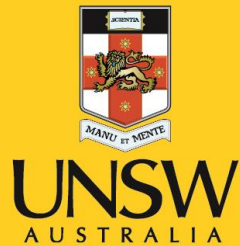




CENTRE FOR
BIG DATA RESEARCH
IN HEALTH



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Never Stand Still

Medicine



THE EPIDEMIOLOGY OF CUP

- Classification
- Incidence and mortality
- Survival
- Risk factors

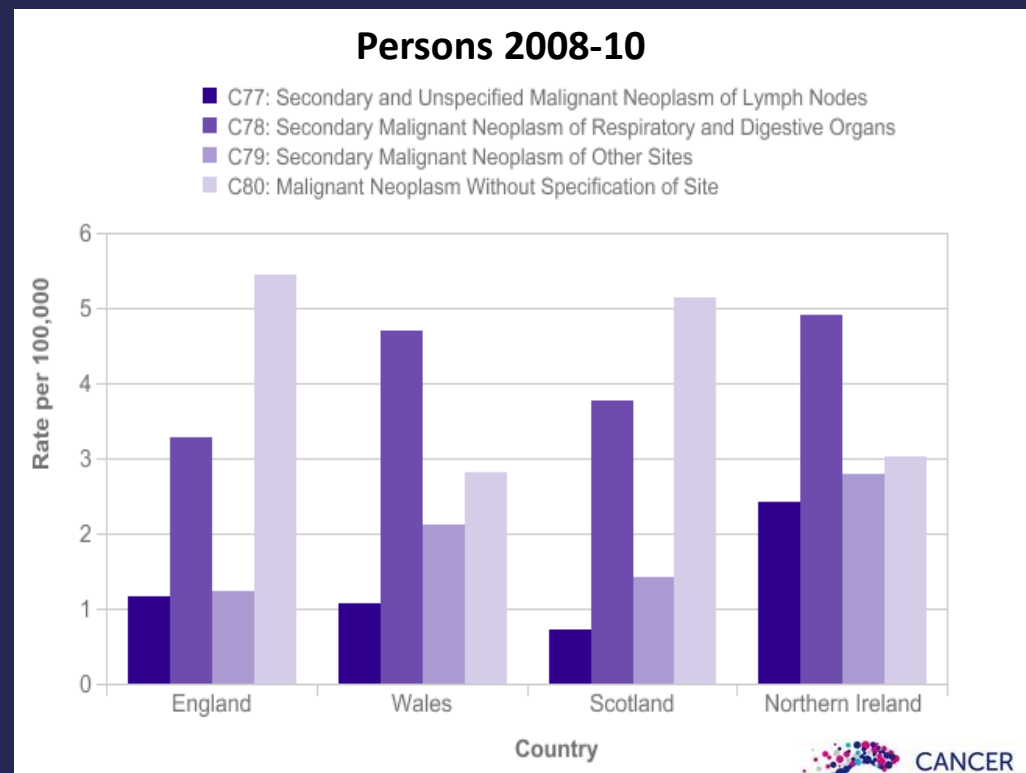
Classification

- NICE Guideline (July 2010) subtypes: MUO, pCUP and cCUP, depending on extent of clinical and histopathological investigation
 - Subtype incidence unknown
- CUP statistics include above plus
 - ✓ Non-epithelial morphologies
 - ✓ Cases without any excision/biopsy/aspirate
 - ✓ Death certificate only cases
 - ? Cases treated for presumed primary site

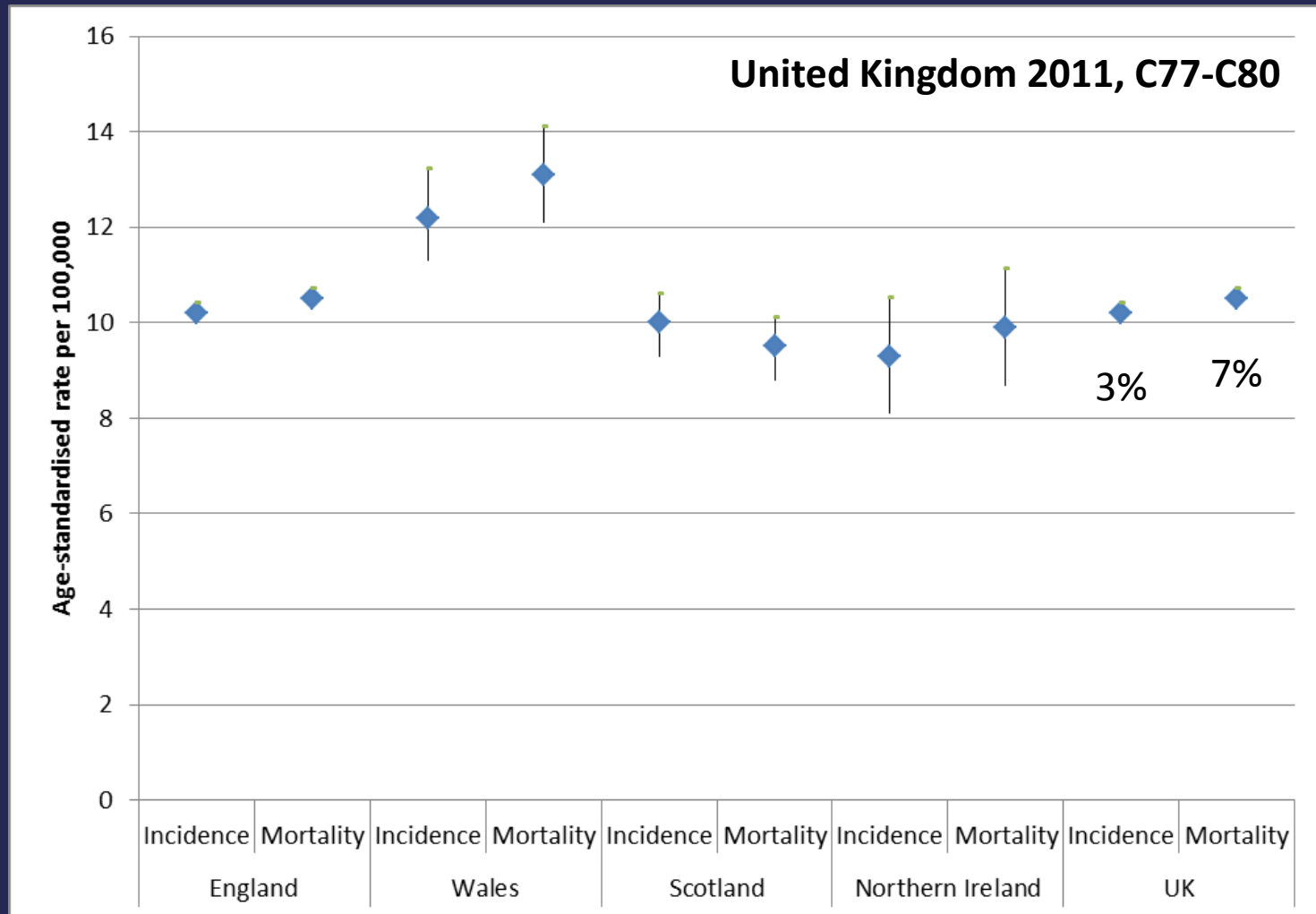
Classification and reporting

- Inconsistent use of ICD codes
- Ill-defined, secondary and unspecified sites
- Caution required

