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ORIGINAL RESEARCH ARTICLE

Healthcare Costs Before and After Diagnosis of Cancer of Unknown Primary Versus Ovarian Cancer in Australia

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Abstract

Background Little is known about the healthcare resource usage and costs for patients with cancer of unknown primary (CUP).

Objective The aim of this study was to describe and quantify healthcare resource use and costs in Australia, 6 months prior to and after a diagnosis of CUP, and compare to those of women with ovarian cancer.

Methods Individual-level data combining baseline surveys, clinical records and Medicare Benefits Schedule (MBS) claim records were analysed for 149 patients with CUP and 480 patients with ovarian cancer from two prospective cohort studies. MBS data were aggregated for the period 6 months prior to diagnosis date and 6 months after diagnosis. Data included doctor consultations, pathology, diagnostics, therapeutic procedures, imaging, allied health and medicines. Generalised linear models were used to evaluate the cost differences between CUP and ovarian cancer using gamma family and log link functions. Models were adjusted for age, employment, marital status, surgery, chemotherapy and number of comorbidities.

Results The mean healthcare costs in the 6 months prior to diagnosis of CUP were Australian (AU) $3903 versus AU$1327 for ovarian cancer (adjusted cost ratio 2.94, 95% confidence interval [CI] 2.08–4.15). Mean healthcare costs 6 months post-diagnosis were higher for patients with CUP versus ovarian cancer (AU$20,339 vs AU$13,819, adjusted cost ratio 1.47, 95% CI 1.13–1.92). Higher costs for patients with CUP were driven by imaging (AU$1937 vs AU$1387), procedures (AU$5403 vs AU$2702) and prescribed medicines for all conditions (AU$10,111 vs AU$6717).

Conclusions Pre-diagnosis costs for patients with CUP are nearly triple those for ovarian cancer. Six months after diagnosis, healthcare costs for CUP remained higher than for ovarian cancer due to imaging, procedures and medicines.

Key Points for Decision Makers

Higher pre- and post-diagnosis costs were found for patients with cancers of unknown primary compared with ovarian cancer.

After diagnosis, healthcare costs for cancers of unknown primary were higher than for ovarian cancer due to imaging, procedures and cancer medicines. If cancers of unknown primary were diagnosed earlier, for example with the use of molecular testing, investigational costs may be minimised.

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1 Introduction

A diagnosis of cancer of unknown primary (CUP) occurs when metastatic cancer has been found but the primary site cannot be identified, despite extensive imaging, clinical assessment and pathological investigation [1]. In Australia, CUP is the fifth and sixth most common cause of cancer death in 2019 among females and males, with 1173 and 1258 deaths, respectively [2]. Patients with CUP have one of the lowest 5-year survival rates of all cancers at 14% [2].

Many CUPs are aggressive and have unpredictable metastatic spread [3]. Only around 30% of patients with CUP receive curative cancer treatments, with the majority of patients being offered chemotherapy with palliative intent or palliative care alone [3]. Anti-cancer therapies matched to the site of origin are the best therapeutic option for these patients; hence, a comprehensive diagnostic work-up is critically important. Many CUP patients do not receive a complete standard workup, often due to deteriorating health, lack of availability of diagnostic modalities or expert opinion [4]. Conversely, there may also be a risk of over-investigation, leading to a prolonged diagnostic odyssey. Treatment decisions and government reimbursement of Pharmaceutical Benefits Scheme (PBS) medications are based on confirmed tumour sites, and oncologists are not permitted to prescribe many restricted anti-cancer therapies based on a suspected but unconfirmed cancer origin. However, a prior survey study found that 83% of medical oncologists in Australia will assign a primary tumour type diagnosis to a patient in order to obtain pharmaceutical benefits funding of medical therapy based on their clinical assessment of the likely site of origin [5].

Avoiding delays in diagnosis of CUP will not only potentially improve patient outcomes, but also contribute to more efficient use of healthcare resources and costs. There are few studies on the economic and clinical value of diagnostic tests for CUP [6–8]. Therefore, to inform resource planning and allocation, there is a need to evaluate both the cost of diagnosing and treating CUP in addition to cost-effective treatments. A comparison with an advanced cancer of known primary site provides context in which to learn the extent of any additional burden of CUP. Therefore, the purpose of this study was to describe and quantify healthcare resource use and costs, during the 6 months prior to and after a diagnosis of CUP, and compare to those for women diagnosed with ovarian cancer during a similar period. Although ovarian cancer affects women only and CUP affects both sexes, ovarian cancer was chosen as a suitable comparator because patients typically present with advanced-stage cancer, and consequently the timeliness of management is key to optimal care. The researchers had access to a relatively large linked dataset of healthcare use for women with ovarian cancer and similar for CUP, acknowledging the rarity of these cancer types and the challenges involved in recruiting participants with advanced-stage disease.

