CUP epidemiology and health service utilisation in Australia

Never Stand Still

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on behalf of the CUP Team

How is CUP defined?

	Clinical definition		Population-based cancer registry definition
A metastatic cancer with no identifiable primary site despite all clinically appropriate diagnostic investigations.	A metastatic cancer with no identifiable primary site despite some diagnostic investigations.	A clinically diagnosed metastatic cancer; further investigation of no clinical benefit or declined by patient.	A metastatic cancer with no identifiable primary site, irrespective of the extent of diagnostic investigation.
Basis of diagnosis - pathology AND -clinical/imaging **i.e. "confirmed" CUP**	Basis of diagnosis - pathology OR - cytology AND -clinical/imaging **i.e. "provisional" CUP**	Basis of diagnosis - clinical/imaging ONLY **i.e. malignancy of undefined primary origin (MUO)**	Basis of diagnosis - pathology OR - cytology OR - clinical/imaging OR - death certificate only **i.e. cCUP, pCUP and MUO**

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What is the incidence of "confirmed" CUP?

- We can't answer this question!

- We could use enhanced data to count only histologically confirmed CUP, but that is only part of the equation because..

- We do not currently identify those CUP patients registered as a known primary on the basis of a <u>suspected</u> site, and…

- Confirmed CUP are not the only subgroup of interest from a public health perspective:

CUP distribution by patient characteristics in Australia[1]:

- 2.0x higher rates in Indigenous Australians

- 1.4x higher rates in remote and very remote areas

- 1.2x higher rates in lowest SES areas

[1] Australian Institute of Health and Welfare and Australasian Association of Cancer Registries 2010. Cancer in Australia: an overview, 2010. Cancer series no. 60. Cat no CAN 56. Canberra: AIHW.

CUP epidemiology in Australia

	No.	ASR (Aust) per 100,000	Ranking
CUP incidence 2007*			
Males	1496	14.9 (14.2-15.7)	9th
Females	1401	11.0 (10.4-11.6)	7th
CUP mortality 2007^			
Males	1247	12.5 (11.8-13.2)	5th
Females	1097	8.5 (8.0-9.1)	5th
CUP 5-year relative survival			
Males	11%		
Females	8%		

*C80   ^C77-C80

[1] Australian Institute of Health and Welfare and Australasian Association of Cancer Registries 2010. Cancer in Australia: an overview, 2010. Cancer series no. 60. Cat no CAN 56. Canberra: AIHW.
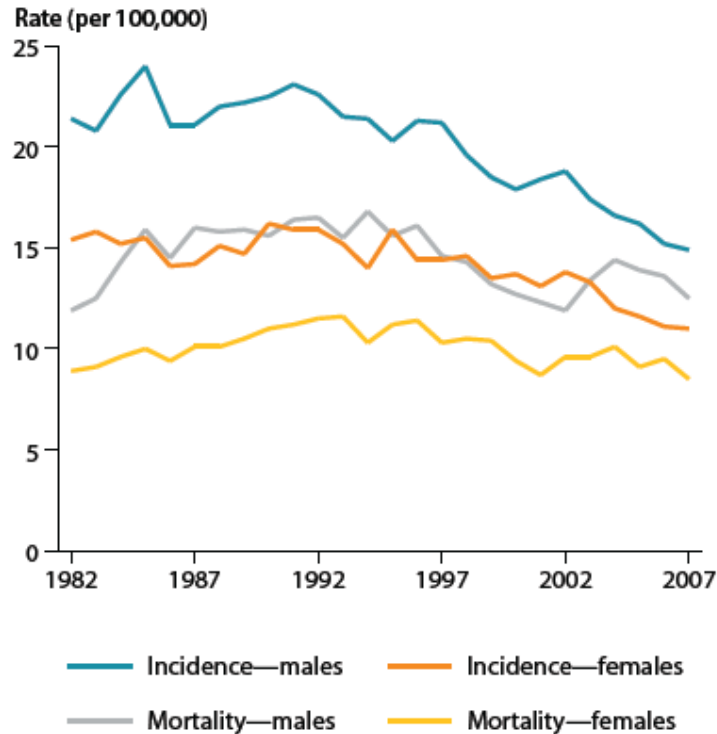
CUP epidemiology in Australia

Rate (per 100,000)

Figure B.36a: Cancer of unknown primary site incidence and mortality rates(c), 1982–2007

Rate (per 100,000)
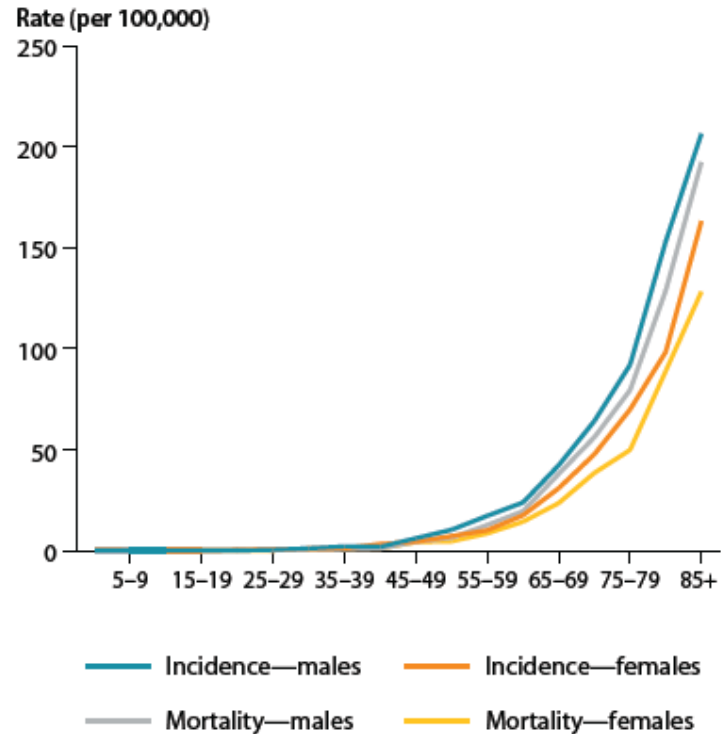
Figure B.36b: Cancer of unknown primary site incidence and mortality rates(d) by age at diagnosis, 2007

Legend:
- Incidence—males
- Incidence—females
- Mortality—males
- Mortality—females

(a) For mortality data, the applicable codes are C77–C80.

(b) The estimates were based on data for 1998 to 2007. See Appendix F for further details on the methodology used. The estimates for males and females may not add to the estimates for persons due to rounding.

(c) The rates were age-standardised to the Australian population as at 30 June 2001 and are expressed per 100,000 population.

