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Demographic, social and lifestyle risk factors for cancer registry-notified cancer of unknown primary site (CUP)

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ABSTRACT

Background: Little is known about the risk factors for cancer of unknown primary site (CUP). We examined the demographic, social and lifestyle risk factors for CUP in a prospective cohort of 266,724 people aged 45 years and over in New South Wales, Australia.

Methods: Baseline questionnaire data were linked to cancer registration, hospitalisation, emergency department admission, and mortality data. We compared individuals with incident cancer registry-notified CUP (n = 327) to two sets of controls randomly selected (3:1) using incidence density sampling with replacement: (i) incident cancer registry-notified 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 a fully adjusted model incorporating self-rated overall health and comorbidity, people diagnosed with CUP were more likely to be older (OR 1.05, 95% CI 1.04–1.07 per year) and more likely to have low educational attainment (OR 1.77, 95% CI 1.24–2.53) than those diagnosed with metastatic cancer of known primary. Similarly, compared to general cohort population controls, people diagnosed with CUP were older (OR 1.10, 95% CI 1.08–1.12 per year), of low educational attainment (OR 1.69, 95% CI 1.08–2.64), and current (OR 3.42, 95% CI 1.81–6.47) or former (OR 1.95, 95% CI 1.33–2.86) smokers.

Conclusion: The consistent association with educational attainment suggests low health literacy may play a role in CUP diagnosis. These findings highlight the need to develop strategies to achieve earlier identification of diagnostically challenging malignancies in people with low health literacy.

1. Introduction

Cancer of unknown primary site (CUP) is a high-burden malignancy, with high mortality rates and marginal advances in survival over time [1–3]. The clinical presentation of CUP is highly heterogeneous, ranging from a single metastatic site to disseminated disease. The primary site is classified as unknown after clinically indicated investigations, either exhaustive if the cancer is considered treatable, or limited in advanced disease where ongoing diagnostic investigations is considered unlikely to improve patient survival or quality of life [4]. Indeed, only a minority of CUP cases notified to population-based cancer registries have histological confirmation of metastatic cancer [3,5].

The risk factors for CUP are poorly defined. Older age is a consistently strong risk factor, while male gender, socio-economic deprivation, black race, distance from medical services, and non-migrant populations have been shown to increase risk in one or more studies [3,5–9]. In two prospective cohort studies, an increased risk of CUP was observed for smokers [10,11], but no other lifestyle factors. There have been no assessments of the association between a cancer registry notification of CUP and social connectedness. Furthermore, no prior studies have comprehensively adjusted for potential confounders, such as comorbid disease. We sought to identify the independent demographic, social and lifestyle-related risk factors for a cancer registry notification of CUP in a prospective Australian cohort study.

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2. Methods

2.1. Study population

The Sax Institute's 45 and Up Study [12] is a prospective cohort study with comprehensive information on self-reported lifestyle behaviours and a range of health, functional and social measures at baseline. NSW residents aged at least 45 years were randomly sampled from the Department of Human Services (formerly Medicare Australia) enrollment database, which provides near complete coverage of the population. People 80 + years of age and residents of rural and remote areas were oversampled. A total of 266,933 individuals joined the study by completing a postal baseline questionnaire between 2006 and 2009 and giving signed consent for follow-up and linkage of their information to routine health databases. Around 18% of those invited participated, and the cohort included 11% of the NSW population aged 45 years or more.

The 45 and Up Study cohort was probabilistically linked to population-based health datasets by the Centre for Health Record Linkage. The linkage was based on all elements of name, sex, date of birth and address. Records from the NSW Cancer Registry 1994–2012 were used to identify prevalent and incident invasive cancer diagnoses, the NSW Admitted Patients Data Collection 2001–2015 and the NSW Emergency Department Data Collection 2005–2016 were used to identify aged care residency, and the NSW Registry of Births, Deaths and Marriages 2006–2016 was used to identify deaths. Parallel analyses of health service use based on Medicare Benefits Scheme (MBS) 2001–2015 and Pharmaceutical Benefits Scheme (PBS) 2004–2015 records required us to exclude 209 cohort participants who did not have a linked MBS or PBS record [13].