2 Methods

2.1 Study Design and Participants

A cost-analysis was performed using linked data from a prospective multi-centre cohort of men and women diagnosed with CUP. Participants were from the Solving Unknown Primary cancER (SUPER) study recruited from 11 health services across Australia between November 2013 and November 2015. Inclusion criteria were (1) presenting with cancer of no confirmed primary site despite having had preliminary diagnostic work-up, including detailed clinical assessment, a computerised tomography (CT) scan of the chest, abdomen and pelvis and pathological review of tumour tissue; and (2) either yet to commence treatment or had commenced treatment no more than 6 months ago. Exclusion criteria were age under 18 years, poor Eastern Cooperative Oncology Group (ECOG) performance status (> 2), limited English language skills, and uncontrolled medical or psychological conditions that prevented completion of study requirements. Some participants ($n = 21$) from the original sample of CUP participants ($n = 170$) did not consent to Medicare Benefits Schedule (MBS) data being obtained and were excluded from the analysis. The study was approved by the Peter MacCallum Cancer Centre Human Ethics Research Committee and all participating sites. Ethical approval for this economic sub-study was waived by the QIMR Berghofer Human Ethics Research Committee P3609.

2.2 Comparison Group

The comparison group was women from the Ovarian cancer, Prognosis and Lifestyle (OPAL) study cohort, enrolled through 18 clinics across Australia. OPAL participants had a confirmed first diagnosis of primary invasive epithelial ovarian, primary peritoneal or fallopian tube cancer between January 2012 and May 2015, were age 18–79, and could self-complete questionnaires in English. Women with ovarian cancer were chosen as a comparator group because both CUP and ovarian cancer are characterised by patients typically presenting with metastatic disease, patients often having symptoms for some time, the relative rarity of the cancers, their occasional familial component and the increasing use of genetic profiling. Neither cancer type has a dedicated screening program nor are there very specific risk factors [3]. The main risk factors for CUP are advancing age, male sex, lower socio-economic status, smoking and diabetes [3, 9], while those for ovarian cancer include female sex, advancing

age, inherited mutations in the *BRCA1* or *BRCA2* genes, nulliparity, lack of use of oral contraceptive pill, hormone replacement therapy and endometriosis [10, 11]. Women with stage I and II ovarian cancer were excluded to create a more comparable group to patients with CUP.

2.3 Data

Medicare is Australia's national government payment scheme that subsidises most medical services to Australian citizens. Claims data were available for medical services covered by the MBS and prescription medicines covered by the PBS. All services for health professional consultations, investigations, pathology, imaging, procedures, allied health and pharmaceuticals claimed from June 2013 to April 2017 (4.5 years) for CUP and January 2011 to September 2016 for OPAL were included. All participants had data recorded within 6 months of diagnosis, and CUP participants who did not consent to Medicare data being obtained were excluded ($n = 21$). Any services conducted in public hospitals and not billed through Medicare were not captured, nor were any out-of-pocket costs incurred by patients. MBS and PBS data linkage was performed by the data custodians at Services Australia. Using the unique patient identifiers, we obtained all MBS and PBS items processed for each participant. Item numbers, benefits (i.e. cost to government), item category, description and date of services were used for this analysis. Although genomic analyses (not subsidised on the MBS at the time) were performed for patients in both the CUP and ovarian groups, these costs were excluded as they were performed as part of the trials and were not a benefit or cost to the government.

These data were linked to the baseline survey data used in each study that captured socio-demographic (age, sex, occupation, employment status, country of birth) and clinical and treatment-related information (date of diagnosis, chemotherapy, radiation therapy, surgery) and deaths. Using PBS medicines data, an index of comorbidities was created using the mapping approach by Pratt et al. [12] using the Anatomical Therapeutic Chemical Classification System of medicines. From a possible 46 comorbidities, the most common 15 comorbidities were presented (excluding malignancies as the index condition) and all comorbidities were considered for calculating 'number of comorbidities' categories.

2.4 Analysis

The cost analyses take a provider perspective, that is, Australian Government costs through the Medicare schemes. Socio-demographic data were presented as frequencies and proportions for categorical data, and means and standard deviations for age. Pearson's chi square tests were performed to assess differences in socio-demographic and comorbidity profiles between the CUP and ovarian cancer groups, but *p* values were not presented, as per Strengthening The Reporting of OBservational Studies in Epidemiology (STROBE) guidelines [13]. Costs were presented in Australian dollars (AU$) and inflated to 2022 prices using the health group component of the Consumer Price Index [14].

2.4.1 Pre-diagnosis Costs

MBS data were aggregated for the period 6 months prior to diagnosis date when most diagnostic services are concentrated [6]. Total costs to government prior to diagnosis were aggregated for five of the seven major categories on the MBS that are most relevant to diagnosis: doctor consultations, diagnostics, imaging, pathology and therapeutic procedures (allied health and oral and maxillofacial services were excluded, as were PBS medicines). While 'imaging' includes CT scans and ultrasounds among others, the category 'diagnostics' included investigations such as positron emission tomography (PET) scans, invasive endoscopic investigations and nuclear medicine services. Similarly, 'therapeutic procedures' included services such as biopsy, fine needle aspiration and anaesthesia required in the diagnostic work-up. We included all services within these categories as it is not possible to identify whether individual MBS items were attributable to the work-up of cancer or not. Therefore, the results include all costs for cancer plus any other concurrent health conditions in the lead up to the cancer diagnosis.