(d) The rates shown are age-specific rates.

Source: AIHW Australian Cancer Database; AIHW National Mortality Database.

Prior studies

Author, year	Country, period	Registry or hospital-based?	Key findings
Abbruzzese, 1994	US, 1987-92	Single hospital n=657 consecutive referrals Carcinomas only	<u>LNs</u>: Supraclavicular 31% , mediastinal 20%, axillary 14%, retroperitoneal 12%, inguinal 8% <u>Organs</u>: liver 31%, bone 28% , lung 28%, brain 8%, peritoneum 6% Single site 39% Median age 59 yrs Chemotherapy 49%
Muir, 1995	US, 1973-87	SEER registries n=35078	Histology confirmed 74% Adenocarcinoma 54% ↑age → ↓ %histology
Levi, 2002	Switzerland, 1984-93	Registry n=699	Histology confirmed 78% ↑age → ↓ %histology

Prior studies

Author, year	Country, period	Registry or hospital-based?	Key findings
Pimiento, 2007	US, 1995-05	Single hospital, n=91	Liver 37%, neck 14% No record of imaging 6%
Shaw, 2007	UK, 2003	Single hospital, n=166	Liver 25% Histology confirmed 55% Median age 68 years
Seve, 2009	France & Canada, 2000-04	Two hospitals, n=200	*Cytology* 30% Inadequate immunohistochemistry 40%
Tracey, 2008	Aust (NSW), 1999-03	Registry	Histology confirmed 58%, *cytology* 15%, clinical 23%, DC 4%

Prior CUP studies - therapy

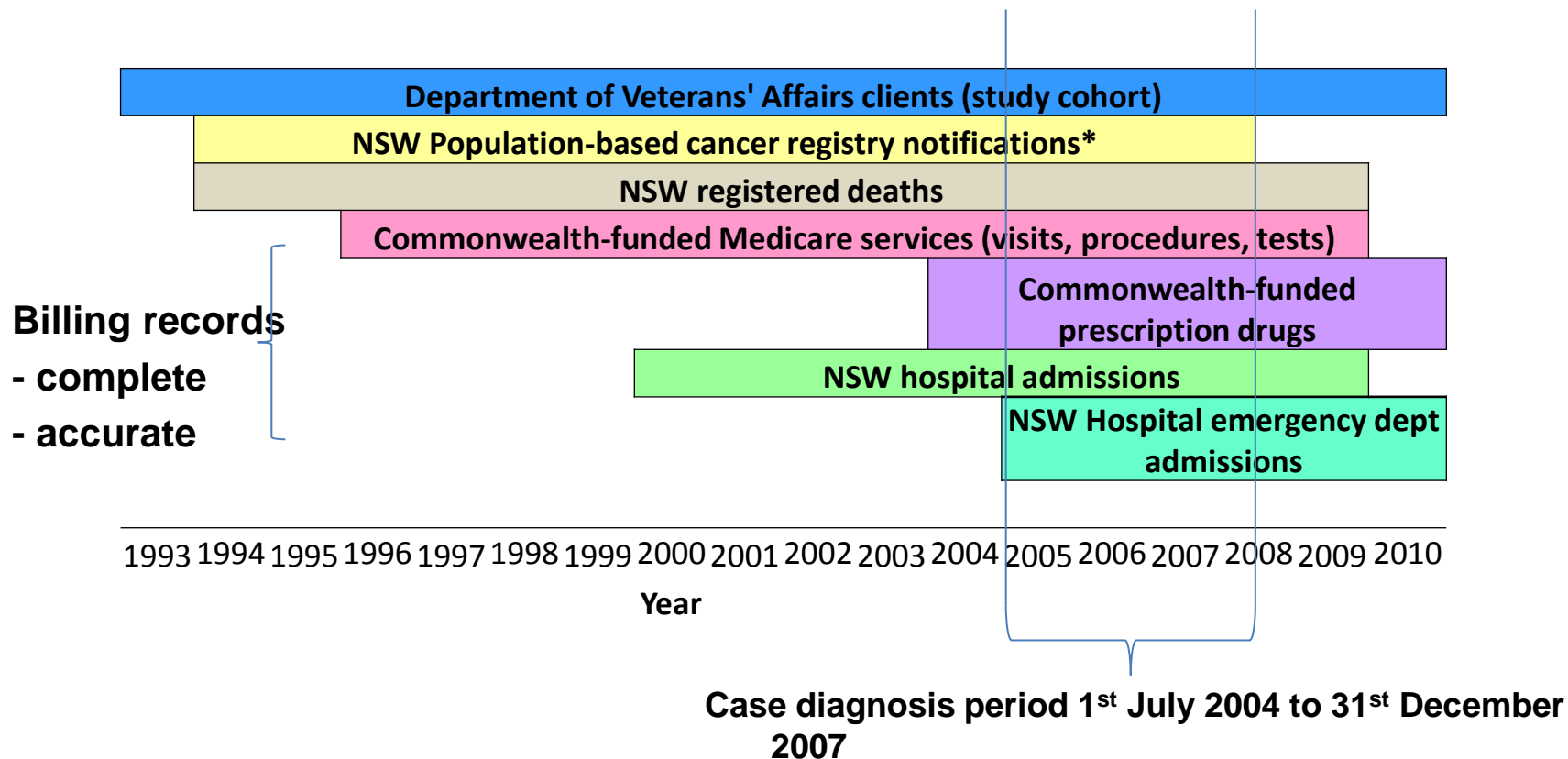| Author, year	Country, period	Registry or hospital-based?	Key findings
Shaw, 2007	UK, 2003	Single hospital, n=166	Supportive care 35% Radiotherapy 28% Chemotherapy 18% Combination 10% Endocrine 2% Unknown 6%
NICE, 2010	Thames Region of England, 2002-06	Registry Distribution by treatment type not patients	No treatment 37% Surgery 32% DC only 8% Chemotherapy 8% Cancer surgery 8% Radiotherapy 7%

Population-based CUP research objectives

1. Extract enhanced data from CUP notifications for an incident case series

2. Ascertain health service utilisation prior to CUP diagnosis

3. Ascertain health service utilisation after CUP diagnosis

4. Compare patient demographics and health service utilisation for CUP and metastatic cancer of known primary site

5. Examine risk and prognostic factors for CUP

Our methods

Study design	Population-based health record linkage
	Cancer registry case review + enhanced data collection
	Nested case-control study
Study population	Australian Government Department of Veterans' Affairs clients resident in NSW
	- 143,956 veterans and their dependants
	- 51% male, 83% ≥70years
	- median age 81 (IQR 76-85) years
Diagnosis period	July 2004 – December 2007
Health service utilisation data	Administrative health datasets – Commonwealth and state level, unique

