Cancer Epidemiology 61 (2019) 1–7

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Health-related predictors of cancer registry-notified cancer of unknown primary site (CUP)

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ARTICLE INFO

Keywords:
Cancer of unknown primary
Cohort
Epidemiology
Health services
Consultations
Comorbidity

ABSTRACT

Background: The relationship between comorbid disease and health service use and risk of cancer of unknown primary site (CUP) is uncertain.

Methods: A prospective cohort of 266,724 people aged 45 years and over in New South Wales, Australia. Baseline questionnaire data were linked to cancer registration, health service records 4–27 months prior to diagnosis, and mortality data. We compared individuals with incident registry-notified CUP (n = 327; 90% C80) to two sets of randomly selected controls (3:1): (i) incident metastatic cancer of known primary site (n = 977) and (ii) general cohort population (n = 981). We used conditional logistic regression to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Results: In fully adjusted models incorporating sociodemographic and lifestyle factors, people with cancer registry-notified CUP were more likely to have fair compared with excellent self-rated overall health (OR 1.78, 95% CI 1.01–3.14) and less likely to self-report anxiety (OR 0.48, 95% CI 0.24 − 0.97) than those registered with metastatic cancer of known primary. Compared to general cohort population controls, people registered with CUP were more likely to have poor rather than excellent self-rated overall health (OR 6.22, 95% CI 1.35–28.6), less likely to self-report anxiety (OR 0.28, 95% CI 0.12 − 0.63), and more likely to have a history of diabetes (OR 1.89, 95% CI 1.15–3.10) or cancer (OR 1.62, 95% CI 1.03–2.57). Neither tertiary nor community-based health service use independently predicted CUP risk.

Conclusion: Low self-rated health may be a flag for undiagnosed cancer, and an investigation of its clinical utility in primary care appears warranted.

1. Introduction

Cancer of unknown primary site (CUP) has a poor prognosis, with 5-year survival rates around 15% [1]. A diagnosis of CUP follows the clinical or histopathological diagnosis of one or more metastatic lesions and an undetected primary site, with further diagnostic investigations guided by the extent of disease and performance status [2]. The clinical presentation is highly heterogeneous and the late-stage at diagnosis appears related to an aggressive tumour biology, non-specific symptoms or symptom masking by one or more concurrent illnesses [3].

People with complex and life-threatening health conditions have an increased risk of CUP. For example, population-based studies of HIV/AIDS [4] and solid organ transplantation cohorts [5] consistently show an elevated risk of CUP compared to the general population. A heightened risk has also been observed in people with diabetes [6], autoimmune disease [7] and those with renal failure, liver disease, hypertension, congestive heart failure or psychotic illness [3]. However, none of these studies accounted for shared behavioural risk factors, the most common and convincing of which is smoking where the comparison group is the general cohort population [8–10].

Reduced access to, or utilisation of, primary care may also increase the risk of being diagnosed with CUP, as evident from excess emergency department presentations prior to CUP diagnosis [3,11] and higher CUP incidence rates in disadvantaged subgroups [12–14]. The relationship

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https://doi.org/10.1016/j.canep.2019.05.001
Received 21 March 2019; Received in revised form 2 May 2019; Accepted 5 May 2019
Available online 10 May 2019
1877-7821/

Table 1
Age- and sex- adjusted association between health conditions and risk of CUP.