ICD-10 code	WHO definition
C26	Malignant neoplasm of other and ill-defined digestive organs with exclusion of peritoneum and retroperitoneum
C39	Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs with exclusion of intrathoracic NOS, thoracic NOS
C76	Malignant neoplasm of other and ill-defined sites. Excludes: malignant neoplasm of: genitourinary tract NOS: female, male. Lymphoid, haematopoietic and related tissue, unspecified site
C77	Secondary and unspecified malignant neoplasm of lymph nodes
C78	Secondary malignant neoplasm of respiratory and digestive organs
C79	Secondary malignant neoplasm of other and unspecified sites
C80	Malignant neoplasm without specification of site

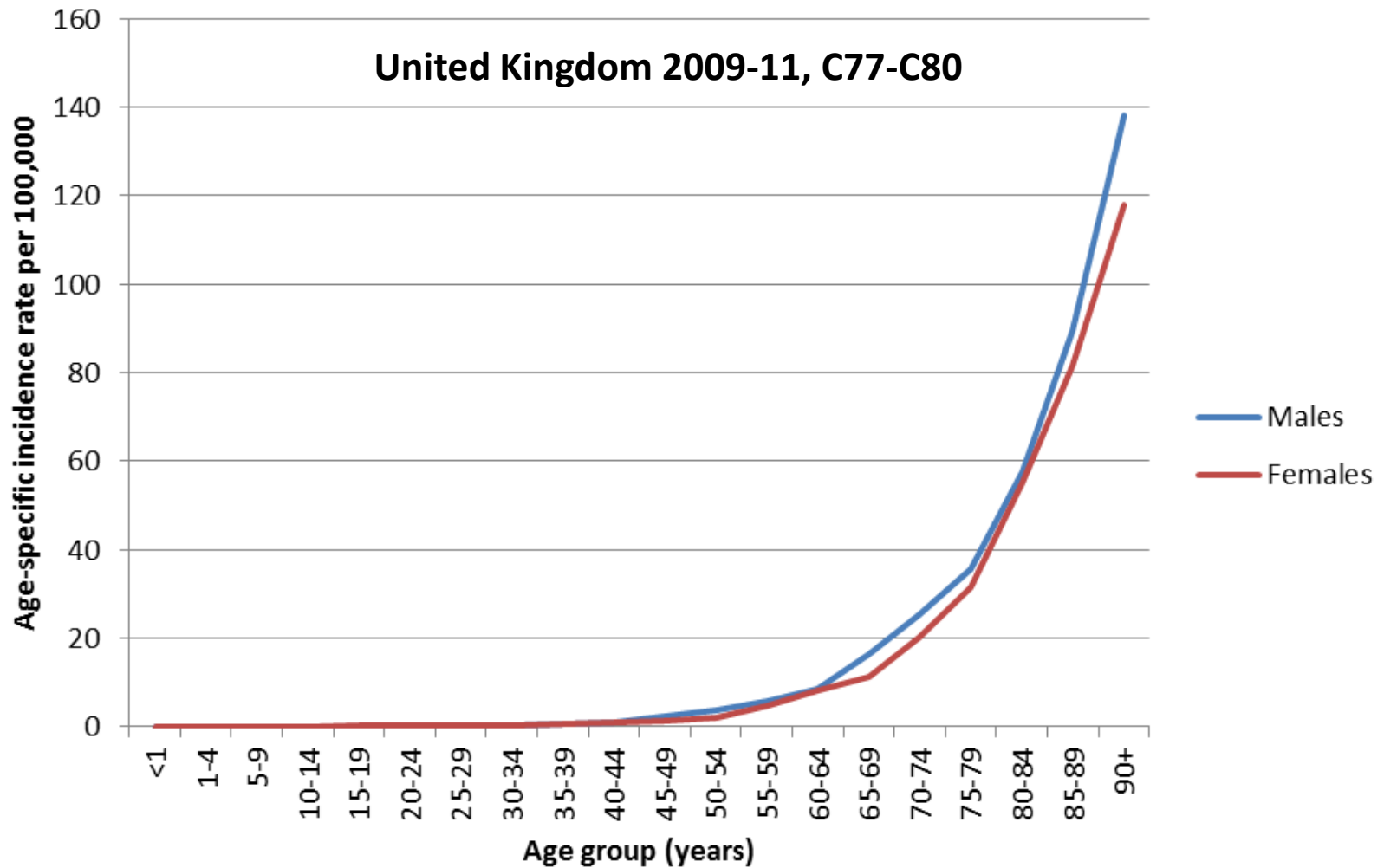


Incidence and mortality by region

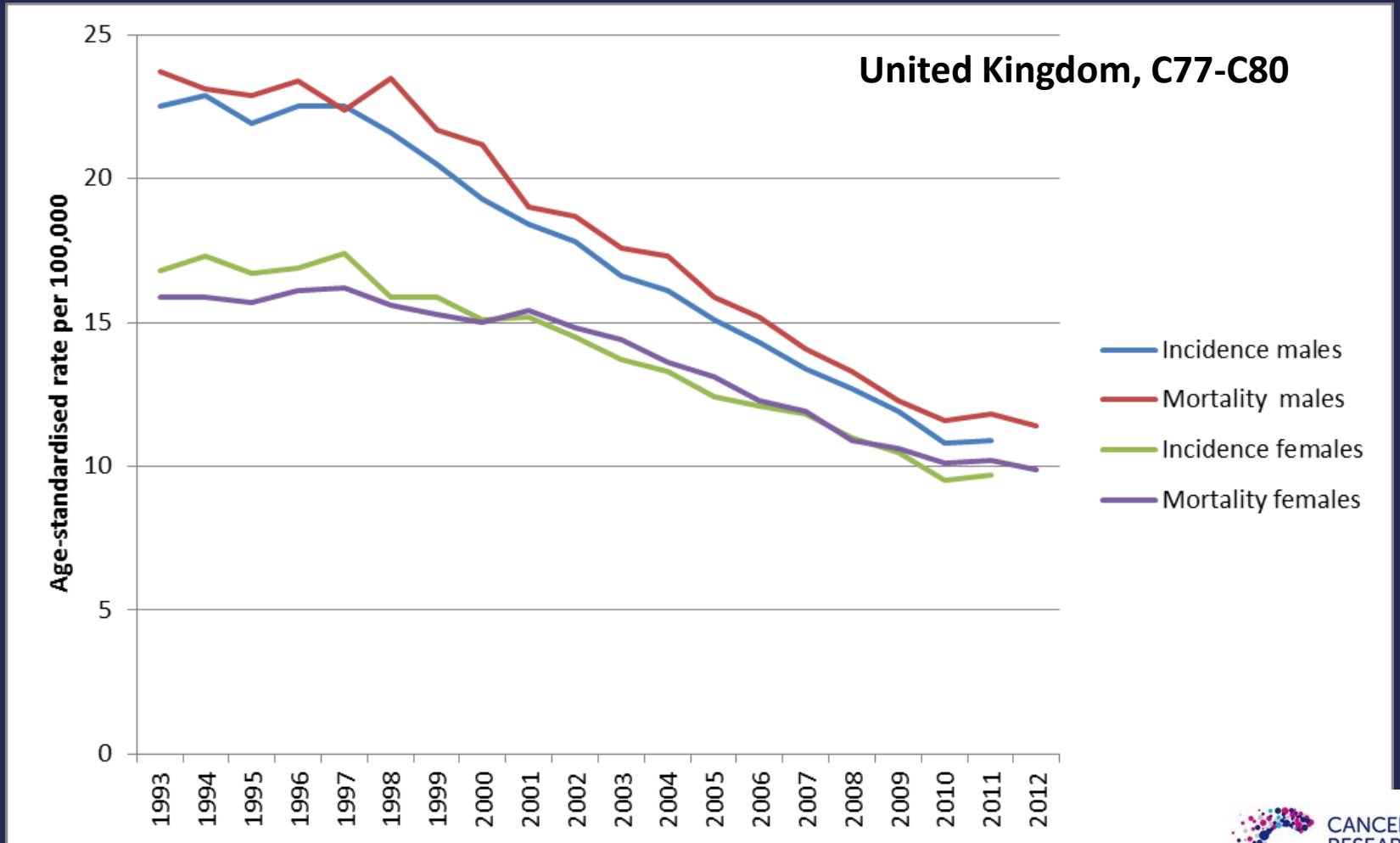


Source: CRUK, <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cancer-of-unknown-primary/incidence#heading-Zero>, accessed Sept 2015