Linked datasets

Department of Veterans' Affairs clients (study cohort)

NSW Population-based cancer registry notifications*

NSW registered deaths

Commonwealth-funded Medicare services (visits, procedures, tests)

Commonwealth-funded prescription drugs

Billing records
- complete
- accurate

NSW hospital admissions

NSW Hospital emergency dept admissions

1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010

Year

Case diagnosis period 1st July 2004 to 31st December 2007

* Due to privacy legislation during 2004-2007, NSW Cancer Registry coders were unable to write to doctors to seek further information about notified cases   CASE REVIEW AND FOLLOW-UP

Case review methods

Incident CUP (ICDO3: C809) cases identified by linkage

Case review performed by cancer registry staff:

1. For each case, all notifications reviewed

   – Pathology reports, cytology reports, cancer notification forms, inpatient and outpatient electronic records, death certificate

2. If confirmation required, a letter requesting further information was sent

3. A determination on the diagnosis was made by the coder

4. Clinical and histopathological data abstracted

   - Basis of diagnosis, LN involved, organs involved, tumour grade, tumour morphology
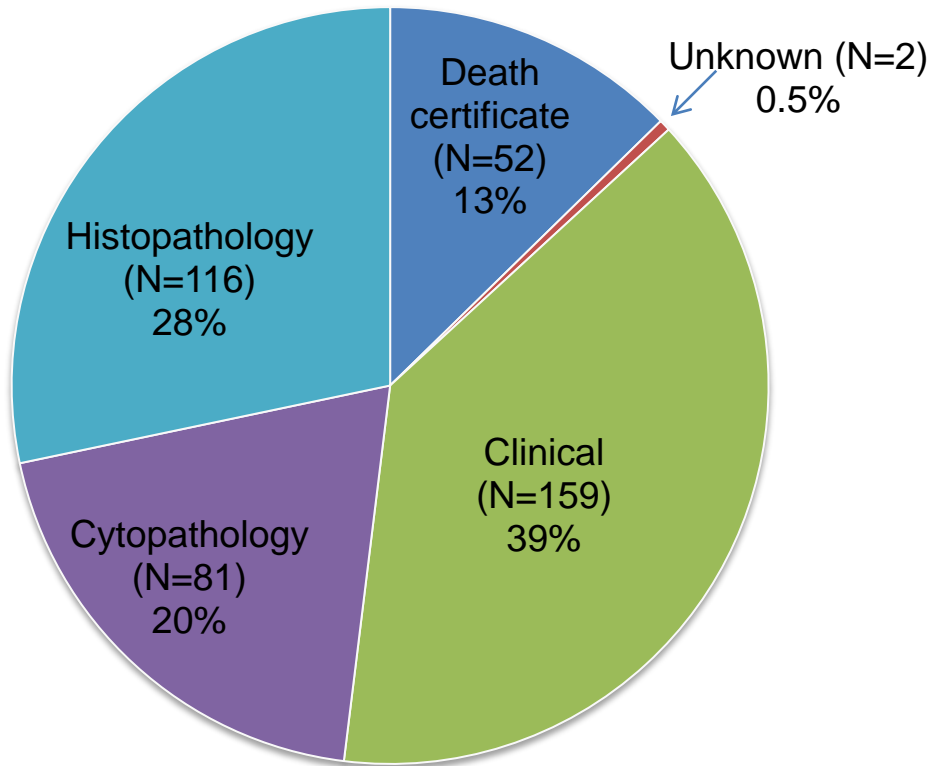
Case review results
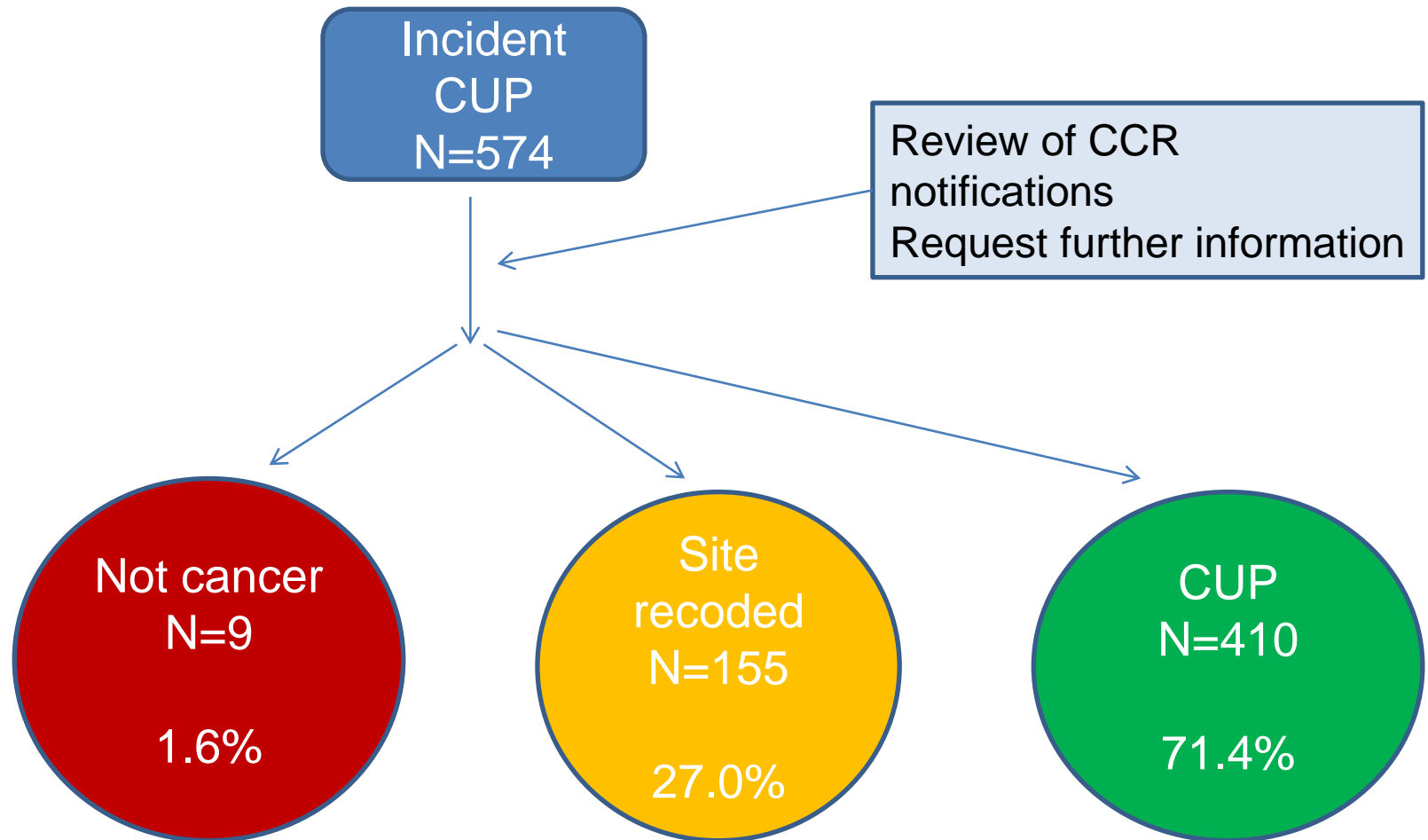
Primary site recoded (n=155)
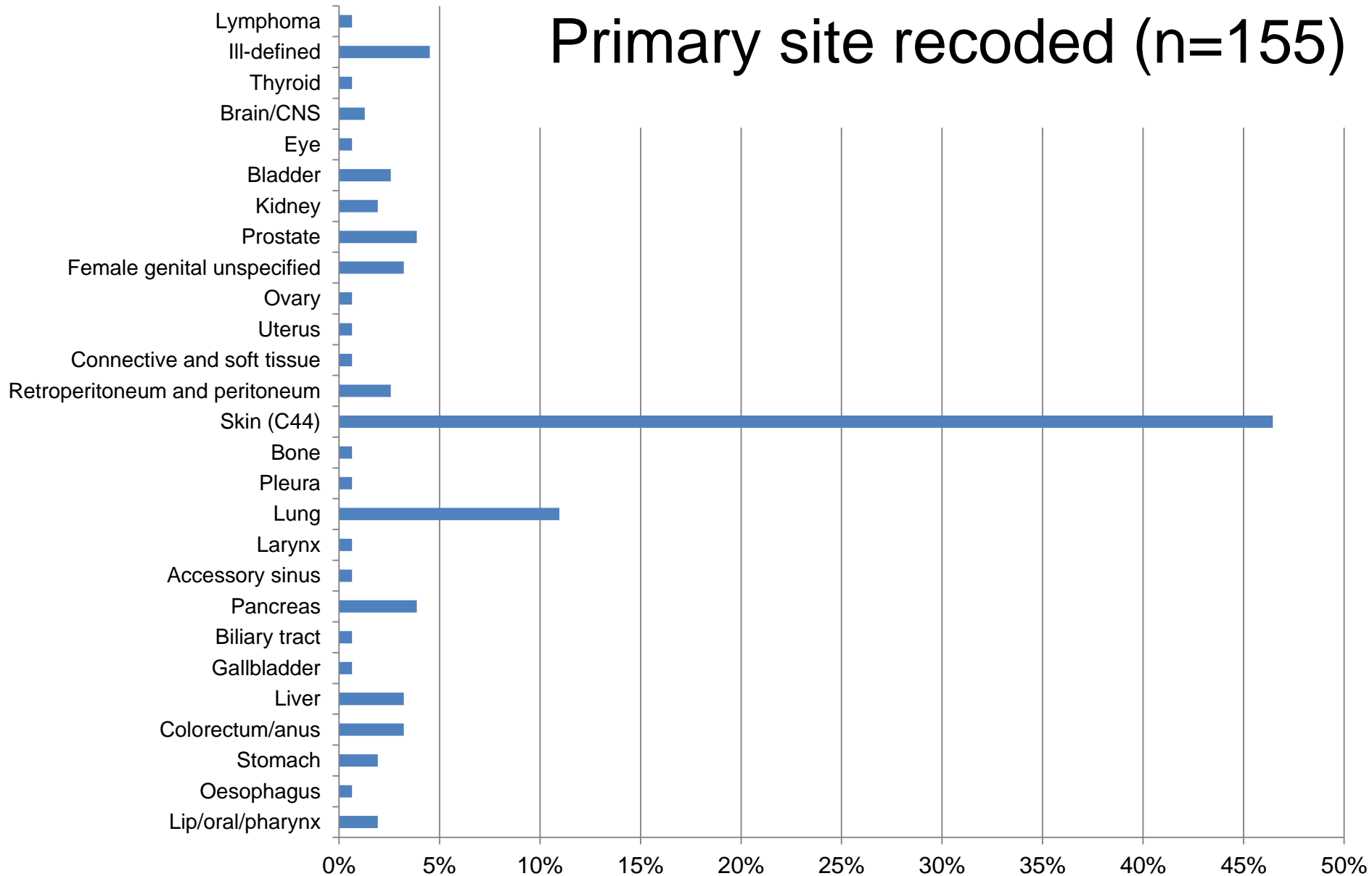
Proportion of cases
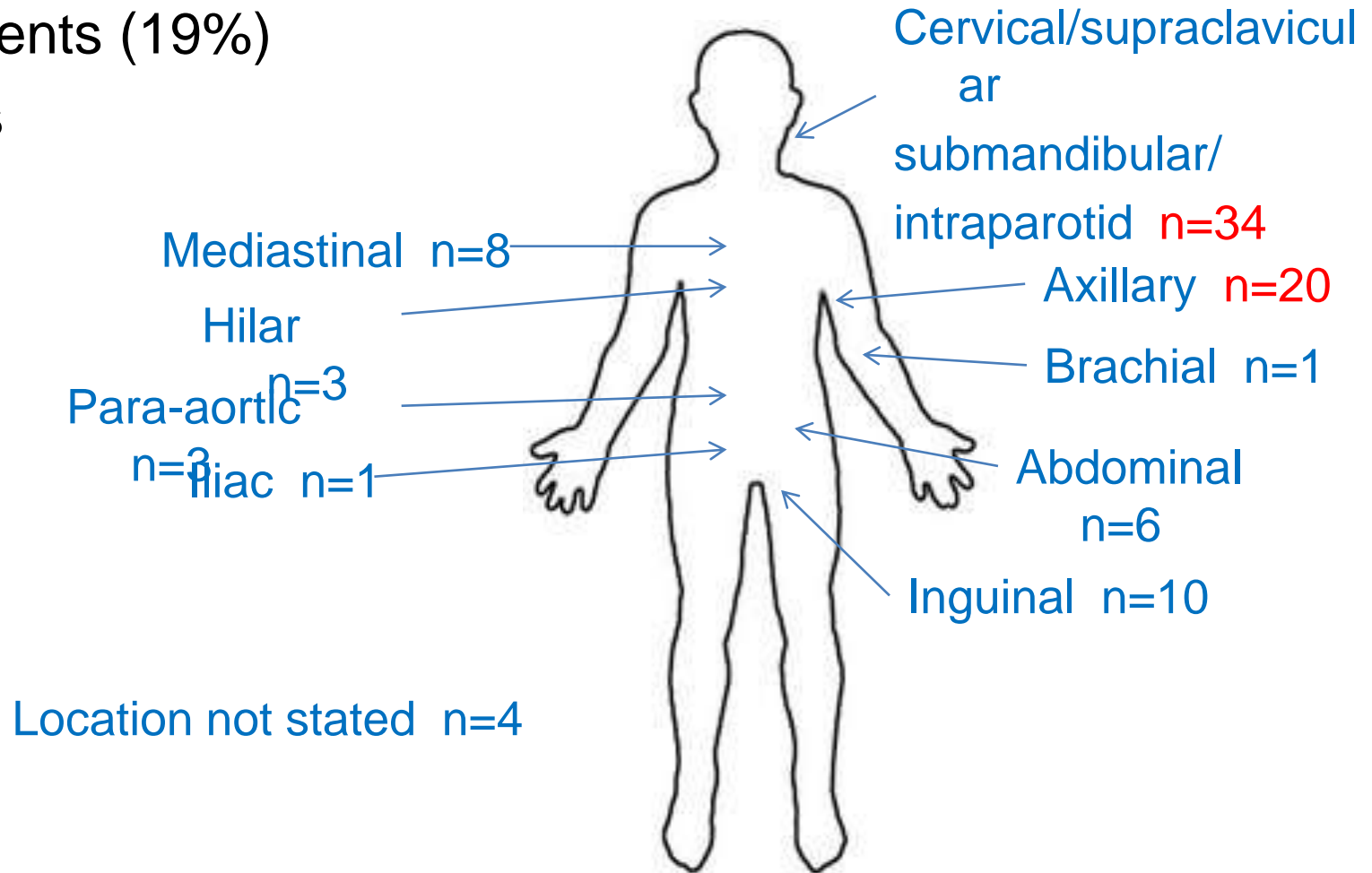
CUP cases, basis of diagnosis