Health measure	CUP (n = 327)	Metastatic cancer known primary controls (n = 977)		General cohort population controls (n = 981)	
	N	N	OR (95% CI)	N	OR (95% CI)
Number of self-reported comorbidities (continuous variable)[1]	–	–	1.06 (0.97–1.15)	–	1.02 (0.93–1.13)
Self-reported health condition					
Diabetes	61	127	1.58 (1.11–2.26)	84	2.36 (1.54–3.62)
Stroke	26	43	1.41 (0.84–2.38)	26	1.33 (0.70–2.56)
Heart disease	78	166	1.12 (0.81–1.57)	105	1.30 (0.89–1.91)
Hypertension	161	451	0.96 (0.74–1.25)	386	1.03 (0.76–1.39)
Blood clot	22	60	0.95 (0.56–1.60)	53	0.81 (0.45–1.47)
Asthma/Hay fever	55	181	0.99 (0.70–1.39)	220	0.78 (0.54–1.15)
Depression	38	106	1.22 (0.80–1.84)	147	0.97 (0.62–1.52)
Anxiety	13	63	0.61 (0.32–1.15)	82	0.51 (0.26–0.99)
Self-reported family history of cancer	138	398	1.16 (0.89–1.51)	384	1.07 (0.79–1.44)
Self-reported personal cancer history[2]	92	199	1.36 (1.01–1.84)	131	1.77 (1.22–2.56)
Registered personal cancer history[2]	69	131	1.52 (1.09–2.12)	97	1.70 (1.14–2.53)
Hospital-recorded health conditions[3]					
Diabetes, uncomplicated	10	14	2.41 (1.04–5.60)	6	4.55 (1.42–14.6)
Diabetes, complicated	20	38	1.61 (0.89–2.89)	17	3.14 (1.50–6.60)
Cardiac arrhythmia	39	61	1.41 (0.91–2.20)	28	2.19 (1.16–4.16)
Congestive heart failure	13	16	1.92 (0.89–4.14)	< 5[4]	12.2 (2.26–65.9)
Uncomplicated hypertension	40	76	1.33 (0.87–2.02)	50	1.66 (1.02–2.72)
Peripheral vascular disease	12	11	2.43 (1.00–5.88)	6	4.07 (1.26–13.1)
Chronic pulmonary disease	17	35	1.11 (0.60–2.04)	8	5.02 (1.76–14.3)
Renal failure	10	21	1.05 (0.48–2.31)	< 5[4]	6.60 (1.32–33.0)
Fluid and electrolyte disorder	23	33	1.70 (0.96–2.99)	13	2.21 (0.92–5.29)
Iron deficiency	6	16	0.92 (0.35–2.44)	9	1.53 (0.44–5.35)
Depression	< 5[4]	7	1.13 (0.28–4.62)	5	2.87 (0.51–16.3)

– Not applicable.
[1] Heart disease/heart attack/angina, stroke, hypertension, high cholesterol, diabetes, blood clot, enlarged prostate, asthma/hay fever, depression/anxiety, Parkinson's disease, osteoporosis, thyroid disease reported in cohort baseline questionnaire.
[2] Excluding non-melanocytic skin cancer.
[3] 4–27 months prior to diagnosis; only individuals with one or more hospitalisations during this period.
[4] Exact cell size suppressed for privacy reasons.

between the pattern and type of health service use and later CUP diagnosis has not been investigated. The identification of population subgroups at high risk of CUP may result in earlier detection and thus enhanced treatment options and survival. We sought to identify the health conditions, self-rated health status, and health service use that is independently associated with a cancer registry notification of CUP in a prospective Australian cohort study.

2. Methods

2.1. Study population

The Sax Institute's 45 and Up Study [15] is a prospective Australian cohort study with comprehensive information on self-reported lifestyle behaviours and a range of health, functional and social measures at baseline. Eligible participants were randomly selected from the Department of Human Services (formerly Medicare Australia) enrolment database which provides near complete coverage of the population. People more than 80 years of age and residents of rural and remote areas were oversampled. A total of 266,933 individuals aged at least 45 years and resident in NSW joined the study by completing a postal questionnaire between January 2006 and December 2009 and giving signed consent for linkage of their information to routine health databases. About 18% of those invited participated, corresponding to 11% of the NSW population aged 45 years and over.

