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

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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.

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

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