2.4.2 Post-diagnosis Costs

We also assessed all MBS and PBS costs for 6 months *after* diagnosis (including categories for allied health services and prescription medicines) to compare resource use between the cancer groups after diagnosis. Six months after diagnosis, no deaths had occurred in the ovarian cancer group (consent for MBS data was not obtained if women died within 6 months), while 29 patients (19.5%) had died in the CUP group. To ensure comparable groups in the post-diagnosis analyses, we excluded CUP patients who died within 6 months of diagnosis ($n = 29$).

2.4.3 Statistical Analyses

Generalised linear models (GLMs) were employed to evaluate the cost differences between CUP and ovarian cancer separately before and after diagnosis. Gamma family and log link functions were optimal for the GLMs [15] and were confirmed with statistical diagnostic tests. Models were adjusted for age (as a potential indicator for frailty), marital status, employment status, chemotherapy, surgery and number of comorbidities. To assess the relationship

between pre-diagnosis and post-diagnosis costs in the CUP and ovarian groups, we used the Spearman's rho statistic. We separately assessed costs among women only (excluding male CUP patients) to compare the main results with the mixed gender group. Missing data arose because some CUP patients consented to MBS data but had withdrawn from the study before the first survey ($n = 30$). Multiple imputation methods with ten imputation sets were used for missing socio-demographic details in the CUP data (16–20%), and GLMs were repeated on imputed data.

3 Results

Analyses were undertaken for 629 patients in total, 149 patients with CUP and 480 with ovarian cancer. The CUP group were slightly younger than women with ovarian cancer, with a mean age of 60 years ($p = 0.05$). Proportions within 10-year age groups were similar across cancer groups (Table 1) (excluding 30 missing values for the CUP group). The CUP group were less likely to be married or partnered, less likely to be working, had attained lower education levels and were less likely to be Australian born than women with ovarian cancer (Table 1). The CUP group had higher numbers of comorbidities, with significantly higher proportions of diabetes, anxiety, osteoporosis, pain and psychotic illness.

The mean unadjusted MBS costs in the 6 months prior to diagnosis of ovarian cancer were AU$1357 (95% confidence interval [CI] 1253–1461), while comparable costs for CUP were AU$3381 (95% CI 2894–3867) (Fig. 1a). MBS costs for the CUP group were higher than for ovarian cancer across all categories (doctor consultations, diagnostics, imaging, pathology and procedures), with imaging and procedure costs showing the biggest absolute differences. MBS costs varied widely for both cancer groups (Fig. 1a, b). At pre-diagnosis, the proportions of the total costs within each category were similar across cancer types for pathology, diagnostics and imaging but were lower for doctor consultations and higher for procedures in CUP versus ovarian cancer (Supplementary Figure S1, see the electronic supplementary material).

In multivariable cost models, adjusted for age, employment status, marital status, surgery, chemotherapy and number of comorbidity categories, total MBS costs pre-diagnosis were 2.9-fold higher for patients with CUP than ovarian cancer, ranging from 1.9-fold (for doctor visits) to 7.6-fold (for procedures) higher (Table 2). Only diagnostic costs, which had the fewest items, were similar across cancer groups. Following multiple imputation, the findings were similar to those reported above (not shown).

After diagnosis, unadjusted total 6-month MBS costs and the distributions of costs across categories were similar for the two groups (Fig. 1c, d, Supplementary Figure