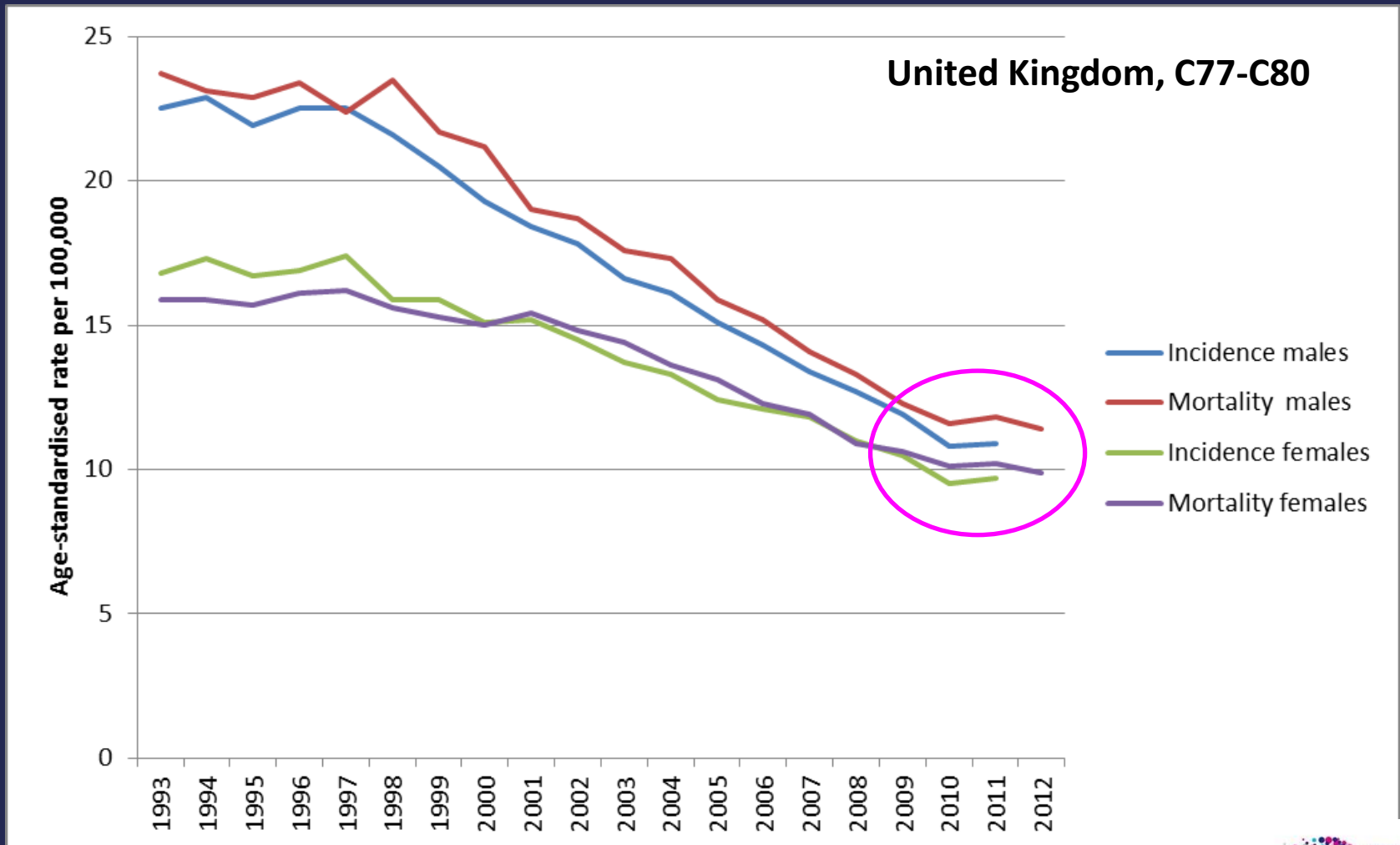
Incidence by age group



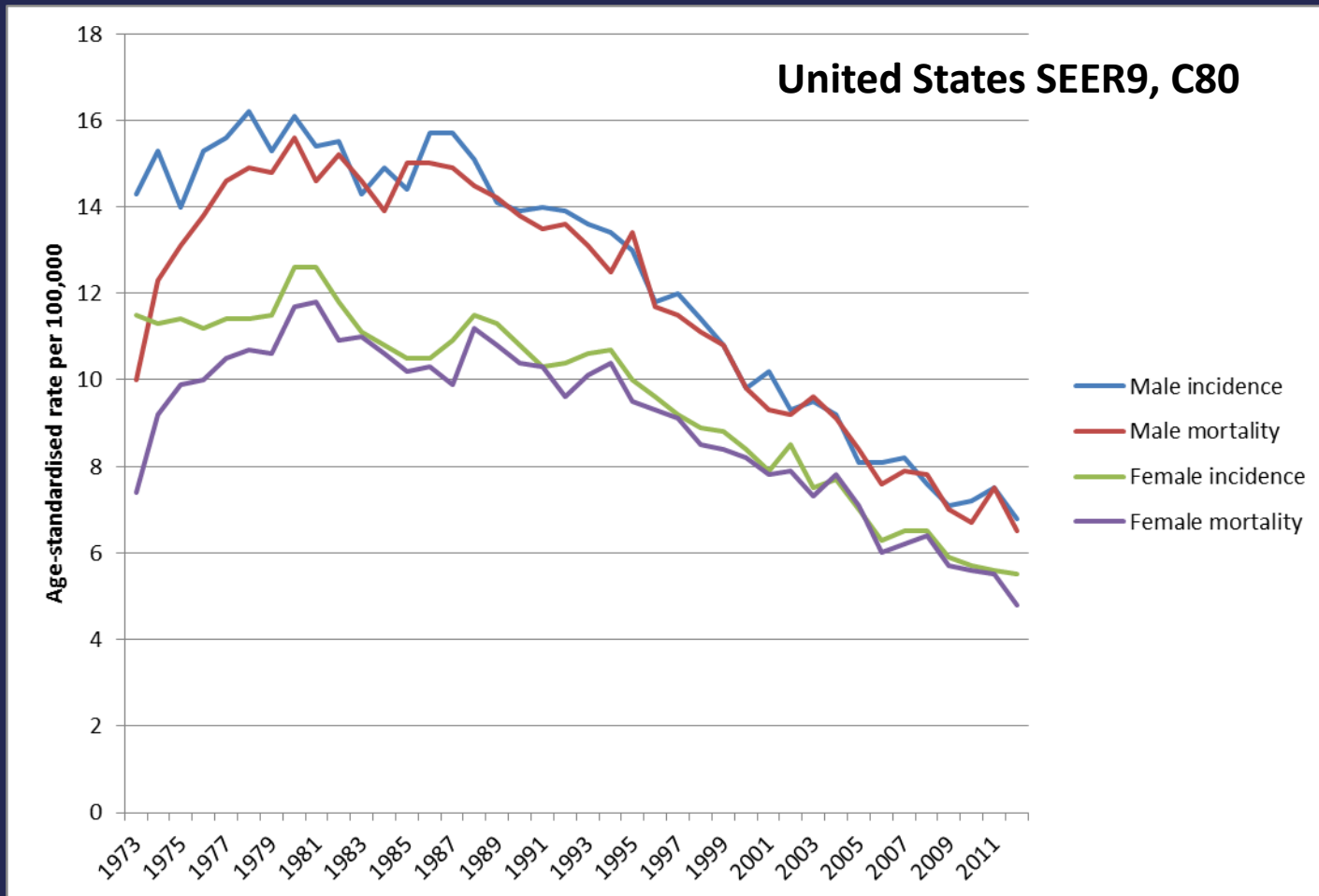
Incidence and mortality trends



Incidence and mortality trends