Cases were defined as 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: 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) 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 [14]. The metastatic cancer controls were individuals with an incident cancer registry diagnosis of solid metastatic malignancy of 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 controls 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 [5], 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. Exposure measurement

The demographic factors we examined were age, sex, country of birth (Australia, elsewhere), language spoken at home (English, other), marital status (married/de-facto, other), highest attained education (no school certificate or other qualification, school or intermediate certificate, higher school or leaving certificate, trade/apprenticeship, certificate/diploma, university degree or higher), employment status, private health insurance, usual yearly household income ($AUD), residential location (major city, inner regional, outer regional or rural using the Accessibility/Remoteness Index of Australia), area-based index of social disadvantage (Socio-Economic Indexes For Areas or SEIFA), and aged care residency.

In the baseline questionnaire, cohort participants reported whether they were a full-time carer for a family member or friend who was sick or had a disability, and the number of people that they could depend upon. They recorded their history of tobacco smoking (never, former, current < 20/day, current ≥ 20/day), their height and weight which we used to calculate body mass index (BMI; underweight < 18.5 kg/m^2, healthy weight 18.5–24.9 kg/m^2, overweight 25.0–30.0 kg/m^2, obese > 30.0 kg/m^2), and their regular daily alcohol consumption (none and < 1, 1–2 and > 2 standard drinks). They reported the duration and number of times in the last week that they (i) walked continuously for at least 10 min, (ii) were moderately physically active and (iii) were vigorously physically active. We calculated participants total cumulative physical activity (duration and times, regardless of intensity), and we determined whether they met the Australian recommendation for physical activity (at least 150 min of moderate intensity activity or 75 min of vigorous intensity activity, or an equivalent combination of both, per week) [15]. Participants also recalled the usual number of serves of vegetables and fruit they consumed daily, as well as the number of times a week they usually ate red meat and processed meat.

2.3. Statistical analysis

For each set of controls we used conditional logistic regression to estimate the odds of CUP associated with demographic, social and lifestyle factors. 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 factors related to health status and thus fitness for diagnostic investigation, as potential confounding factors, as identified in parallel analyses [13]. 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 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 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) (Table 1).

3.1. CUP compared to metastatic cancer of known primary site

In age- and sex-adjusted analyses, people registered with CUP were older, less educated and more likely to live in an aged care facility compared to those registered with metastatic cancer of known primary site (Table 1). There was no trend in risk with decreasing educational attainment; the excess risk was confined to individuals with the lowest

Table 1
Age- and sex- adjusted association between demographic and social factors and risk of CUP.