Table 1 Baseline socio-demographic characteristics by cancer type

	Unknown primary $n = 149$	Ovarian $n = 480$
Gender		
Male	69 (46.3%)	0 (0%)
Female	80 (53.7%)	480 (100%)
Age (years)		
Mean (SD)	60.0 (12.4)	62.1 (9.6)
< 40 years	9 (6.0%)	12 (2.5%)
40–49 years	15 (10.1%)	57 (11.9%)
50–59 years	43 (28.9%)	132 (27.5%)
60–69 years	54 (36.2%)	187 (39.0%)
70 +	28 (18.8%)	92 (19.2%)
Marital status[1]		
Married/de facto	79 (64.8%)	340 (70.8%)
Divorced/separated	10 (8.2%)	67 (14.0%)
Never married/single	24 (19.7%)	37 (7.7%)
Widowed	9 (7.4%)	36 (7.5%)
Education[1]		
Secondary	53 (43.1%)	224 (46.8%)
Trade/technical college	42 (34.1%)	118 (24.6%)
University	28 (22.8%)	137 (28.5%)
Employment[1,2]		
Working	42 (35.0%)	260 (54.3%)
Retired	54 (45.0%)	160 (33.4%)
Other	24 (20.0%)	59 (12.3%)
Country of birth[1]		
Australia	96 (76.8%)	353 (73.5%)
Other	29 (23.2%)	127 (26.5%)
Comorbidities[3]		
Disorders requiring anticoagulants	61 (40.9%)	380 (79.2%)
Anxiety	30 (20.1%)	40 (8.3%)
Reactive airways disorders	42 (28.2%)	118 (24.6%)
Depression	41 (27.5%)	119 (24.8%)
Diabetes	19 (12.8%)	29 (6.0%)
Gastric acid disorders	114 (76.5%)	339 (70.6%)
Hyperlipidaemia	41 (27.5%)	129 (26.9%)
Hypertension	27 (18.1%)	96 (20.0%)
Ischemic heart disease/hypertension	27 (18.1%)	93 (19.4%)
Disorders requiring NSAIDs	61 (40.9%)	216 (45.0%)
Liver failure	17 (11.4%)	47 (9.8%)
Osteoporosis/Paget's	18 (12.1%)	31 (6.5%)
Pain (opioids)	138 (92.6%)	354 (73.8%)
Steroid responsive diseases	121 (81.2%)	391 (81.5%)
Psychotic illness	31 (20.8%)	34 (7.1%)
Other	74 (49.7%)	179 (37.3%)
No. comorbidities[3]		
0–2	13 (8.7%)	32 (6.7%)
3–4	26 (17.4%)	149 (31.0%)
5–6	51 (34.2%)	155 (32.3%)

Table 1 (continued)

	Unknown primary $n = 149$	Ovarian $n = 480$
7–8	43 (28.9%)	106 (22.1%)
8 +	16 (10.7%)	38 (7.9%)

CUP cancer of unknown primary, *NSAID* non-steroidal anti-inflammatory drug, *OPAL* Ovarian cancer, Prognosis and Lifestyle, *PBS* Pharmaceutical Benefits Scheme

[1]Excludes between 26 and 30 CUP patients with no sociodemographic data

[2]Excludes 1 participant from the OPAL study

[3]Derived for 46 conditions using PBS data and Anatomical Therapeutic Classification codes of medicine groups as developed by Pratt et al. 2018 [12]. The most common 15 conditions are shown here, excluding 'malignancies', and 'other' represents all other groups

S1). Adjusted mean MBS and PBS costs post-diagnosis were higher for patients with CUP versus ovarian cancer (AU$20,339 vs AU$13,819, adjusted cost ratio 1.47, 95% CI 1.13–1.92). MBS costs were higher for patients with CUP for imaging (AU$1937 vs AU$1387, adjusted cost ratio 1.39, 95% CI 0.99–1.98), procedures (AU$5403 vs AU$2702, adjusted cost ratio 2.00, 95% CI 1.20–3.34) and PBS medicines for cancer (AU$9500 vs AU$5613, adjusted cost ratio 1.69, 95% CI 1.04–2.75) (Table 2). Pre-diagnosis costs were not associated with post-diagnosis costs for patients with CUP (Spearman's rho = 0.071, $p = 0.38$) and were weakly associated for ovarian cancer (Spearman's rho = 0.234, $p < 0.001$), where Spearman's rho > 0.5 is considered strong correlation (Supplementary Figure S2a and b). When male CUP patients were excluded from the analyses, the cost ratios were similar to the full analyses, and overall