Basis of diagnosis	Proportion male	Median age (years)
Histology	72%	83
Cytology	53%	83
Clinical/ other	57%	86

CUP cases, reported involved lymph nodes

79 patients (19%)

90 LNs

Cervical/supraclavicular submandibular/ intraparotid n=34

Mediastinal n=8

Hilar n=3

Para-aortic n=3

Iliac n=1

Axillary n=20

Brachial n=1

Abdominal n=6

Inguinal n=10

Location not stated n=4

CUP cases, reported involved organs and other sites

209 patients (51%)

Brain n=32

Lung n=65

Liver n=125

Breast n=3

Adrenal gland n=4

Spleen n=3

Kidney n=3

Bowel n=6

Abdomen n=39

Skin n=3

Bone n=45

Other specified n=8

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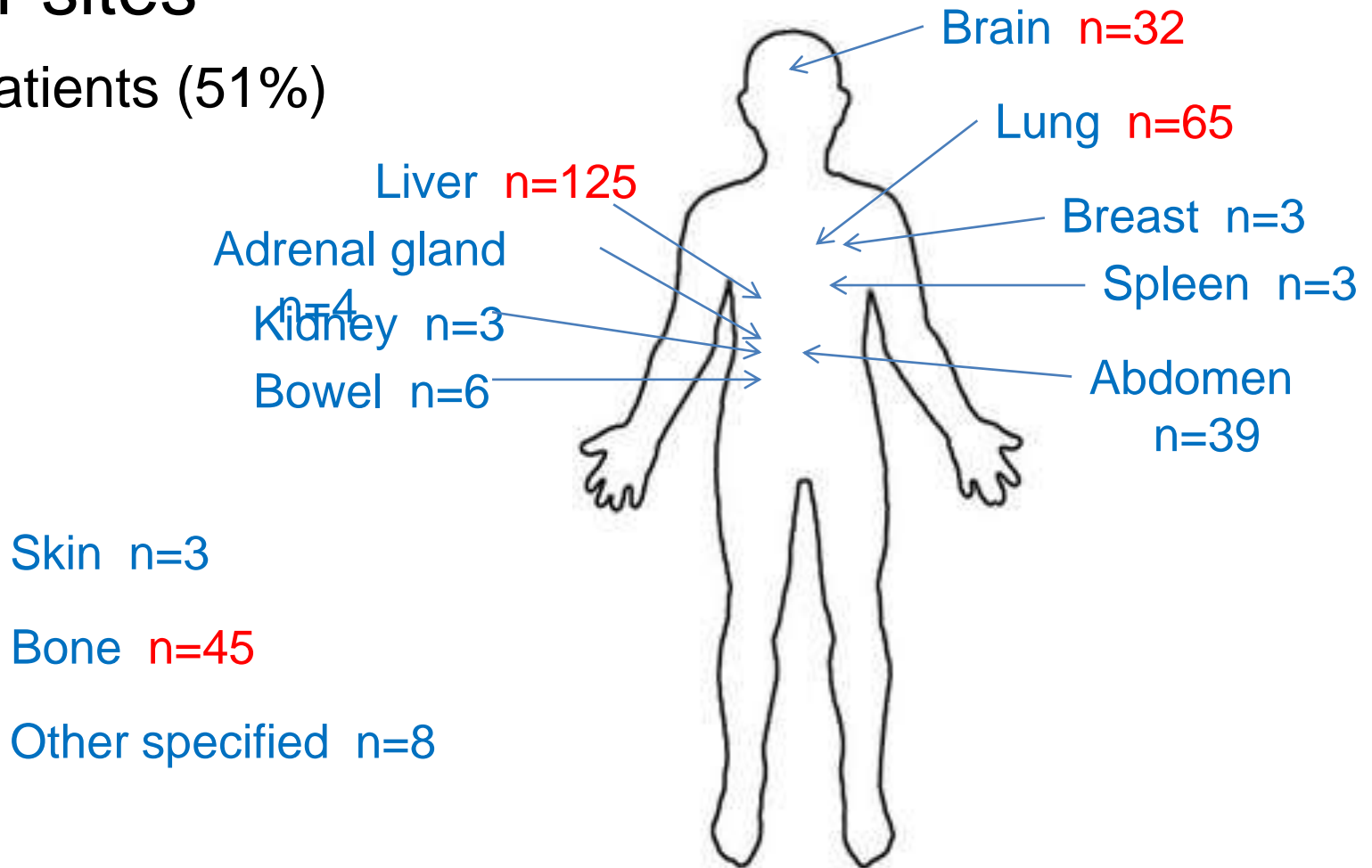
CUP cases, number of reported sites*
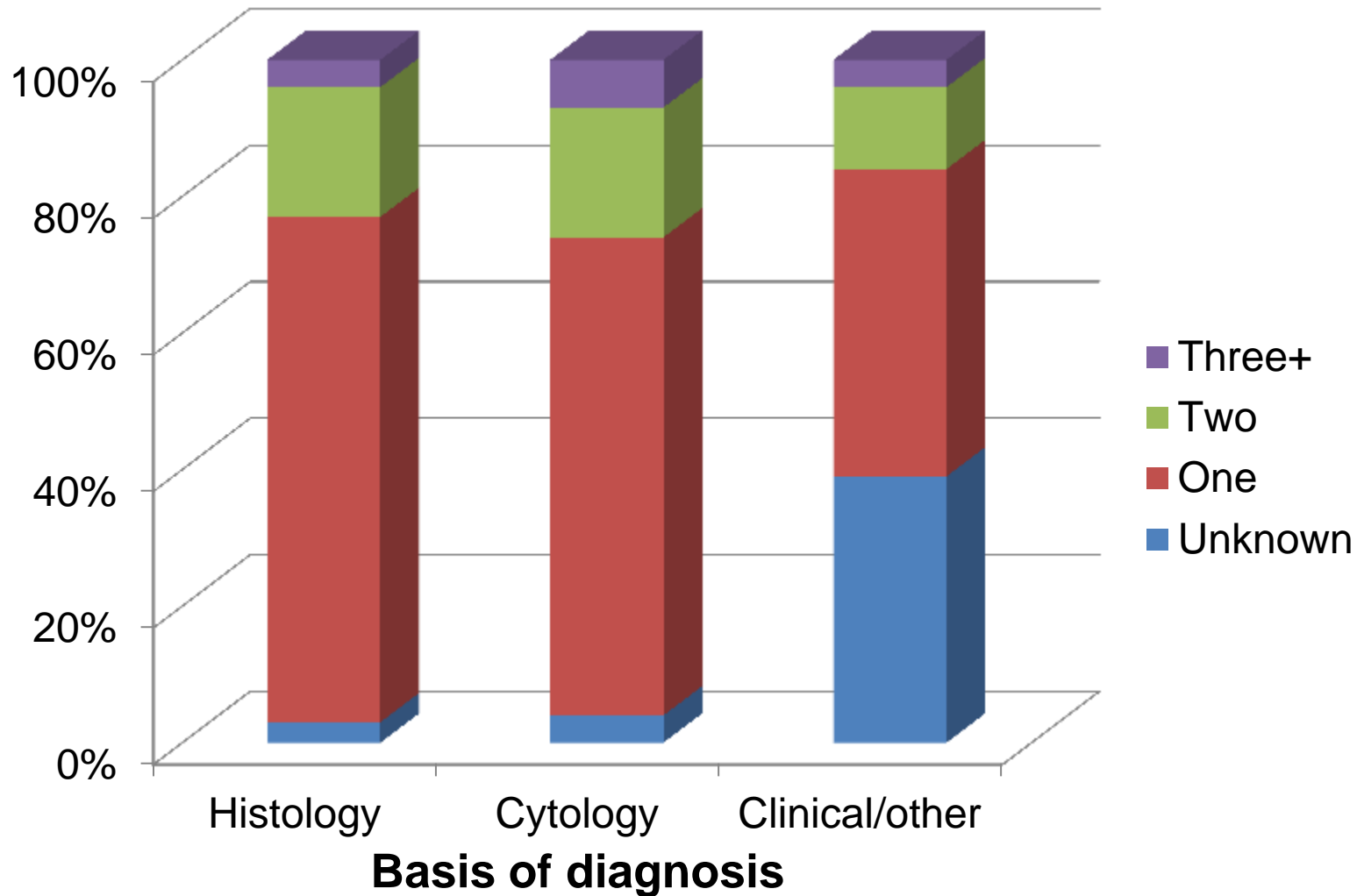
*Specified lymph nodes, specified organs or other tissues

CUP cases, common reported sites

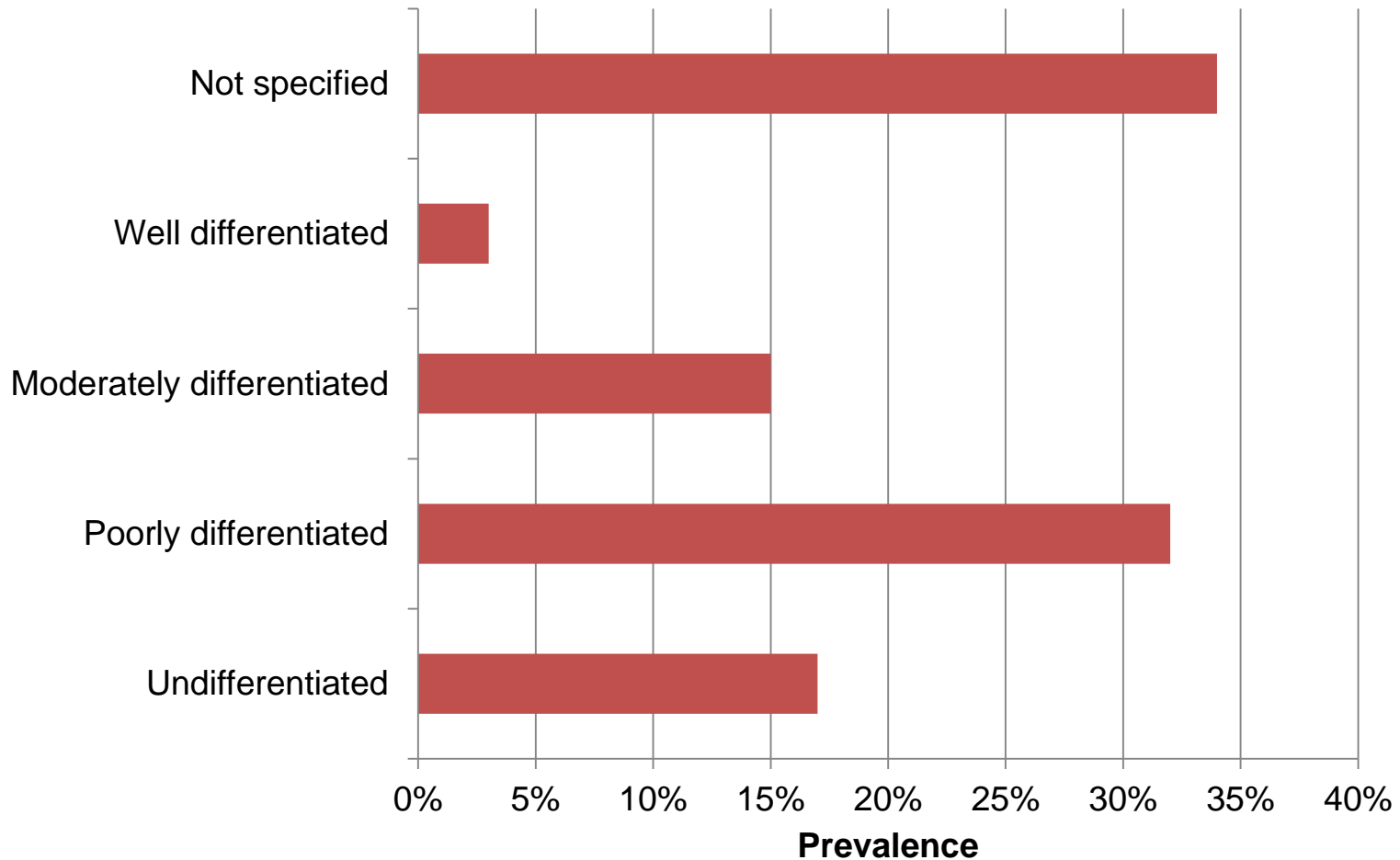| Organ(s) involved	Basis of diagnosis n (%)		
	Histology n=116	Cytology n=81	Clinical/Othe r n=213
Liver	28 (24%)	33 (41%)	64 (30%)
Lung	11 (9%)	24 (30%)	29 (14%)
Bone	14 (12%)	8 (10%)	23 (11%)
Brain	4 (3%)	1 (1%)	27 (13%)