Demographic or social factor	CUP (n = 327)	Metastatic cancer known primary controls (n = 977)[d]		General cohort population controls (n = 981)	
	N (%)	N (%)	OR (95% CI)	N (%)	OR (95% CI)
Age (per year)	–	–	1.06 (1.04-1.07)	–	1.11 (1.09-1.12)
Male gender	196 (60%)	540 (55%)	1.25 (0.96-1.64)	466 (48%)	1.81 (1.37-2.38)
Born outside Australia	84 (26%)	261 (27%)	0.89 (0.59-1.30)	224 (23%)	1.11 (0.77-1.61)
Non-English language spoken at home	31 (9%)	93 (10%)	0.82 (0.51-1.30)	87 (9%)	1.07 (0.63-1.82)
Married or living with partner	199 (61%)	671 (69%)	0.83 (0.63-1.10)	740 (75%)	0.69 (0.49-0.97)
Educational attainment (6-category)					
No school certificate or qualification	78 (24%)	130 (13%)	1.00 (ref)	107 (11%)	1.00 (ref)
School or intermediate certificate	68 (21%)	226 (23%)	0.52 (0.34-0.79)	239 (24%)	0.47 (0.29-0.75)
Higher school or leaving certificate	27 (8%)	103 (11%)	0.43 (0.25-0.74)	96 (10%)	0.49 (0.26-0.94)
Trade/apprenticeship	52 (16%)	134 (14%)	0.63 (0.40-0.99)	100 (10%)	0.75 (0.44-1.29)
Certificate/diploma	52 (16%)	176 (18%)	0.53 (0.34-0.83)	220 (22%)	0.50 (0.30-0.85)
University degree or higher	40 (12%)	193 (20%)	0.42 (0.27-0.67)	201 (20%)	0.51 (0.30-0.86)
Educational attainment (2-category)					
Any school certificate or qualification	239 (73%)	832 (85%)	1.00 (ref)	856 (87%)	1.00 (ref)
No school certificate or qualification	78 (24%)	130 (13%)	1.95 (1.39-2.72)	107 (11%)	1.91 (1.29-2.83)
Employment (multiple options possible)					
Full-time, part-time or self-employed	56 (17%)	331 (34%)	0.75 (0.51-1.10)	489 (50%)	0.85 (0.56-1.28)
Fully or part retired	239 (73%)	554 (57%)	1.17 (0.84-1.62)	408 (42%)	0.85 (0.58-1.27)
Disabled/sick	19 (6%)	43 (4%)	1.72 (0.95-3.13)	32 (3%)	3.33 (1.67-6.65)
Doing unpaid work	13 (4%)	48 (5%)	0.80 (0.41-1.55)	53 (5%)	0.63 (0.30-1.34)
Studying	< 5[d] (< 2%)	9 (1%)	1.45 (0.37-5.71)	18 (2%)	1.50 (0.35-6.40)
Looking after home/family	24 (7%)	91 (9%)	0.88 (0.52-1.47)	106 (11%)	0.92 (0.52-1.61)
Unemployed	9 (3%)	23 (2%)	1.27 (0.56-2.90)	18 (2%)	2.71 (1.01-7.31)
Hold private health insurance	146 (45%)	538 (55%)	0.79 (0.60-1.04)	638 (65%)	0.62 (0.45-0.85)
Usual yearly household income ($AUD)					
$70,000 or more	26 (8%)	141 (14%)	1.00 (ref)	215 (22%)	1.00 (ref)
$50,000-$69,999	20 (6%)	83 (8%)	1.13 (0.58-2.21)	115 (12%)	1.38 (0.67-2.85)
$20,000-$49,999	79 (24%)	252 (26%)	1.14 (0.68-1.89)	252 (26%)	1.30 (0.73-2.30)
< $20,000	116 (35%)	266 (27%)	1.26 (0.75-2.10)	182 (19%)	1.91 (1.08-3.37)
Not reported	86 (26%)	235 (24%)	1.17 (0.70-1.98)	217 (22%)	1.79 (1.00-3.21)
Residential location (ARIA index)[a]					
Major city	182 (56%)	550 (56%)	1.00 (ref)	513 (52%)	1.00 (ref)
Inner regional	99 (30%)	320 (33%)	1.01 (0.75-1.35)	343 (35%)	1.01 (0.73-1.41)
Outer regional or rural	42 (13%)	93 (10%)	1.40 (0.91-2.16)	99 (10%)	1.46 (0.90-2.35)
Not reported	< 5[d](< 2%)	14 (1%)	0.84 (0.26-2.72)	26 (3%)	0.59 (0.17-1.98)
Area-based index of social disadvantage (SEIFA index)[b]					
Quintile 1 (least disadvantaged)	56 (17%)	188 (19%)	1.00 (ref)	176 (18%)	1.00 (ref)
Quintile 2	47 (14%)	149 (15%)	1.09 (0.70-1.71)	174 (18%)	0.81 (0.46-1.41)
Quintile 3	52 (16%)	153 (16%)	1.05 (0.68-1.64)	195 (20%)	0.81 (0.48-1.35)
Quintile 4	61 (19%)	224 (23%)	0.96 (0.62-1.47)	208 (21%)	1.02 (0.61-1.69)
Quintile 5 (most disadvantaged)	104 (32%)	242 (25%)	1.37 (0.93-2.01)	198 (20%)	1.85 (1.15-2.95)
Aged care resident[c]	23 (7%)	15 (2%)	2.90 (1.45-5.83)	< 5[e] (< 1%)	6.66 (2.10-21.1)
Full-time carer	19 (6%)	64 (7%)	0.80 (0.47-1.36)	51 (5%)	0.84 (0.44-1.62)
Number of people can depend upon					
None	19 (6%)	49 (5%)	1.00 (ref)	56 (6%)	1.00 (ref)
1–2	66 (20%)	189 (19%)	0.87 (0.46-1.64)	178 (18%)	0.84 (0.40-1.73)
3–8	146 (45%)	434 (44%)	0.81 (0.44-1.50)	453 (46%)	0.72 (0.37-1.39)
≥9	63 (19%)	251 (26%)	0.68 (0.36-1.28)	266 (27%)	0.56 (0.28-1.13)