Australia's publicly funded health care system provides all citizens and permanent residents with a range of health services including treatment in public hospitals, subsidised treatment in private hospitals, subsidised outpatient (community) services including consultations, procedures and tests, and subsidised medicines. Records of these transactions are made available for ethically approved health research. The 45 and Up Study cohort was probabilistically linked to NSW population-based health datasets by the Centre for Health Record Linkage: (i) the NSW Cancer Registry (NSWCR), a population-based registry of invasive cancer diagnoses (excluding basal and squamous cell carcinoma of the skin) in NSW 1994–2012; (ii) the NSW Admitted Patients Data Collection 2001–2015; (iii) the NSW Emergency Department Data Collection 2005–2016; and (iv) the NSW Registry of Births, Deaths and Marriages 2006 – 2016. The cohort was deterministically linked to Medicare Benefits Schedule (MBS) 2001–2015 and Pharmaceutical Benefits Scheme (PBS) 2004–2015 data by the Sax Institute using a unique identifier supplied to the Department of Human Services (DHS). We excluded 209 cohort participants because they did not have a single linked MBS or PBS record.

Cases were individuals with an incident cancer registry diagnosis of CUP on the basis of the following WHO International Classification of Diseases for Oncology (third edition; ICD-O-3) topography codes used to register CUP in Australia: C80 (unknown primary site), C76 (other and ill-defined sites), C26 (other and ill-defined digestive organs) or C39 (other and ill-defined sites within respiratory system and intrathoracic organs). We included all incident cases registered with CUP, regardless of the number or location of metastases, as this information was not recorded by the population-based cancer registry.

We randomly selected two sets of controls from the remaining cohort participants: (i) incident metastatic cancer and (ii) the general 45 and Up Study Cohort (hereafter termed "general cohort population"), selecting up to three controls per case using incidence density sampling with replacement [16].

The metastatic cancer controls consisted of individuals with an incident cancer registry diagnosis of solid metastatic malignancy of

Table 2
Age- and sex- adjusted association between baseline self-rated health and risk of CUP.

Self-rated health at baseline	CUP (n = 327)	Metastatic cancer known primary controls (n = 977)		General cohort population controls (n = 981)	
	N	N	OR (95% CI)	N	OR (95% CI)
Long-term illness or disability necessitating help with daily tasks	50	57	2.36 (1.51–3.69)	44	2.87 (1.68–4.91)
Extent to which health limits daily tasks[1]					
None	39	240	1.00 (ref)	320	1.00 (ref)
Minor	34	110	1.80 (1.05–3.06)	141	1.35 (0.77–2.37)
Mild	41	154	1.14 (0.68–1.91)	178	0.92 (0.52–1.61)
Moderate	65	182	1.40 (0.87–2.25)	161	1.28 (0.76–2.15)
Severe	98	174	2.15 (1.36–3.41)	101	2.88 (1.74–4.77)
Overall health					
Excellent	24	104	1.00 (ref)	150	1.00 (ref)
Very good	73	281	0.89 (0.52–1.52)	384	0.89 (0.50–1.57)
Good	120	375	1.14 (0.69–1.91)	328	1.62 (0.93–2.80)
Fair	79	135	1.91 (1.10–3.32)	77	4.36 (2.29–8.31)
Poor	13	32	1.29 (0.56–2.99)	9	4.15 (1.24–13.9)
Quality of life					
Excellent	42	186	1.00 (ref)	217	1.00 (ref)
Very good	79	302	0.94 (0.60–1.46)	383	0.90 (0.55–1.46)
Good	113	296	1.34 (0.88–2.06)	253	1.57 (0.98–2.53)
Fair	50	97	1.70 (1.02–2.83)	68	2.28 (1.24–4.17)
Poor	12	19	2.25 (0.93–5.48)	10	6.02 (1.89–19.2)
Teeth and gums					
Excellent	18	68	1.00 (ref)	90	1.00 (ref)
Very good	43	198	0.80 (0.42–1.56)	253	0.84 (0.42–1.67)
Good	108	341	1.31 (0.72–2.41)	348	1.34 (0.71–2.52)
Fair	78	218	1.26 (0.67–2.36)	187	1.48 (0.76–2.88)
Poor	45	70	2.62 (1.32–5.22)	59	2.86 (1.36–6.02)
Vision					
Excellent	21	81	1.00 (ref)	112	1.00 (ref)
Very good	76	265	1.23 (0.70–2.18)	283	1.23 (0.66–2.29)
Good	139	396	1.47 (0.85–2.53)	414	1.40 (0.76–2.57)
Fair	56	169	1.27 (0.70–2.32)	122	1.77 (0.90–3.49)
Poor	13	24	1.99 (0.84–4.70)	19	2.62 (0.88–7.81)
Memory					
Excellent	28	142	1.00 (ref)	125	1.00 (ref)
Very good	82	263	1.94 (1.17–3.20)	317	1.02 (0.59–1.76)
Good	117	355	1.81 (1.13–2.90)	369	1.06 (0.61–1.84)
Fair	65	140	2.11 (1.25–3.55)	119	1.55 (0.84–2.88)
Poor	17	37	2.33 (1.10–4.97)	21	2.43 (0.95–6.23)
Hearing loss	167	458	0.95 (0.71–1.26)	362	1.10 (0.81–1.51)
Fallen over in last 12 months	92	184	1.46 (1.08–1.99)	136	1.61 (1.10–2.36)