CUP cases, reported sites

Basis of diagnosis
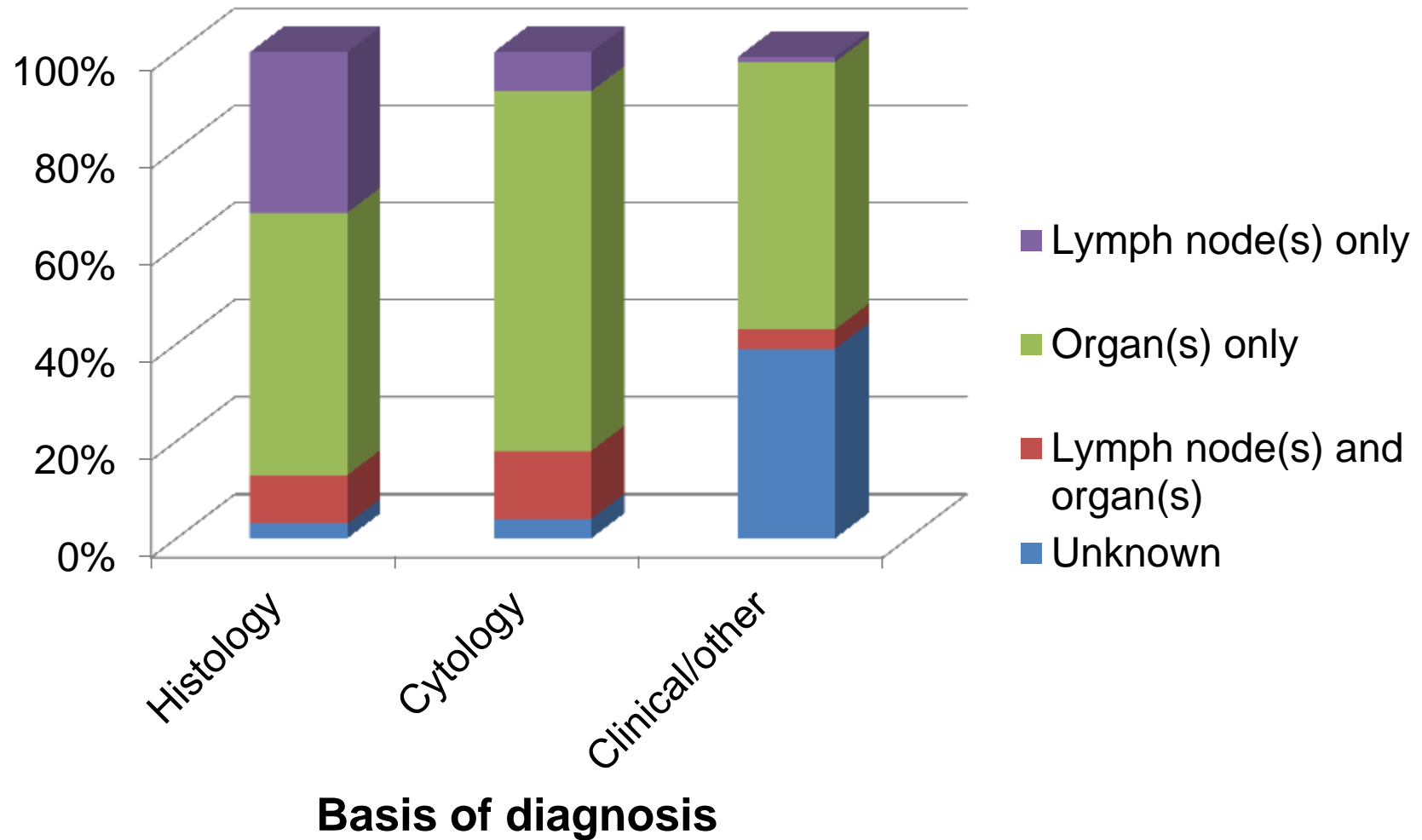
Morphology for CUP with histology
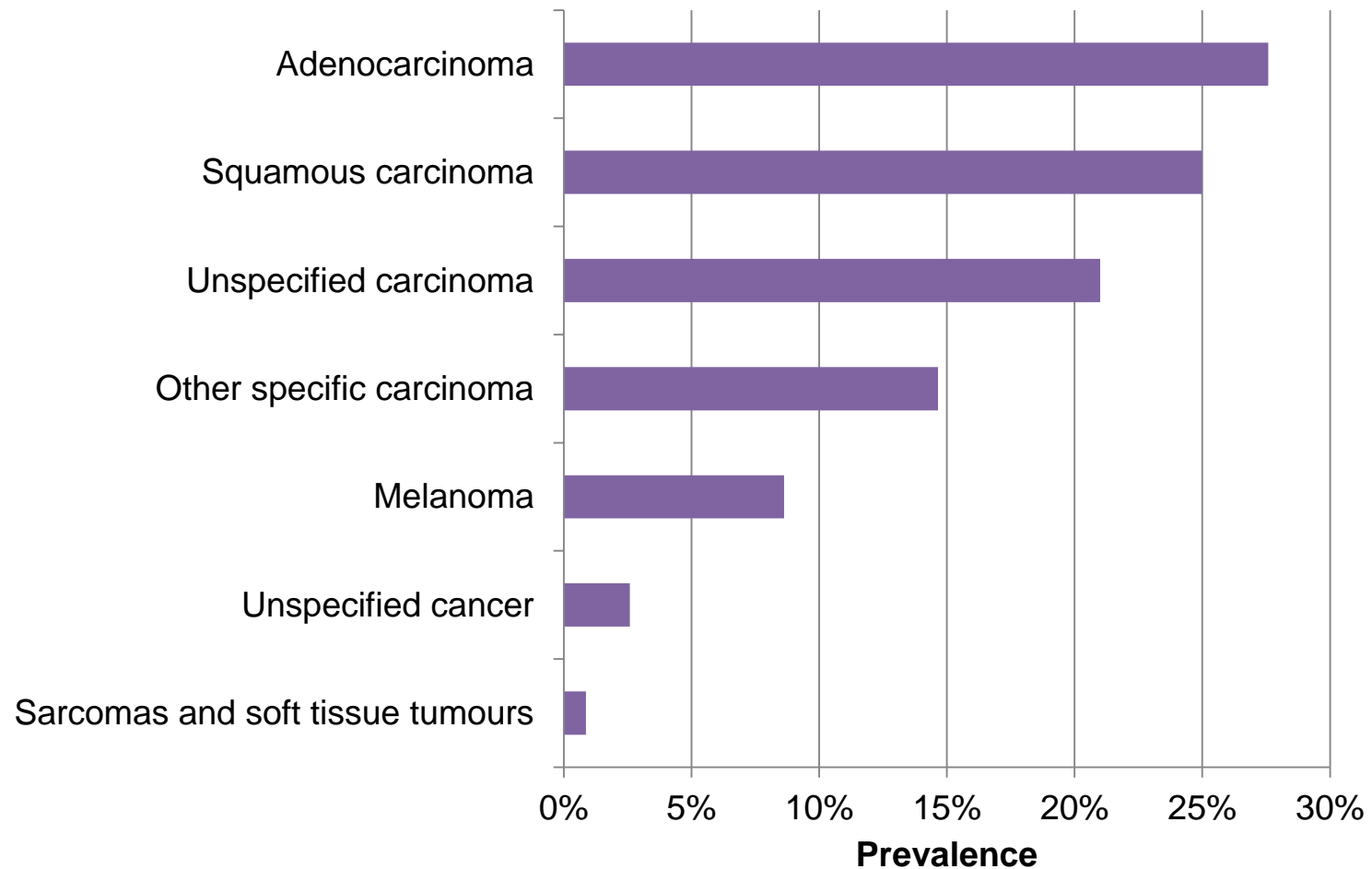
Tumour grade for CUP with histology