[a] ARIA, Accessibility/Remoteness Index of Australia.
[b] SEIFA, Socio-Economic Indexes For Areas.
[c] 1–24 months prior to month of diagnosis.
[d] Breast (C50; n = 168), bronchus and lung (C34; n = 163), colon (C18; n = 152), prostate (C61; n = 123), rectum (C20; n = 57), pancreas (C25; n = 51), skin (C44; n = 42), stomach (C16; n = 32), ovary (C56; n = 23), kidney (C64; n = 22), bladder (C67; n = 22), oesophagus (C15; n = 19), rectosigmoid junction (C19; n = 17), tonsil (C09; n = 15), liver and intrahepatic bile ducts (C22; n = 14), small intestine (C17; n = 13), corpus uteri (C54; n = 13), thyroid (C73; n = 11), retroperitoneum and peritoneum (C48; n = 10), biliary tract (C24; n = 7), heart/mediastinum/pleura (C38; n = 7), gallbladder (C23; n = 5), renal pelvis (C65; n = 5), tongue (C02; n = 4), gum (C03; n = 4), larynx (C32; n = 4), connective/subcutaneous/other soft tissue (C49; n = 4), floor of mouth (C04; n = 3), parotid gland (C07; n = 3), anus/anal canal (C21; n = 3), thymus (C37; n = 3), vulva (C51; n = 3), cervix uteri (C53; n = 3), other female genital organs (C57; n = 3), eye/adnexa (C69; n = 3), brain (C71; n = 3), lip (C00; n = 2), other mouth (C06; n = 2), oropharynx (C10; n = 2), nasopharynx (C11; n = 2), palate (C05; n = 1), nasal cavity/middle ear (C30; n = 1), accessory sinuses (C31; n = 1), bones/joints/articular cartilage of limbs (C40; n = 1), bones/joints/articular cartilage of other sites (C41; n = 1), uterus (C55; n = 1), other urinary organs (C68; n = 1), meninges (C70; n = 1) and adrenal gland (C74; n = 1) cancers.
[e] Exact cell size suppressed for privacy reasons.

level of education, that is, those who did not attain a school certificate or any other qualification. People registered with CUP were also less moderately or vigorously physically active, and conversely more sedentary (Table 2). In the final multivariable model controlling for self-rated overall health and self-reported anxiety, the factors associated with risk of being registered with a diagnosis of CUP compared to a metastatic cancer with known origin were older age (OR 1.05, 95% CI 1.04–1.07 per year of age) and low educational attainment (OR 1.77,

Table 2
Age- and sex- adjusted association between lifestyle factors and risk of CUP.