[1] Missing responses for 50 cases, 117 metastatic cancer controls and 80 general population controls.

known primary site, also regardless of the number or location of metastases. As for CUP patients, the first manifestation of this cancer was metastatic disease, either distant or regional. We matched the metastatic cancer controls to cases by month and year of enrolment in the cohort and by month and year of cancer diagnosis. The general cohort population were matched to cases by month and year of enrolment and were alive at the time of case diagnosis. For both sets of controls we allowed variations of up to one-month in the month of enrolment and/or diagnosis. We excluded participants diagnosed with CUP or metastatic cancer of known primary within three months of the month of cohort enrolment [3] to minimise the impact of undiagnosed cancer on their self-reported lifestyle characteristics and self-rated health.

The study was approved by the NSW Population and Health Services and Human Research Ethics Committee (2012/11/428) and the 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee (HREC 15408).

2.2. Ascertainment of health conditions and self-rated health

We ascertained select self-reported health conditions and family history of cancer from the 45 and Up Study baseline questionnaire. We also used the Elixhauser comorbidity index to identify health conditions from primary and secondary diagnosis codes in hospital records prior to the month of diagnosis (or matching month and year of follow-up for general population controls). As it was important to exclude hospitalisations associated with the diagnosis or treatment of the cancer (CUP or metastatic cancer of known origin), we disregarded hospitalisations during the month of diagnosis and the preceding 3 months, creating a look-back period of 4–27 months. Additionally we ascertained all registered notifiable cancers prior to diagnosis of the cancers of interest (or equivalent for general population controls).

In the baseline questionnaire, cohort participants reported whether they had a long-term illness or disability necessitating help with daily tasks, and they rated the extent to which their health limited their daily tasks including vigorous or moderate activities, lifting or carrying shopping, climbing one or several flights of stairs, walking several distances, bending, kneeling and stooping and bathing or dressing oneself. We used these measures to calculate The Medical Outcomes Study Physical Functioning Scale in order to ascertain physical functioning (none, minor, mild, moderate, severe) [17]. They further rated their overall health, quality of life, teeth and gum health, vision and memory (excellent, very good, good, fair, poor), and reported whether they had hearing loss or had fallen over in the 12 months prior to baseline.

2.3. Ascertainment of health service utilisation

We quantified all subsidised health care utilised in the 4–27 months

Table 3
Age- and sex- adjusted association between health service use and risk of CUP.