Incidence and mortality trends

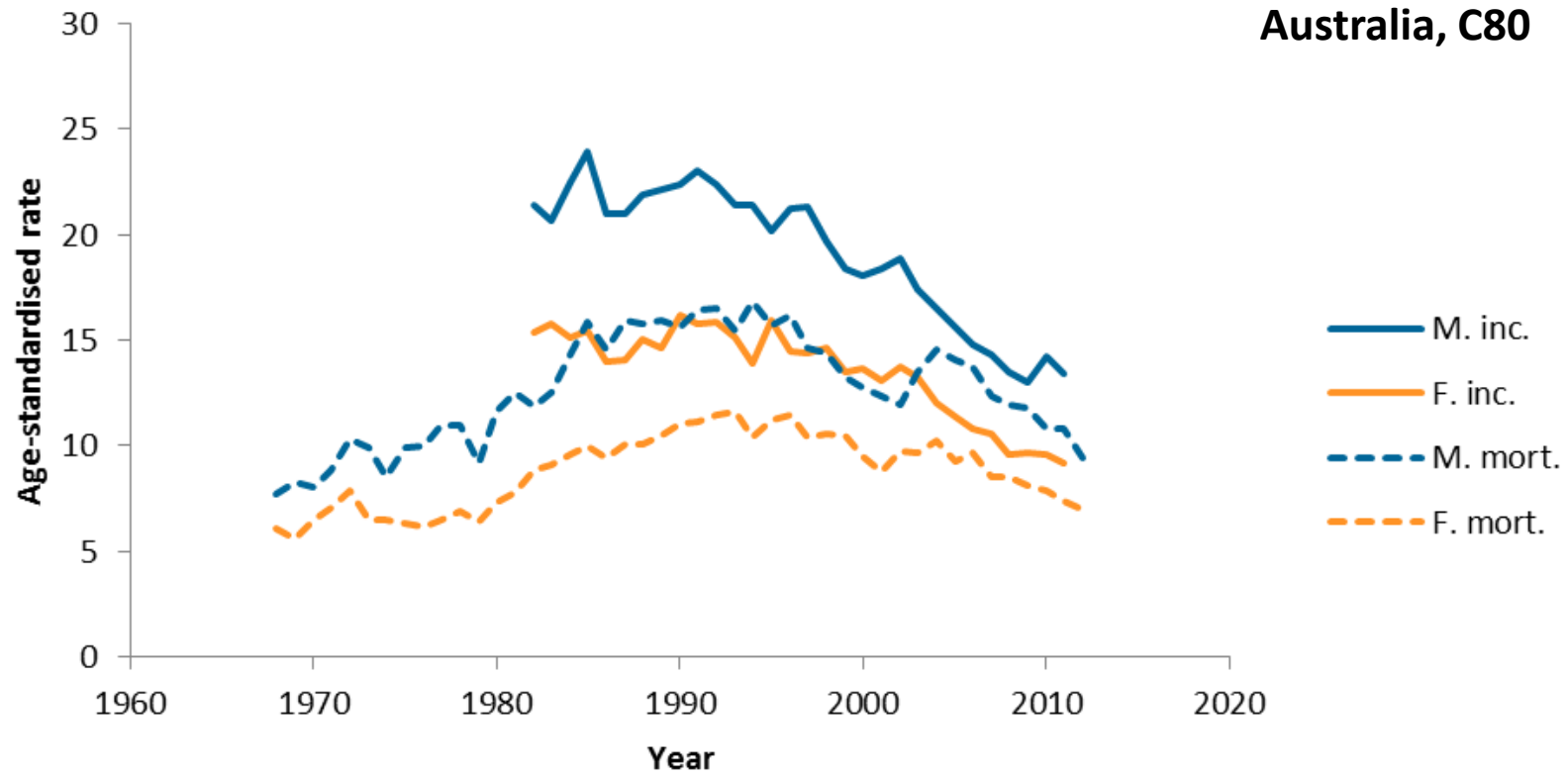


Source: Surveillance, Epidemiology and End Results (SEER) Program (www.seer.cancer.gov) SEER*Database. November 2014 (1973-2012). National Cancer Institute, released April 2015

Incidence and mortality trends

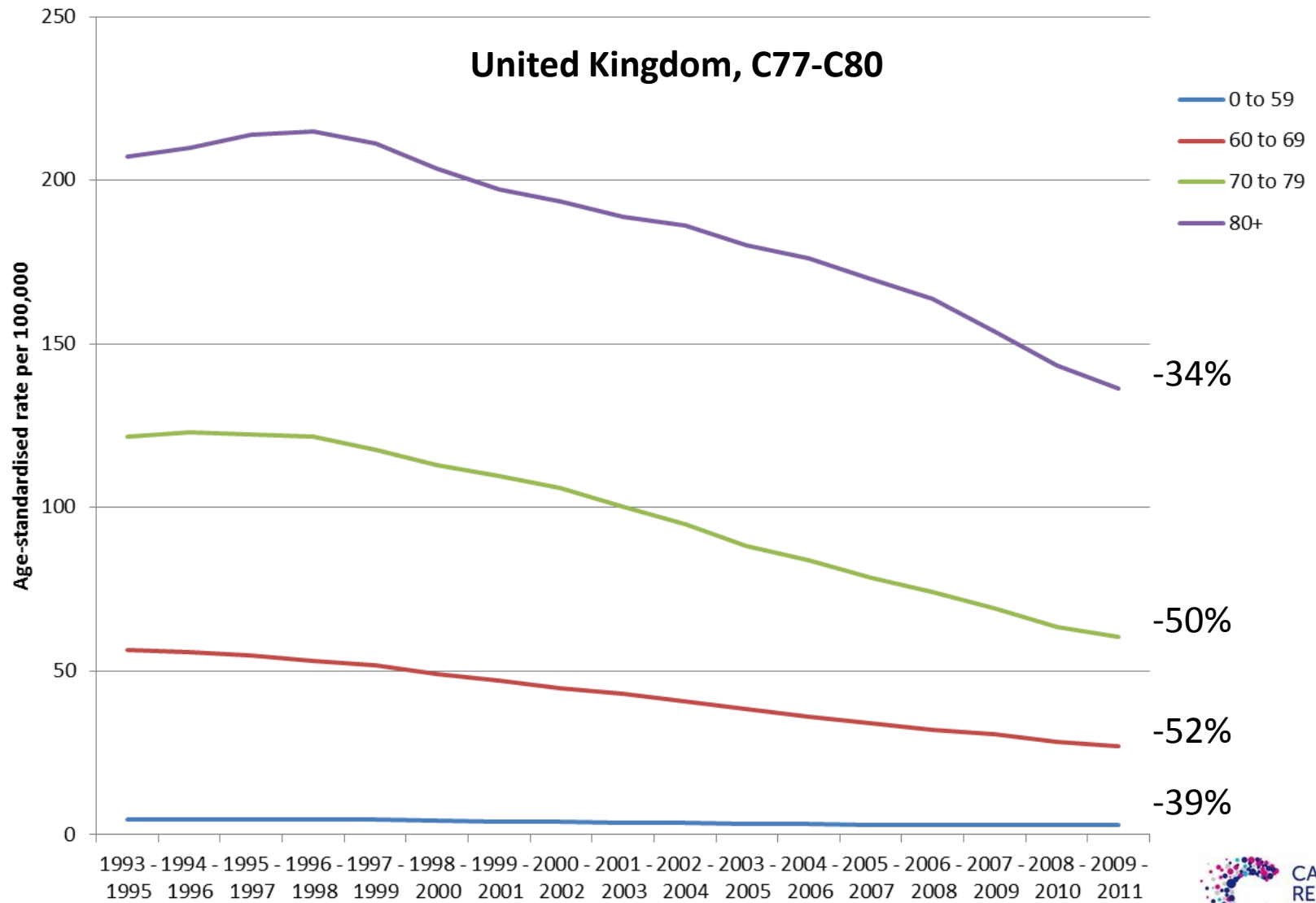
Age-standardised incidence and mortality rates by year