Lifestyle factor	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)
Regular tobacco smoking					
Never	136 (42%)	460 (47%)	1.00 (ref)	583 (59%)	1.00 (ref)
Former	157 (48%)	396 (41%)	1.28 (0.96-1.70)	334 (34%)	2.03 (1.44-2.86)
Current	33 (10%)	118 (12%)	1.23 (0.78-1.93)	63 (6%)	4.19 (2.33-7.55)
Current, < 20/day	17 (5%)	45 (5%)	1.56 (0.84-2.88)	30 (3%)	4.05 (1.80-9.11)
Current, ≥20/day	15 (5%)	65 (7%)	1.13 (0.61-2.11)	31 (3%)	4.32 (2.00-9.34)
Body mass index					
Underweight	6 (2%)	13 (1%)	1.10 (0.39-3.13)	5 (1%)	2.13 (0.52-8.61)
Normal weight	116 (35%)	327 (33%)	1.00 (ref)	349 (36%)	1.00 (ref)
Overweight	108 (33%)	333 (34%)	1.00 (0.72-1.39)	349 (36%)	0.89 (0.61-1.31)
Obese	61 (19%)	230 (24%)	0.98 (0.67-1.42)	213 (22%)	1.37 (0.87-2.13)
Regular daily alcohol consumption					
None	115 (35%)	319 (33%)	1.00 (ref)	283 (29%)	1.00 (ref)
< 1 standard drink	74 (23%)	244 (25%)	1.00 (0.69-1.44)	317 (32%)	0.78 (0.52-1.17)
1-2 standard drinks	78 (24%)	221 (23%)	1.18 (0.83-1.69)	226 (23%)	0.97 (0.64-1.48)
> 2 standard drinks	48 (15%)	166 (17%)	0.97 (0.63-1.50)	135 (14%)	1.07 (0.65-1.77)
Total physical activity ≥150 min/week	198 (61%)	667 (68%)	0.84 (0.62-1.13)	737 (75%)	0.70 (0.49-0.99)
Total moderate and vigorous physical activity ≥150 min/week[a]	136 (42%)	506 (52%)	0.71 (0.53-0.96)	560 (57%)	0.63 (0.44-0.88)
Total physical activity					
< 1 times/week	35 (11%)	57 (6%)	1.00 (ref)	41 (4%)	1.00 (ref)
1-2 times/week	22 (7%)	71 (7%)	0.52 (0.27-1.03)	37 (4%)	0.95 (0.38-2.33)
> 2 times/week	252 (77%)	811 (83%)	0.55 (0.34-0.88)	887 (90%)	0.48 (0.26-0.89)
Usual number of servings					
≥5 vegetables/day	91 (28%)	295 (30%)	0.94 (0.69-1.26)	314 (32%)	0.79 (0.57-1.10)
≥2 fruit/day	176 (54%)	522 (53%)	0.90 (0.68-1.19)	563 (57%)	0.73 (0.53-1.00)
< 3 red meat/week	210 (64%)	632 (65%)	0.98 (0.74-1.30)	625 (64%)	0.95 (0.69-1.32)
< 3 processed meat/week	61 (19%)	172 (18%)	1.10 (0.77-1.57)	145 (15%)	1.28 (0.82-1.99)

[a] Australian recommendation: ≥ 150 min/week of moderate physical activity or ≥ 75 min/week of vigorous physical activity or a combination of the two.

Table 3
Demographic, social and lifestyle factors associated with risk of CUP.

Factor	CUP (n = 299/298)[1]	Metastatic cancer known primary controls (n = 914)		General cohort population controls (n = 931)	
	N (%)	N (%)	OR (95% CI)[b]	N (%)	OR (95% CI)[c]
Age (per year)	–	–	1.05 (1.04-1.07)	–	1.10 (1.08-1.12)
Educational attainment					
Any school certificate or qualification	224/223[a] (75%)	792 (87%)	1.00 (ref)	829 (89%)	1.00 (ref)
No school certificate or qualification	75 (25%)	122 (13%)	1.77 (1.24-2.53)	102 (11%)	1.69 (1.08-2.64)
Regular tobacco smoking					
Never	122 (41%)		n/a	549 (59%)	1.00 (ref)
Former	144 (48%)			319 (34%)	1.95 (1.33-2.86)
Current	32 (11%)			63 (7%)	3.42 (1.81-6.47)

n/a Not applicable.
[a] One CUP case had missing smoking history data and thus was excluded from the final model comparing CUP to general cohort population controls.
[b] Adjusted for age, educational attainment, self-rated health and self-reported anxiety at baseline.
[c] Adjusted for age, educational attainment, smoking history, self-rated health, self-reported anxiety, self-reported diabetes and history of cancer at baseline.

95% CI 1.24–2.53; Table 3). The final model was unchanged when the analyses were restricted to CUP cases registered as C80 and their matched controls.

3.2. CUP compared to general cohort population

In age- and sex-adjusted analyses, compared to general cohort population controls, people registered with CUP were older, more likely to be male, less educated, and less likely to be working due to disability or sickness, unemployed, in the lowest household income bracket, and living in an aged care facility (Table 1). Again there was no trend in risk with decreasing duration of education; the excess risk was confined to individuals who did not attain a school certificate or any other qualification. People registered with CUP were less likely to be married or living with a partner, and hold private health insurance (Table 1). People registered with CUP were also more likely to be current or former smokers, less physically active, more sedentary, and less likely to eat at least 2 serves of fruit a day (Table 2). For current smokers, there was no difference in risk associated with smoking < 20 or ≥20 cigarettes a day. In the final multivariable model controlling for self-rated overall health, self-reported anxiety, self-reported diabetes and a history of cancer-registry notified cancer, older age (OR 1.10, 95% CI 1.08–1.12), low educational attainment (OR 1.69, 95% CI 1.08–2.64), and current (OR 3.42, 95% CI 1.81–6.47) or former (OR 1.95, 95% CI 1.33–2.86) smoking were associated with risk of cancer registry-notified CUP compared to general population controls (Table 3). The final model was again unchanged when the analyses were restricted to CUP cases registered as C80.