Health service use prior to diagnosis	CUP (n = 327)	Metastatic cancer known primary controls (n = 977)		General cohort population controls (n = 981)	
	N	N	OR (95% CI)	N	OR (95% CI)
Tertiary care[1]					
≥1 hospitalisation	205	490	1.34 (1.02–1.76)	387	1.41 (1.04–1.90)
≥1 emergency department visit	130	279	1.35 (1.03–1.78)	218	1.37 (1.00–1.88)
Consultations[1]					
General practitioner (GP)					
Low	82/52[2]	332	1.00 (ref)	319	1.00 (ref)
Moderate	93/65[2]	323	0.91 (0.64–1.31)	333	1.01 (0.63–1.60)
High	152/210[2]	322	1.23 (0.88–1.73)	329	1.74 (1.13–2.67)
Specialist/consultant physician					
Low	87/64[2]	338	1.00 (ref)	293	1.00 (ref)
Moderate	98/100[2]	292	1.22 (0.87–1.72)	366	1.16 (0.76–1.78)
High	142/163[2]	347	1.23 (0.89–1.70)	322	1.30 (0.86–1.99)
Allied health practitioner					
Low	93/93[2]	278	1.00 (ref)	285	1.00 (ref)
Moderate	130/84[2]	423	1.00 (0.72–1.38)	332	0.87 (0.58–1.31)
High	104/150[2]	276	1.06 (0.74–1.50)	364	0.92 (0.63–1.33)
Nurse					
Low	174/174[2]	617	1.00 (ref)	627	1.00 (ref)
Moderate/High	153/153[2]	360	1.36 (1.04–1.77)	354	1.13 (0.83–1.56)
≥1 GP: home, institution or hospital[3]	39	53	1.48 (0.93–2.35)	36	1.49 (0.85–2.60)
≥1 GP: management and multidisciplinary care plans[4]	139	323	1.29 (0.98–1.70)	268	1.24 (0.91–1.69)
≥1 specialist: complex case[5]	38	77	1.51 (0.97–2.33)	52	1.98 (1.17–3.37)
Continuity of GP care by usual provider[1]					
Low	104/93[2]	296	1.00 (ref)	293	1.00 (ref)
Moderate	95/104[2]	293	0.92 (0.65–1.30)	297	0.90 (0.61–1.32)
High	109/11[2]	322	0.96 (0.65–1.44)	297	1.01 (0.64–1.59)
Cancer screening (self-reported)[6]					
Bowel	159	465	1.09 (0.83–1.44)	468	0.78 (0.56–1.07)
Breast	110	382	0.78 (0.29–2.11)	464	0.49 (0.15–1.62)
Prostate (PSA test)	146	377	1.20 (0.75–1.93)	326	1.16 (0.65–2.07)

[1] 4–27 months prior to month of diagnosis.
[2] The first number is the number of cases in the tertile defined by the metastatic cancer known primary controls and the second number is the number of cases in the tertile defined by the general population controls.
[3] MBS item numbers 4, 24, 37, 47, 58, 59, 60, 65, 5003, 5023, 5043, 5063, 5220, 5223, 5227, 5228.
[4] MBS item numbers 721, 723, 729, 731, 732, 735, 739, 743, 747, 750, 758, 820, 822, 823, 825, 826, 828, 830, 832, 834, 835, 837, 838, 900.
[5] MBS item numbers 132, 133.
[6] Prior to baseline.

Table 4
Health conditions, self-reported health status and health service use predictive of CUP.

Factor	CUP (n = 299/ 298)[3]	Metastatic cancer known primary controls (n = 914)		General cohort population controls (n = 931)	
	N	N	OR (95% CI)[1]	N	OR (95% CI)[2]
Self-rated overall health					
Excellent	24	103	1.00 (ref)	148	1.00 (ref)
Very good	67	278	0.76 (0.44–1.32)	375	0.73 (0.40–1.32)
Good	120/119[3]	370	1.13 (0.68–1.89)	324	1.48 (0.84–2.63)
Fair	76	132	1.78 (1.01–3.14)	75	3.44 (1.70-6.93)
Poor	12	31	1.08 (0.44–2.62)	9	6.22 (1.35–28.6)
Self-reported anxiety	12	57	0.48 (0.24–0.97)	79	0.28 (0.12–0.63)
Self-reported diabetes	56		–	77	1.89 (1.15–3.10)
Registered personal cancer history[4]	63		–	93	1.62 (1.03–2.57)