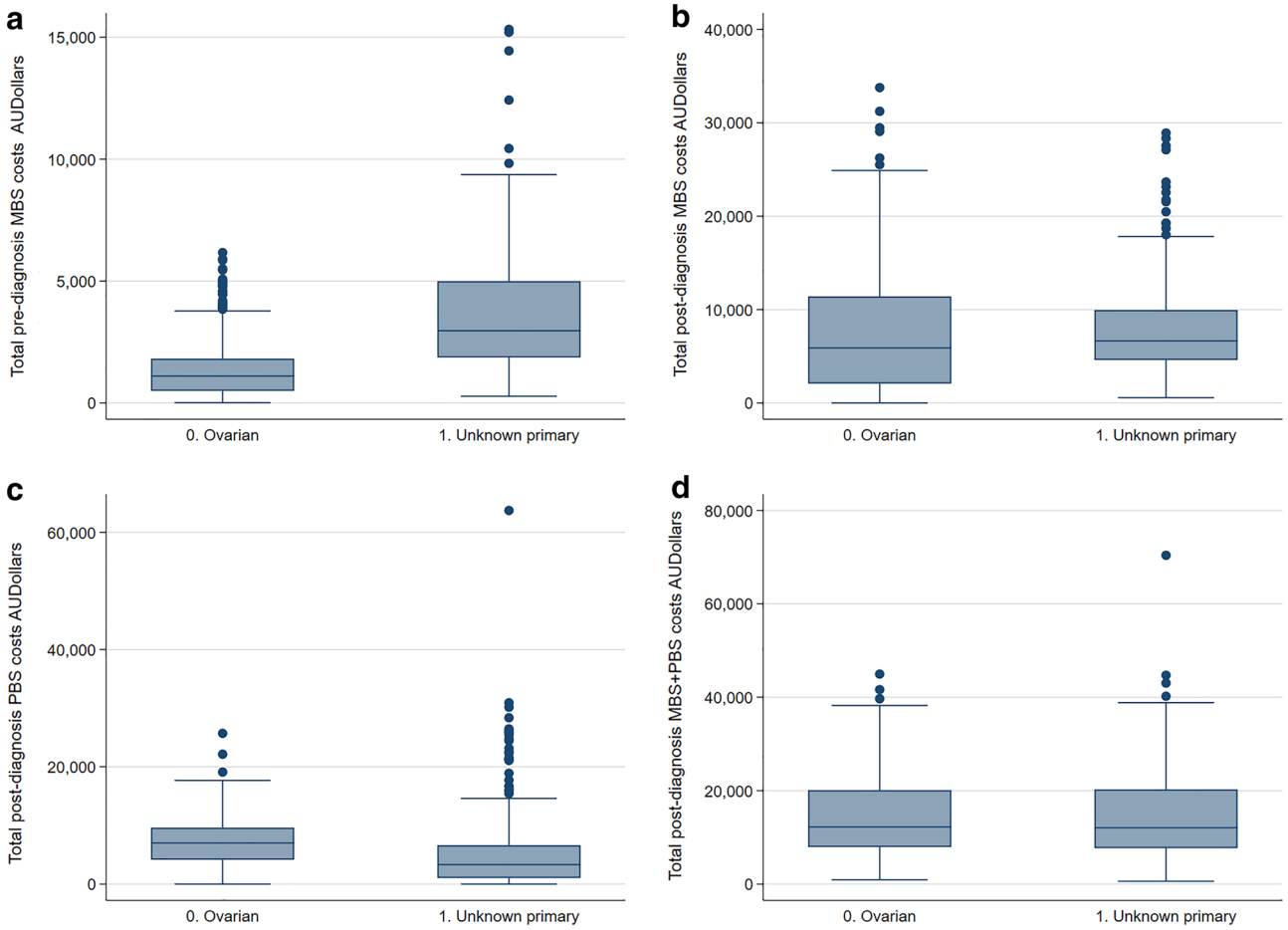

Fig. 1 Healthcare costs (unadjusted) by cancer type: **a** 6 months pre-diagnosis[1] (MBS costs); **b** 6 months post-diagnosis[2] (MBS costs); **c** 6 months post-diagnosis (PBS costs); **d** 6 months post-diagnosis[3] (MBS+PBS). *AU* Australian, *MBS* Medicare Benefits Schedule, *PBS* Pharmaceutical Benefits Schedule. [1]Includes 5 major MBS categories (doctor consults, diagnostics, imaging, pathology and therapeutic procedures). [2]Includes MBS categories: doctors' consults, diagnostics, imaging, pathology, therapeutic procedures, allied health services. [3]Includes MBS categories above in [2] and PBS medicines

Table 2 Results of generalised linear models[1] for 6-month pre- and post-diagnosis mean costs, CUP vs ovarian cancer (2022 AU$)

	exp(b)[2]	Std. Err.	*p* value	95% CI	Unknown primary	Ovarian
6 months pre-diagnosis						
Total cost	2.94	0.52	< 0.001	2.08–4.15	$3903	$1327
Doctors	1.86	0.33	< 0.001	1.32–2.62	$719	$386
Diagnostics	0.57	0.33	0.3	0.18–1.76	$16	$28
Imaging	3.01	0.61	< 0.001	2.02–4.49	$1631	$541
Pathology	2.79	0.53	< 0.001	1.93–4.04	$585	$210
Procedures	7.56	3.00	< 0.001	3.47–16.46	$1262	$167
6 months post-diagnosis						
Total cost	1.47	0.20	0.01	1.13–1.92	$20,339	$13,819
Doctors	0.82	0.13	0.21	0.60–1.12	$1385	$1692
Diagnostics	1.37	0.71	0.55	0.49–3.79	$53	$39
Imaging	1.39	0.25	0.06	0.99–1.98	$1937	$1387
Pathology	0.84	0.15	0.34	0.59–1.20	$1152	$1373
Procedures	2.00	0.52	0.01	1.20–3.34	$5403	$2702
Allied health	1.61	1.02	0.45	0.47–5.56	$90	$56
Medicines (all)	1.51	0.36	0.09	0.94–2.41	$10,111	$6717
Cancer medicines[3]	1.69	0.42	0.03	1.04–2.75	$9500	$5613

AU$ Australian dollars, *CI* confidence interval, *CUP* cancer of unknown primary, *Std. Err.* standard error,

[1]Adjusted for age, employment status, marital status, surgery, chemotherapy and no. of comorbidities

[2]This is the cost ratio of CUP vs ovarian cancer costs

[3]Derived from Anatomical Therapeutic Chemical Classification System codes of 'malignancies' medicine group developed by Pratt et al. 2018 [12] (codes L01AA01-L01XX41)

cost values were slightly lower for the CUP group (Supplementary Tables S1 and S2).