4. Discussion

In a large, contemporary cohort of well-characterised Australian adults, we found that older age and low educational attainment differentiated individuals with metastatic cancer registered with CUP compared to known primary site, after controlling for self-rated overall health and self-reported anxiety. Similarly, compared to all other cohort participants, older age and low educational attainment were independent risk factors for a cancer registry notification of CUP, as was current or former history of regular tobacco smoking. These factors may thus be associated with advanced stage of metastatic disease at diagnosis.

Our findings confirm the previously reported strong association between a cancer registry notification of CUP and older age [5,6,8,9] and smoking [10,11], and indicate these factors increase risk independent of overall health. As for previous studies, we did not observe an association with body fatness or alcohol consumption [10,11]. Whilst several descriptive studies have pointed to an increased risk of a CUP notification in association with measures of deprivation associated with living in a particular neighbourhood, including low socio-economic position [6,9] and low educational status [3], this is the first time self-reported educational attainment has been observed to independently predict a cancer registry notification of CUP. Whilst a number of other characteristics related to deprivation were associated with CUP in our cohort, they did not remain associated after adjustment. The only previous cohort study to examine self-reported level of education observed no association with risk of CUP, either before or after adjustment for smoking [10]. The reasons for this variation are uncertain, as the categorisation of education levels was similar for the two cohorts. The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort enrolled 35–70 year olds between 1992 and 2000 and, unlike the 45 and Up Study, excluded individuals with a history of cancer at the time of recruitment [10].

The relationship between educational attainment and health outcomes is complex [16]. The consistently strong association with low educational attainment and registration of CUP in our study, independent of overall health and smoking history, suggests low health literacy may play a role in the late diagnosis of cancer. Low educational attainment and thus low literacy is a barrier to health information seeking, comprehension and self-management [17], it can negatively influence the way doctors communicate with patients [18], and it is associated with poorer health outcomes [19]. Our data do not appear to support an independent association with person-level economic and social relationship factors, although we had no data on the strength of social connectedness.

We utilised a large, contemporary prospective cohort study with comprehensive data on demographic, social and lifestyle risk factors, and incident cancers and deaths 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. Further, given the consistent prior evidence of an increased risk of a CUP diagnosis in association with comorbid disease [5,20,21], we minimised confounding by adjusting for relevant comorbid conditions and self-reported overall health at baseline [13]. Nevertheless, we cannot exclude residual confounding for individuals whose health status changed between the cohort baseline and their cancer diagnosis, or for individuals whose self-reported overall health poorly correlated with performance status. We also cannot discount residual confounding due to unmeasured demographic, social, occupational, environmental and lifestyle factors, for example, waist circumference, which may be a more accurate measure of body fatness than BMI [10].

Whilst the 45 and Up cohort study was designed to be representative of the general population, the participation rate was 18% [12], and comparisons with a representative population health survey [22] and all cancer patients in NSW [23] indicate that cohort participants are on average healthier than the general population. Even so, risk estimates calculated from within-cohort comparisons are expected to be valid. Our statistical power was constrained by a relatively small number of incident CUP cases. We had no information on the location or extent of metastatic disease, and nor were we able to conclusively differentiate CUP subgroups (for example: confirmed and inadequately evaluated) using the cancer registry data alone. We also had no direct measure of health literacy for the cohort participants.

5. Conclusions

It is exceptionally challenging to balance the early diagnosis of cancer against over-investigation. Increasing the difficulty for clinicians and patients, the median age at CUP diagnosis is 70–80 years, and CUP is described as exhibiting rapid and aggressive dissemination [24]. If replicated in other cohorts, our findings may help in the identification of high-risk patient subgroups that may benefit from assistance in understanding their health priorities and health care needs, in particular encouraging and empowering effective communication and self-management [18,25]. The strong relationship with educational attainment is further evidence of the many benefits of investment in education, and completion of compulsory education, over the human lifecycle.

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.

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