– Not applicable.
[1] Adjusted for age, self-rated overall health, self-reported anxiety and self-reported educational attainment.
[2] Adjusted for age, self-rated overall health, self-reported anxiety, self-reported diabetes, registered personal cancer history, self-reported educational attainment and smoking status.
[3] One CUP case had missing smoking history data and thus was excluded from the final model comparing CUP to general cohort population controls.
[4] Excluding non-melanocytic skin cancer.

prior to the month of diagnosis, including hospitalisations, emergency department visits and consultations with general practitioners (GP), specialists, allied health practitioners and nurses. This two-year time period was chosen to precede the onset of signs or symptoms related to the cancer diagnosis. For each service, we classified the number of consultations as low, moderate or high, with the cut-points for these categories based on the tertile distribution of the number of consultations for controls. We also identified GP consultations in the home, an institution or hospital, as a marker of patient frailty. We further distinguished GP consultations for the preparation, contribution or review of a GP management plan or multidisciplinary/team care plan, as a marker of chronic disease. We separately identified specialist

consultations for the initial assessment or review of patients with at least two comorbidities, classified as complex cases.

In Australia, individuals may visit more than one GP, so we additionally assessed continuity of care for individuals with more than three GP consultations over the two year period [18,19]. We defined a patient's principal GP as the GP with the highest number of consultations; if two GPs had the same number of consultations, we randomly chose one as the principal. We calculated three common continuity of care metrics [20], namely (i) usual provider continuity (UPC) [21], the proportion of care provided by the principal GP; (ii) Bice-Boxerman continuity (BBC), reflecting the number of visits to different GPs and their distribution (the dispersion of care); and the (iii) sequential continuity (SECON), which considers the order of consultations. The three metrics were classified based on the tertile distribution in controls, and also fixed categories as per Tran et al. [22].

In the baseline questionnaire, cohort participants reported whether they had ever been screened for bowel cancer, breast cancer, or prostate disease.

2.4. Statistical analysis

For each set of controls we used conditional logistic regression to estimate the odds of CUP associated with specific health conditions, self-rated health and health service use. We first modelled each factor adjusted by age and sex; for those variables with $p < 0.2$, we assessed the correlation between pairs of factors using Cramér's V statistic. We also considered self-reported attained education level and smoking history as potential confounding factors, as identified in parallel analyses [10]. Factors with Cramer's V correlation coefficient ≥ 0.25 were considered correlated. We built conditional logistic regression models using backward elimination, stopping when all factors were significantly associated with CUP ($p < 0.05$). We built as many models as combinations of non-correlated variables, and the model with the lowest Akaike Information Criterion (AIC) was selected as the final multivariable model.

3. Results

We identified 327 incident CUP cases, 977 incident solid metastatic cancer of known primary site controls, and 981 general cohort population controls over a median of 33 months follow-up (interquartile range, IQR 21–46 months). The median age at diagnosis of CUP was 76 years (IQR 66–82 years). Most CUP cases were registered with the ICD-O-3 code C80 (n = 295, 90%), the remainder were registered with C26 (n = 21, 6%) and C76 (n = 11, 3%), none were registered with C39. The most common primary sites for the solid metastatic cancer controls were breast (C50; n = 168), bronchus and lung (C34; n = 163), colon (C18; n = 152), prostate (C61; n = 123) and rectum (C20; n = 57).

3.1. CUP compared to metastatic cancer of known primary site

In age- and sex-adjusted analyses, people registered with a diagnosis with CUP were more likely to have a history of diabetes and a prior cancer diagnosis, identified by self-report or through linked health records (Table 1). They were also more likely to have a history of peripheral vascular disease in hospitalisation records.

Individuals registered with a CUP diagnosis were twice as likely to report a history of long-term illness or disability that necessitated help with daily tasks, and to rate the disruption to daily tasks as severe (Table 2). They were more likely to rate their overall health as fair, and their oral health and memory, as poor. Further, they were more likely to have fallen over in the last 12 months.