Patients with CUP used a wide range of healthcare resources. The most frequent MBS items 6 months pre-diagnosis were general practitioner and specialist consultations, general chemistry tests, blood pathology and chest radiology (Table 3). After diagnosis, the most common items were similar but with added chemotherapy and radiation therapy services. PET scans, thought to be an important clinical tool in oncology, were received by 29 patients with CUP at a mean AU$905 per scan. For cancer therapies, compared to patients with ovarian cancer, who are predominantly treated with combination paclitaxel and carboplatin, treatment of CUP was much more varied and included gemcitabine (26% of scripts), carboplatin (17% of scripts) and several high-cost monoclonal antibody therapies (Table 4).

4 Discussion

These findings show that patients with CUP incurred nearly threefold higher healthcare costs in the months leading up to diagnosis than patients with ovarian cancer. These were spread across consultations, imaging, pathology and all types of investigations, in keeping with the extensive diagnostic work-up for suspected CUP. Following diagnosis, use of healthcare services was higher for CUP patients compared with women with ovarian cancer, driven by higher costs for imaging, procedures and pharmacotherapies (the last for other health conditions but not cancer specifically).

Few studies have documented the costs of CUP during the diagnosis phase. In a Canadian study, healthcare costs were significantly higher 6 months prior to diagnosis across most resource types in those with CUP compared with a mixed and matched sample of patients with known primary cancers, yet treatment costs after diagnosis were lower [6]. Our findings contradict these results in the treatment phase where cancer therapy costs appear to be higher and MBS costs similar for CUP patients (Table 2). However, our study compared patients with CUP to women with ovarian cancer, with all patients having stage III or IV disease, unlike the mixed cancer sample used in the Hannouf et al. (2018) study [6]. Australian studies in older patients with CUP have shown higher use of general practitioner consultations, palliative care services, hospitalisations and emergency department visits 3 months before and after diagnosis, compared with metastatic cancer of known primary site [9, 16]. This is likely due to comorbidities rising with age and heavily influencing use of healthcare services and costs. Presence of comorbidities is well-known to strongly determine healthcare costs, rising steeply with each subsequent comorbid condition [17]. While there are guidelines for the routine diagnostic work-up for suspected CUP, the extent of investigations performed is partly determined by the patient's age,

Table 3 Most frequent Medicare MBS items 6 months pre- and post-diagnosis for patients with CUP ($n = 149$)

Category	Sub-category	Description	Item no.	Freq.	Percentage
Pre-diagnosis[1]					
Doctor consultations	A1 General practitioner	Level B consultation	23	641	12.3%
Pathology	P2 Chemical	General chemistry × 5 or more[2]	66512	300	5.8%
Pathology	P10 Patient episode initiation	Initiation of a patient episode	73928	279	5.3%
Pathology	P1 Haematology	Hb, ESR or viscosity 1 or more tests	65060	247	4.7%
Doctor consultations	A1 General practitioner	Level C consultation	36	204	3.9%
Doctor consultations	A3 Specialist	Initial specialist attendance	104	107	2.1%
Doctor consultations	A4 Consultant specialist	Subsequent consultant physician attendance	116	96	1.8%
Pathology	P10 Patient episode initiation	Initiation of a patient episode	73938	86	1.6%
Imaging	I3 Diagnostic radiology	Chest (lung fields) by direct radiography	58503	80	1.5%
Doctor consultations	A3 Specialist	Subsequent specialist attendance	105	70	1.3%
Imaging	I1 Ultrasound	Ultrasonic cross-sectional echography, in conjunct	55054	60	1.2%
Therapeutic procedures	T6 Anaesthesia	Pre-anaesthesia brief consultation	17610	57	1.1%
Pathology	P2 Chemical	Iron studies	66596	57	1.1%
Pathology	P3 Microbiology	Urine examination	69333	57	1.1%
Pathology	P2 Chemical	2 or more tests described in item 66650 malignancy associated antigens	66653	56	1.1%
Pathology	P10 Patient episode initiation	Initiation of a patient episode	73931	53	1.0%
Pathology	P2 Chemical	TSH quantitation	66716	52	1.0%
Therapeutic procedure	T8 Surgical operations	Diagnostic percutaneous aspiration biopsy	30094	50	1.0%
Imaging	I2 Computerised tomography	CT chest, abdomen	56807	49	0.9%
All MBS items			Total	5217	
Post-diagnosis[3]					
Pathology	P1 Haematology	Erythrocyte count, haematocrit	65070	1707	11.9%
Pathology	P2 Chemical	General chemistry × 5 or more	66512	1670	11.6%
Doctor consultations	A4 Consultant specialist	Subsequent consultant physician attendance	116	1047	7.3%
Therapeutics	T1 Miscellaneous therapeutic procedures	Cytotoxic chemotherapy	13918	513	3.6%
Pathology	P10 Patient episode initiation	Initiation of a patient episode	73928	485	3.4%
Doctor consultations	A1 General practitioner	Level B consultation	23	480	3.3%
Therapeutics	T2 Radiation oncology	Radiation oncology treatment	15269	459	3.2%
Therapeutics	T2 Radiation oncology	Radiation oncology treatment verification	15705	413	2.9%
Pathology	P10 Patient episode initiation	Initiation of a patient episode	73939	386	2.7%
Pathology	P10 Patient episode initiation	Initiation of a patient episode	73931	334	2.3%
Doctor consultations	A3 Specialist	Subsequent specialist attendance	105	222	1.5%
Doctor consultations	A1 General practitioner	Level C consultation	36	213	1.5%
Pathology	P10 Patient episode initiation	Initiation of a patient episode	73938	212	1.5%
Therapeutics	T2 Radiation oncology	Radiation oncology treatment	15272	211	1.5%
Pathology	P10 Patient episode initiation	Initiation of a patient episode	73930	208	1.4%
Pathology	P2 Chemical	Malignancy associated antigens	66650	195	1.4%
All MBS items			Total	14365	