CUP (C809) incidence in the NSW DVA

A predominantly <u>elderly cohort</u>

Cases included	Number of cases	Crude incidence per 100,000 PY
Prior to case review	574	437
After case review	410	312
Histopathological diagnosis only	116	88

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Demographics, co-morbidity & health service utilisation: methods

Study population	Cases	Controls
	Post-audit CUP (n=410)	Incident site-specific metastatic solid cancer (n=2574)
Exclusion criteria	Prior cancer within 5 years Not resident in NSW continuously Less than 3mths linked records prior to ddx Card type 3mths prior to ddx not gold or white No linked Commonwealth records Inconsistency between linked records N=137 N=501	
Incidence density sampling 4:1	Matched for month & year of diagnosis and t0	
	N=273	N=1076

Results for CUP with histology

	Cases (n=82) n (%)	Controls (n=324) n (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Sex				
Male	55 (67)	202 (62)	1.00 (ref)	1.00 (ref)
Female	27 (33)	122 (38)	0.82 (0.49-1.39)	0.95 (0.55-1.62)
Age group (years)				
≤81	29 (35)	117 (36)	1.00 (ref)	1.00 (ref)
82-85	28 (34)	118 (36)	0.98 (0.53-1.78)	0.90 (0.49-1.68)
≥86	25 (30)	89 (27)	1.14 (0.62-2.01)	1.17 (0.61-2.24)
RxRisk score^				
0	5 (6)	113 (35)	1.00 (ref)	1.00 (ref)
1-8	40 (49)	114 (35)	7.45 (2.84-19.5)	7.54 (2.87-19.8)
≥9	37 (45)	97 (30)	7.90 (3.03-20.6)	7.99 (3.05-20.9)

+ Adjusted for age, sex and RxRisk score

^Fishman et al. Risk adjustment using automated ambulatory pharmacy data: the RxRisk model. Medical Care 2003;41:84-99. Also referred to as 'chronic disease score'

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Results for CUP with histology

	Cases (n=82) n (%)	Controls (n=324) n (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Imaging				
No	76 (93)	173 (53)	1.00 (ref)	1.00 (ref)
Yes	6 (7)	151 (47)	0.06 (0.02-0.17)	0.12 (0.03-0.48)
Immunohistochemistry				
No	42 (51)	300 (93)	1.00 (ref)	1.00 (ref)
Yes	40 (49)	24 (7)	9.00 (5.02-16.2)	5.52 (2.83-10.8)

[+] Adjusted for age, sex and Rx-risk score

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Strengths and limitations

Strengths	Limitations
Population-based outcomes and health service utilisation - no bias by hospital or clinic type	"Involved" sites – limited to information recorded on notifications, likely bias to accessible sites & vital organs
Enhanced data abstraction by trained registry staff	No reply to ~20% audit letters
Contemporary data for an elderly cohort	Representativeness of cohort
	Representativeness of cohort subset with linked health service records
	No information on race/ethnicity
	Only considered C809

Conclusions

- Cancer registration practices influence the incidence of CUP; enhanced data quality and health care services could be achieved by integration of multiple data sources to allow subtype classification

- In the elderly

  - registered CUP cases are markedly heterogeneous, and the patient and tumour profile varies by basis of diagnosis

  - few patients appear to have a suite of diagnostic tests

  - the incidence of 'confirmed' CUP appears markedly lower than rates for all CUP

- Among the elderly who present with metastatic cancer, a diagnosis of CUP is significantly more likely in those with co-morbidities

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Future research

- Complete health service utilisation and survival analyses

- Repeat analyses for 45 and Up Study cohort (n~265,000)

  - representative of general population

  - baseline questionnaire data

- At TCRN clinical sites (5,000 patients pa), prospectively identify CUP patients

  - collect medical record information, blood and tumour tissue, and link to clinical cancer registry, population

Acknowledgement

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www.actiononunknownprimary.org