Between 4 to 27 months prior to diagnosis, compared to metastatic cancer controls, people registered with CUP were more likely to have been hospitalised, to have had an emergency department visit, and to consult a nurse more frequently (Table 3). They appeared to be no more or less likely to consult a GP, specialist, or allied health practitioner, but there was weak evidence that they were more likely to have a GP or specialist consultation that indicated frailty or complexity. CUP cases had very similar levels of continuity of care relative to people diagnosed with a known primary site, regardless of the measure (only usual provider shown in Table 3) or categorisation of continuity, and there was no difference in their self-reported uptake of cancer screening tests.

In the final multivariable model controlling for age and attained level of education, the factors associated with risk of being registered with CUP were fair self-rated overall health and being less anxious (Table 4). No health service-related variables were significantly associated with risk of CUP after adjustment.

3.2. CUP compared to general population

Compared to general population controls, people registered with CUP were more likely to have a history of diabetes or cancer, identified by self-report or through linked health records. They were less likely to self-report anxiety, and more likely to have a medical record indicating congestive heart failure, cardiac arrhythmia, peripheral vascular disease, hypertension, chronic pulmonary disease or renal failure (Table 1).

Individuals registered with CUP were nearly three times more likely to report a history of long-term illness or disability that necessitated help with daily tasks, and to rate the disruption to daily tasks as severe (Table 2). They were also more likely to rate their overall health, their quality of life, and their teeth and gum health as poor, and to have fallen over in the last 12 months.

With respect to health service use in the 4–27 months prior to diagnosis, the comparison of CUP cases and general population controls was very similar to that for metastatic cancer controls, with three exceptions (Table 3); people registered with CUP were not more likely to have a nurse consultation, but they attended GPs more frequently, and they were more likely to have at least one complex case consultation with a specialist.

In the final multivariable model controlling for age, attained level of education and smoking status, the factors associated with an increased risk of CUP compared with general population controls were fair or poor self-rated overall health, a history of diabetes, and a prior cancer diagnosis (Table 4). A self-reported history of anxiety reduced the risk of being registered with CUP. Health service use was not significantly associated with risk of CUP after adjustment.

The previous cancer diagnoses (at least five cases, in order of descending frequency) were prostate, skin, haematological, breast, bladder and colorectum for the CUP cases, and prostate, breast, skin, colorectum and haematological for the general population controls.

4. Discussion

In a contemporary cohort of middle- and older-aged Australian adults, low self-rated overall health and specific health conditions, but not tertiary or community-based health service use in the 4–27 months prior to diagnosis, independently predicted risk of cancer registry-notified CUP compared with metastatic cancer of known primary site. These findings support our limited understanding of CUP in several ways. It is more common in less healthy individuals who are potentially unfit for invasive diagnostic investigations. It is also possible that disease progression in CUP is rapid or perhaps the symptoms are masked or attributed to comorbid conditions. The novel association with poor self-rated overall health deserves further exploration as an opportunity for earlier cancer diagnosis.

To the best of our knowledge, no prior study has examined the relationship between self-rated overall health and risk of subsequent CUP registration. Self-rated health is understood to be a complex cognitive assessment incorporating biological, psychological and social factors, as well as age, gender, and culture [23,24]. It is a reliable and widely used

measure of current health status that consistently independently predicts morbidity and mortality [23,25,26]. While the relationship between self-rated health and performance score is unknown, it was strongly associated with performance-based physical function in a study of older adults [27], and there is evidence it may be a stronger predictor of health outcomes than objective measures of health status [28,29]. Additionally, it has been suggested that self-rated health should be used in general practice to screen for undiagnosed health conditions, and to guide informed questioning and patient empowerment [30,31]. This association is worthy of further study, particularly given a Norwegian cohort study observed a strong association between poor self-rated health and increased lung cancer risk, but not risk of any cancer or breast, prostate or colon cancer [32]. In the Norwegian study, as in ours, self-rated health remained a significant predictor after adjustment for relevant lifestyle factors.