CT computerised tomography, *CUP* cancer of unknown primary, *ESR* erythrocyte sedimentation rate, *Hb* haemoglobin, *MBS* Medicare Benefits Schedule, *TSH* thyroid stimulating hormone

[1]50% of all MBS items are listed

[2]Quantitation in serum, plasma, urine or other body fluid (except amniotic fluid), by any method except reagent tablet or reagent strip (with or without reflectance meter) of acid phosphatase, alanine aminotransferase, albumin, alkaline phosphatase, ammonia, amylase, aspartate aminotransferase, bicarbonate, bilirubin (total), bilirubin (any fractions), C-reactive protein, calcium (total or corrected for albumin), chloride, creatine kinase, creatinine, gamma glutamyl transferase, globulin, glucose, lactate dehydrogenase, lipase, magnesium, phosphate, potassium, sodium, total protein, total cholesterol, triglycerides, urate or urea

[3]60% of MBS items are listed

Table 4 Number of scripts for anti-cancer therapies in the 6 months post-diagnosis by cancer type

	Unknown primary		Ovarian	
	Freq.	Percentage	Freq.	Percentage
Bevacizumab	43	2.5%	7	0.1%
Bleomycin sulfate	0	0	4	0.0%
Cabazitaxel	3	0.2%	0	0
Capecitabine	40	2.3%	0	0
Carboplatin	285	16.6%	4121	37.0%
Cetuximab	7	0.4%	0	0
Cisplatin	168	9.8%	222	2.0%
Cyclophosphamide	15	0.9%	0	0
Docetaxel	21	1.2%	5	0.0%
Doxorubicin	21	1.2%	0	0
Doxorubicin HCl pegy injection	6	0.4%	14	0.1%
Epirubicin	5	0.3%	0	0
Erlotinib	2	0.1%	0	0
Etoposide	98	5.7%	18	0.2%
Fluorouracil	175	10.2%	9	0.1%
Gemcitabine	449	26.1%	91	0.8%
Ifosfamide	20	1.2%	0	0
Irinotecan hydrochloride	12	0.7%	0	0
Methotrexate	1	0.1%	0	0
Nanoparticle albumin	137	8.0%	0	0
Oxaliplatin	61	3.6%	4	0.0%
Paclitaxel	108	6.3%	6698	59.8%
Pazopanib	3	0.2%	0	0
Pemetrexed	14	0.8%	0	0
Rituximab	0	0	4	0.0%
Tas imatinib cml	4	0.2%	0	0
Tas pertuzumab	8	0.5%	0	0
Tas trastuzumab	14	0.8%	4	0.0%
	1720	100%	11,201	100%

Tas trastuzumab, *pegy* pegylated, *CML* chronic myeloid leukaemia

presence of comorbid conditions and frailty. Therefore, wide variation in diagnostic testing occurs [18]. Genetic testing undertaken in the CUP and ovarian cancer groups may have influenced the choice and cost of therapies to an unknown extent, but we suspect this occurred for only a small number of patients in both groups. This is because both the prevalence of actionable variants is small and access to personalised therapies has increased only in more recent years in Australia (e.g. access to olaparib for BRCA1/2-positive patients with ovarian cancer occurred after the study). Furthermore, it was previously reported that doctors managing CUP will prescribe therapies on the suspicion of the origin of tumour without molecular testing confirmation [5].

For rare cancers such as ovarian cancer and CUP, detailed disease costs using a 'bottom-up' approach were not possible in previous reports by the Australian Institute of Health and Welfare. The latest 2021 report from 2018 to 2019 data shows CUP cost the Australian health system AU$592 million compared with AU$130 million for ovarian cancer [19]. Over 70% of these costs are for hospitalisations (including highly specialised pharmaceuticals), which are partially captured in our data. PBS pharmaceuticals cost AU$94 million for CUP and AU$35 million for ovarian cancer, while imaging for CUP cost AU$17 million versus AU$3 million for ovarian cancer [19]. These data broadly agree with our findings and provide the overall costs to the health system. While useful, our more granular approach provides a detailed account of the cost differences to Medicare for diagnosing CUP and ovarian cancer and their early treatment. This information is valuable for health service and resource planning and can contribute to future cost-effectiveness and cost-benefit analyses of new interventions that require micro-level data.

