the New South Wales Central Cancer Registry for providing the data used for this study, and Claire Cooke-Yarborough and Maria Arcorace from the New South Wales Cancer Registry for conducting the audit.

### References

- [1] Greco FA, Hainsworth JD. Cancer of unknown primary site. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: principles and practice of oncology*. Philadelphia: Lippincott Williams & Wilkins, 2011: 2033–51.
- [2] National Institute for Health and Clinical Excellence. *Diagnosis and management of metastatic malignant disease of unknown primary origin*. NICE clinical guideline 104. London: NICE, 2010.
- [3] Luke C, Koczwara B, Karapetis C, Pittman K, Price T, Kotasek D, et al. Exploring the epidemiological characteristics of cancers of unknown primary site in an Australian population: implications for research and clinical care. *Aust N Z J Public Health* 2008;32:383–9.
- [4] Urban D, Rao A, Bressel M, Lawrence YR, Mileshekin L. Cancer of unknown primary: a population-based analysis of temporal change and socioeconomic disparities. *Br J Cancer* 2013;109:1318–24.
- [5] Australian Institute of Health and Welfare & Australasian Association of Cancer Registries. *Cancer in Australia: an overview 2012*. Cancer series no. 74. Cat no. CAN 70, Canberra: Australian Institute of Health and Welfare, 2012.
- [6] Tracey EA, Glass P, Roder D, Currow D, Jelfs P, Bishop J. Unknown primary cancer in New South Wales, Sydney, Australia: Cancer Institute NSW, 2008.
- [7] van de Wouw AJ, Janssen-Heijnen ML, Coebergh JW, Hillen HF. Epidemiology of unknown primary tumours: incidence and population-based survival of 1285 patients in Southeast Netherlands, 1984–1992. *Eur J Cancer* 2002;38:409–13.
- [8] Levi F, Te VC, Erler G, Randimbison L, La Vecchia C. Epidemiology of unknown primary tumours. *Eur J Cancer* 2002;38:1810–2.
- [9] Seve P, Ray-Coquard I, Trillet-Lenoir V, Sawyer M, Hanson J, Broussolle C, et al. Low serum albumin levels and liver metastasis are powerful prognostic markers for survival in patients with carcinomas of unknown primary site. *Cancer* 2006;107:2698–705.
- [10] Greco FA, Hainsworth JD. Cancer of unknown primary site. In: DeVita VT, Lawrence TS, Rosenberg SA, DePino RA, Weinberg RA, eds. *Cancer: principles and practice of oncology*. 9th ed., Philadelphia: Lippincott Williams & Wilkins, 2011: 2033–51.
- [11] Hemminki K, Ji J, Sundquist J, Shu X. Familial risks in cancer of unknown primary: tracking the primary sites. *J Clin Oncol* 2011;29:435–40.
- [12] Kaaks R, Sookthai D, Hemminki K, Kramer A, Boeing H, Wirfalt E, et al. Risk factors for cancers of unknown primary site: results from the prospective EPIC cohort. *Int J Cancer* 2014. <http://dx.doi.org/10.1002/ijc.28874>. PMID: 24692151 (in press).
- [13] Repatriation Commission, Military Rehabilitation and Compensation Commission, and Department of Veterans' Affairs. *Annual reports 2011–2102*. Farewells and homecomings. Canberra: Department of Veterans' Affairs, 2012.
- [14] International Association of the Cancer Registries. *Cancer epidemiology: principles and methods: the role of cancer registries*. Lyon: International Agency for Research on Cancer, 1999.
- [15] Tracey EA, Kerr T, Dobrovic A, Currow D. *Cancer in NSW: incidence and mortality report 2008*. Sydney: Cancer Institute NSW, 2010.
- [16] Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heaneu M, et al., eds. *Cancer incidence in five continents*, vol. 2011. Lyon: International Agency for Research on Cancer, 2007.
- [17] International Agency for Research on Cancer. *Manual for cancer registry personnel*. Lyon: International Agency for Research on Cancer, 1995.
- [18] Muir C. Cancer of unknown primary site. *Cancer* 1995;75:353–6.
- [19] Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. *Lancet* 2012; 379:1428–35.
- [20] Shaw PH, Adams R, Jordan C, Crosby TD. A clinical review of the investigation and management of carcinoma of unknown primary in a single cancer network. *Clin Oncol (R Coll Radiol)* 2007;19:87–95.
- [21] Hemminki K, Bevier M, Hemminki A, Sundquist J. Survival in cancer of unknown primary site: population-based analysis by site and histology. *Ann Oncol* 2012;23:1854–63.
- [22] Jereczek-Fossa BA, Jassem J, Orecchia R. Cervical lymph node metastases of squamous cell carcinoma from an unknown primary. *Cancer Treat Rev* 2004;30:153–64.
- [23] Abuzzese SL, Abuzzese M, Hess KR. Unknown primary carcinoma: natural history and prognostic factors in 657 consecutive patients. *J Clin Oncol* 1994;12:1272–80.
- [24] Lenzi R, Hess KR, Abuzzese MC, Raber MN, Ordenez NG, Abuzzese JL. Poorly differentiated carcinoma and poorly differentiated adenocarcinoma of unknown origin: favorable subsets of patients with unknown-primary carcinoma? *J Clin Oncol* 1997;15:2056–66.
- [25] Australian Institute of Health and Welfare (AIHW). *Health care usage and costs. A comparison of veterans and war widows and widowers with the rest of the community*. Cat. no. PHE 42. Canberra: AIHW, 2002.