After adjustment for sociodemographic and lifestyle factors, individuals registered with CUP did not appear to attend tertiary health services, GPs or other health care practitioners more or less often during the 4–27 months prior to diagnosis than either control group. There is no prior data on the association between the pattern and type of "routine" health service use and the risk of a CUP registration. The finding of a reduced risk of CUP in those with self-reported anxiety is novel and may suggest that individuals who are anxious may be more likely to query new signs or symptoms of ill health with their GP.

Compared with the general population cohort we found an increased risk of CUP in people with a personal history of diabetes, consistent with a Swedish cohort study of cancer-registry notified CUP that adjusted for age and sex [6]. In our study this association was observed regardless of whether the diabetes was ascertained via self-report or in hospital records, and somewhat weakened by adjustment for smoking history and the other independent risk factors. Confirmation in larger cohorts, with more detailed risk stratification in relation to the type, duration and management of diabetes, is required before this finding can be used to guide care for people with diabetes. Our finding of a higher incidence of cancer prior to CUP registration is consistent with the previously observed higher risk of cancer after CUP diagnosis [33], and may indicate shared behavioural and genetic risk factors, although this association was also robust to adjustment for smoking and sociodemographic factors. Other than an absence of lung cancers, the site distribution of the previous cancers in our CUP series was broadly similar to those observed after CUP diagnosis by Shu et al. [33] Nevertheless, we must acknowledge the likelihood that some of our CUP cases will have had unrecognised secondary cancer to their prior tumour, and this would have biased towards a positive association with prior cancer.

Our analysis was based on a large, contemporary prospective cohort study with comprehensive data on sociodemographic and lifestyle risk factors and objective measures of health service use. Additionally, incident cancers and deaths were ascertained by high-quality population-based registries. We used two sets of controls to generate a complete risk profile in relation to individuals diagnosed with metastatic cancer of known primary site and to unselected cohort participants. Although we minimised confounding by adjusting for relevant demographic and lifestyle characteristics [10], we cannot discount residual confounding due to unmeasured health conditions or other factors. We are also likely to have some degree of misclassification, for example due to health status changing between cohort baseline and cancer diagnosis.

The participation rate for the 45 and Up Study was 18% [15], and cohort participants have been shown to be healthier on average compared with the general population [34,35]. Even so, risk estimates calculated from within-cohort comparisons are expected to be valid. Despite the large cohort, our power for evaluating CUP risk may have been insufficient, and we had no information on the location or extent of metastatic disease from the population-based cancer registry records. We were also unable to differentiate CUP subgroups (for example: confirmed and inadequately evaluated) using the cancer registry data alone. Finally, some patients may have presented to health services with signs and symptoms related to their cancer diagnosis more than three months prior to their month of diagnosis, and thus we will have over-estimated their regular health service use.

We have identified several novel associations worthy of further investigation to better understand the modifiable risk factors for this high-burden malignancy. Of particular interest is the association with low self-rated overall health; this may warrant exploration as an opportunity for earlier cancer diagnosis.

Authorship contribution statement

Conception and design CV, TD, RLW, SAP, OPC.
Data analysis OPC.
Drafting the article CV.
Revising the article with important intellectual content OPC, TD, RLW, AS, MVL, JR, MAL, CG, SAP.

Conflict of interest statement

None declared.

Acknowledgments

This work was supported by a Cancer Institute of New South Wales (NSW) Epidemiology Linkage Program Grant (10/EPI/2-06). The funder had no role in the study design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication. We thank the 45 and Up Study, the Department of Human Services (DHS), the NSW Ministry of Health, and the NSW Cancer Registry for providing the data used for this study.

This research was completed using data collected through the 45 and Up Study (www.saxinstitute.org.au). The 45 and Up Study is managed by the Sax Institute in collaboration with major partner Cancer Council NSW; and partners: the National Heart Foundation of Australia (NSW Division); NSW Ministry of Health; NSW Government Family & Community Services – Ageing, Carers and the Disability Council NSW; and the Australian Red Cross Blood Service. We thank the many thousands of people participating in the 45 and Up Study.

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