With the increased use of genomic profiling, it is plausible that the protracted puzzle of diagnosing CUP may be shorter and more informative for clinical practice [20, 21]. Methods such as genomic sequencing may assist in identifying the primary tumour site and thus guide effective treatments for CUP, including access to targeted cancer therapies. While diagnostic tests including genomic profiling are expensive, earlier and comprehensive testing is likely to produce benefits for patients and families. As found in rare monogenic disorders, genomic testing has also produced significant cost-savings through earlier use and discontinuation of other planned investigations [22, 23]. In future, pharmacogenomic analysis may also help to identify patients that may or may not benefit from certain therapies, avoiding the potential toxicity and high costs of therapies the patient is unlikely to benefit from.

Our study has several limitations. The use of administration data for cost-analyses means there is a lack of detail important for researchers. In our case, we lacked data on exactly what services were for cancer, not other comorbidities. Many MBS items have non-specific descriptions and cannot be definitive for assessing cancer (e.g. general practitioner and specialist consultations). Nevertheless, metastatic cancer is a very serious diagnosis needing urgent medical attention, and we can reasonably assume the resources leading up to diagnosis were largely due to CUP and ovarian cancers. Data on comorbidities were not collected in the clinical CUP study and were therefore derived for both groups through the use of a validated comorbidity index [12]. The study also excludes hospitalisation data including inpatient and emergency presentations that would have occurred in the post-diagnosis phase for patients requiring hospital care for cancer and adverse events from treatments

for both cancer groups. Reeve et al. (2017) estimated costs in an elderly Australian cancer cohort of AU$22,852 for a mean of three episodes per person, in the last 6 months of life [24]. Linkage to hospital data is preferable to assess the full coverage of healthcare costs. Also excluded were patient-incurred costs to keep with the Medicare provider perspective. This meant that costs accrued for co-payments, travel and parking expenses were in addition to those presented here. Finally, the comparison of a mixed-gender cancer type for CUP with a single-gender group for ovarian cancer may have influenced the findings; however, the key risk factors for healthcare costs relating to socio-demographics and comorbidities were adjusted for in the modelling and accounted for the major influences on costs. Balanced with these limitations, our study had individual-level comparable data across two relatively rare cancer groups using high-quality linked data sources. It is one of the few studies that have documented the healthcare costs leading up to diagnosis and beyond for CUP and provides benchmark costs for evaluating advances in treatment or speedier diagnosis and potential cost reductions.

In general, due to advances in therapies, overall cancer survival rates continue to improve, but there is increasing interest in how patient outcomes can be improved when cancers are detected earlier before they have spread, when tumours are still relatively curable [25, 26]. Delays in receiving cancer care services can arise due to presentational, diagnostic or treatment delays. Timeliness in accessing care and long wait-time intervals between lung cancer diagnosis and treatment have been observed to highlight where improvements in service delivery can be made [25, 27]. Influencing the speed of cancer diagnosis relates to both patient factors (e.g. education, health literacy, access to health services) and provider factors (e.g. medical education, coordinated interprofessional communication, availability of testing technologies) [28]. The rapidly progressive nature of the disease and poor prognosis of CUP patients combined with a lack of standard treatments indicates the need for earlier diagnosis.

In conclusion, costs to Medicare are substantially higher for patients with CUP than those for ovarian cancer 6 months either side of diagnosis. There is potential for an earlier diagnosis of CUP to avert healthcare costs and improve patient outcomes.

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Declarations

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Conflict of interest Authors LGG, PS, RWT, LM and CW declare that they have no conflict of interest. Author PMW has received grant funding from AstraZeneca for an unrelated study of ovarian cancer and a speaker's fee from AstraZeneca.

Ethics approval Ethical approval for this economic sub-study was waived by the QIMR Berghofer Human Ethics Research Committee P3609. The clinical CUP study was approved by the Peter MacCallum Cancer Centre Human Ethics Research Committee and all participating sites.

Consent to participate Participants were informed about the aim of the study, and participant consent was required to start data collection, including separate consent to obtain Medicare data from Services Australia, the Australian Government.

Consent for publication (from patients/participants) Participants were informed about the aim of this study, including the intent to publish findings, and participant consent was required to start the data collection.

Data availability The data used in this study are unable to be shared under the approval provided by data custodians of Services Australia under a Commonwealth of Australia contract.

Code availability The data analysis code written in STATA is available from the authors upon request

Author contributions LGG performed the statistical modelling and data analysis and produced the first written draft of the paper. All authors contributed to conceptualisation, data analysis interpretation, writing and editing. LM and RWT provided clinical expertise, knowledge and intellectual inputs and obtained grants and conducted data collection. CW contributed to data cleaning and management. All authors were involved in writing and editing and approved the final version.

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