Australia, C80

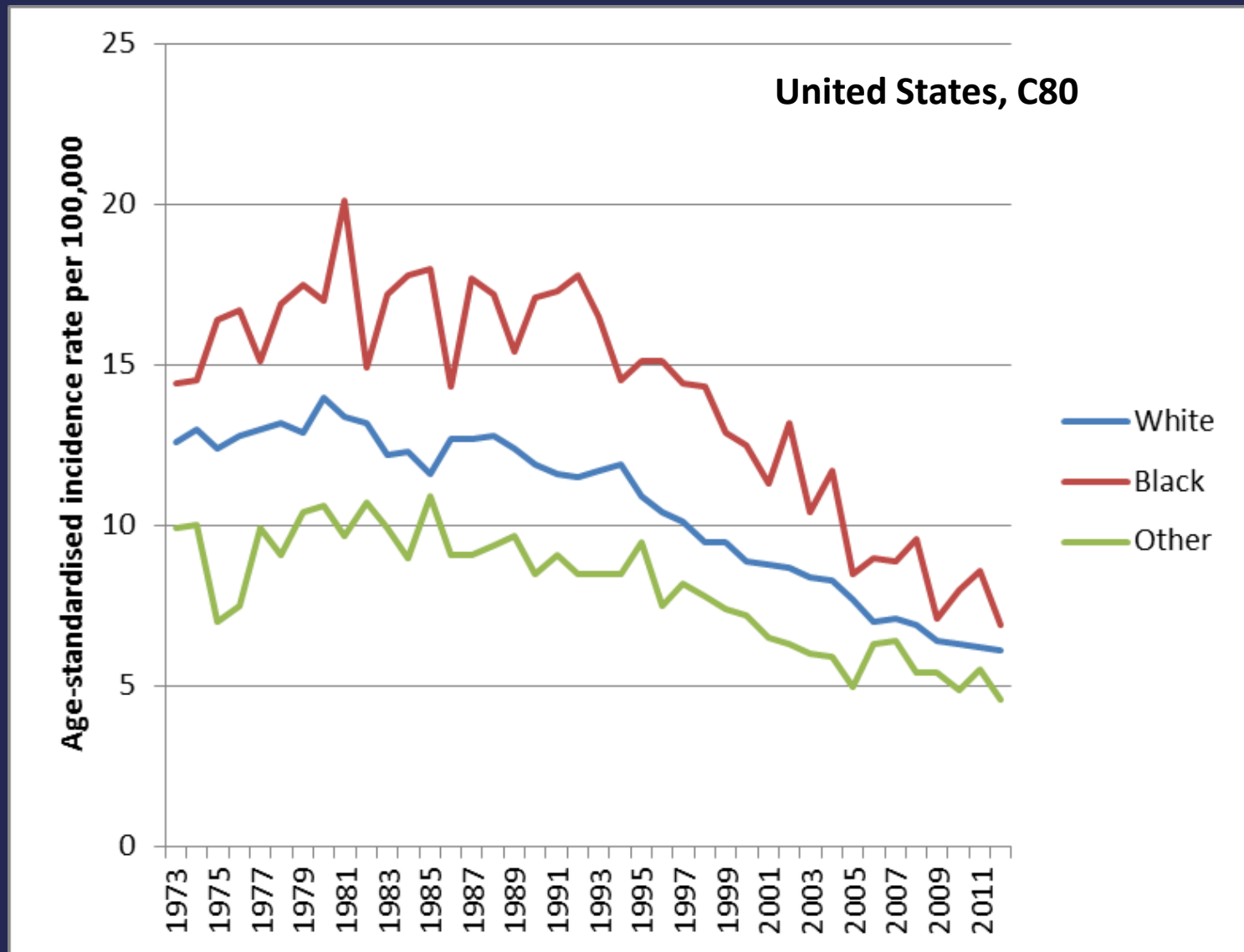


Source: Australian Institute of Health and Welfare

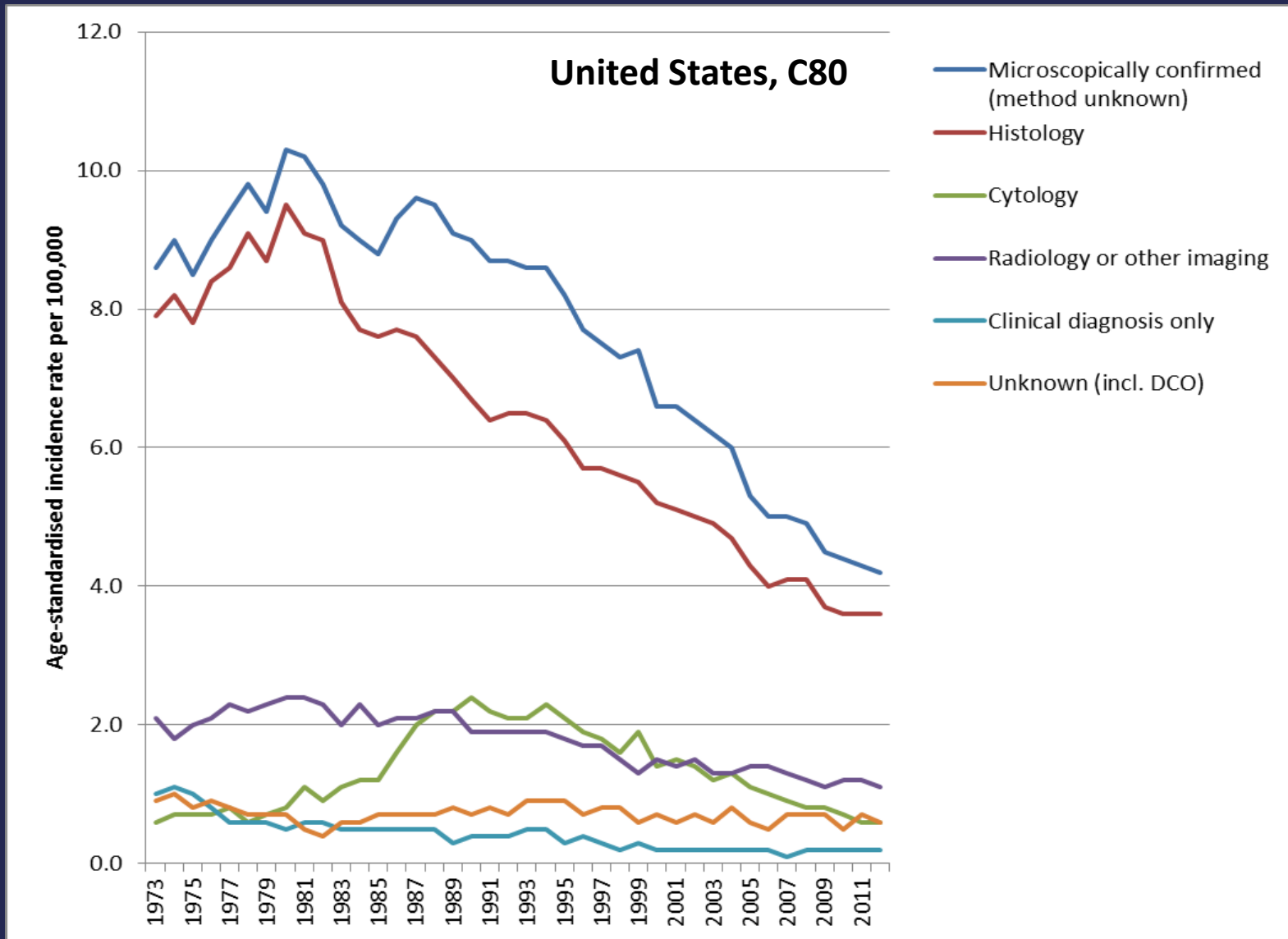
Incidence trends by age group



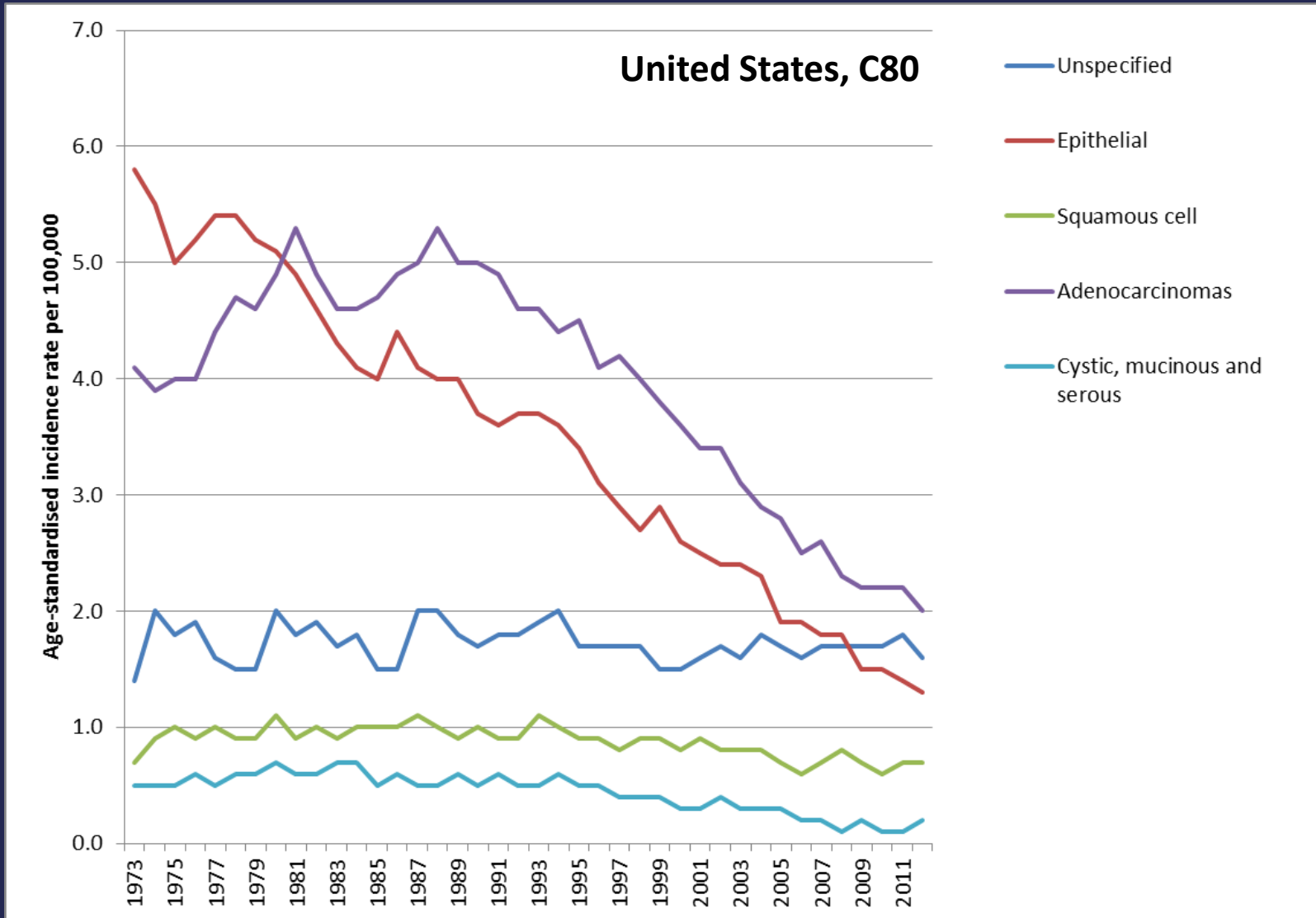
Incidence trends by race



Incidence trends by best basis of diagnosis



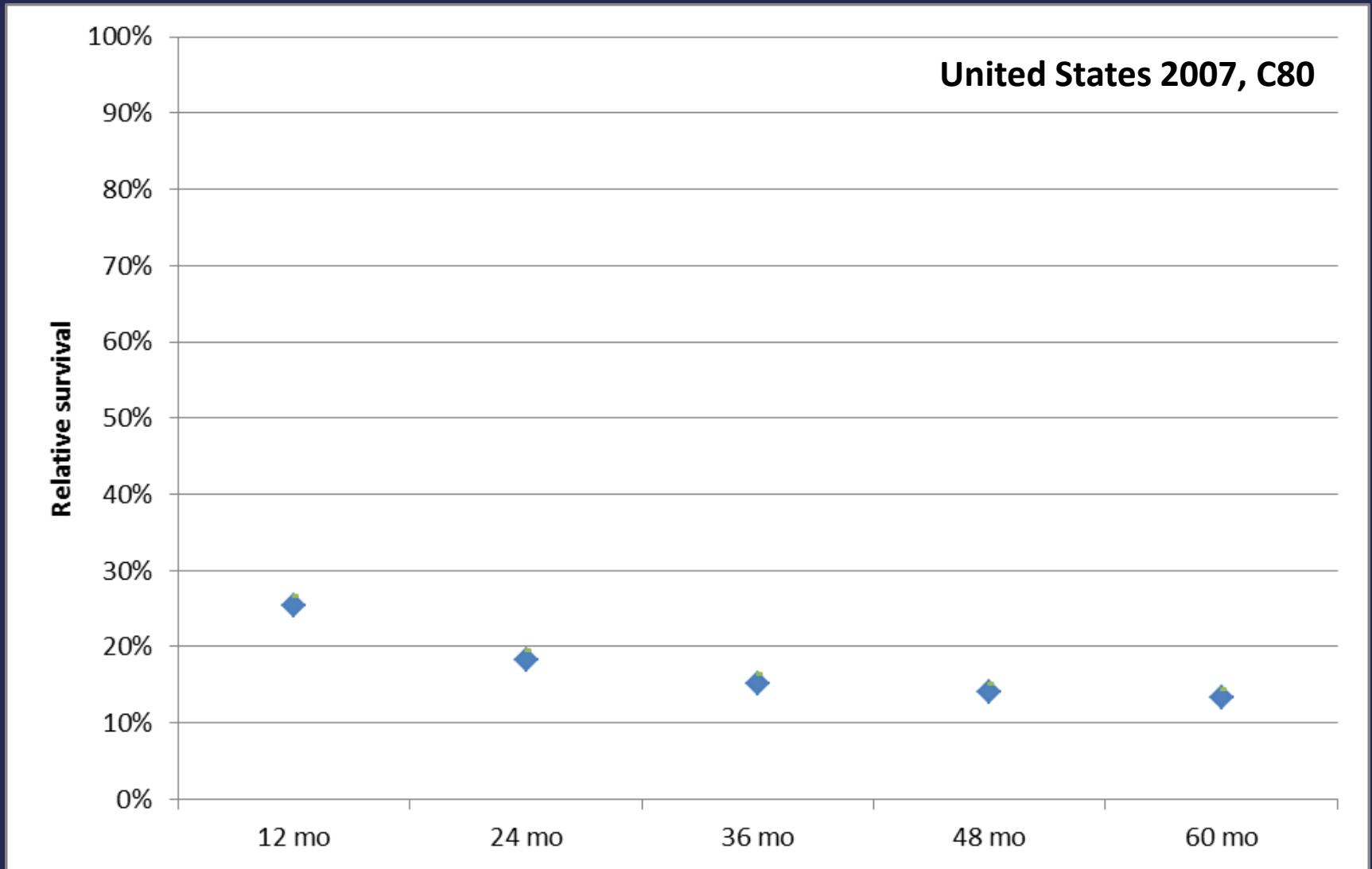
Incidence trends by morphology



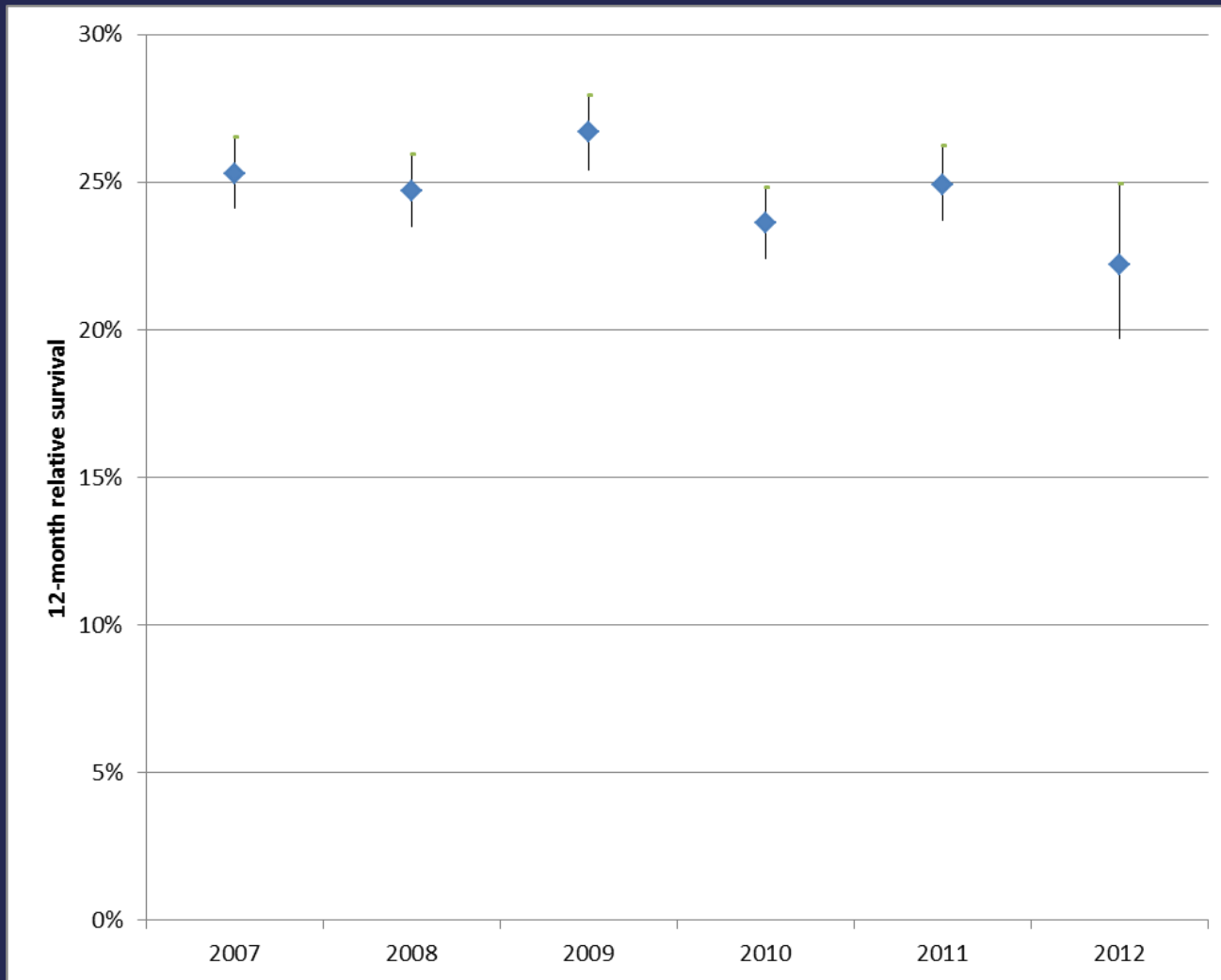
Explanations for trends

- Improved diagnostics
 - Imaging
 - Tissue sampling
 - Histopathology
 - Immunohistochemistry
 - Gene expression profiling
- Reduction in cancer risk factors (e.g. smoking)
- Earlier presentation / diagnosis
- Improved cancer registration practices

Relative survival



12-month relative survival trend United States



Relative survival time trends Northern Ireland

Age-standardised net survival estimates				
Sex	Period of diagnosis	6-month (95% CI)	One-year (95% CI)	Five-year (95% CI)
Male	1993-1998	20.7% (17.8%,23.7%)	13.9% (11.3%,16.5%)	7.4% (5.3%,9.5%)
	1999-2003	21.7% (18.6%,24.7%)	16.9% (14.1%,19.7%)	8.9% (6.6%,11.2%)
	2004-2008	29.8% (25.9%,33.7%)	22.0% (18.3%,25.6%)	13.8% (10.6%,17.1%)
	2009-2013	38.1% (33.8%,42.4%)	28.9% (24.6%,33.1%)	
Female	1993-1998	26.5% (23.5%,29.5%)	18.5% (15.8%,21.2%)	11.5% (9.1%,13.8%)
	1999-2003	26.0% (22.6%,29.3%)	17.3% (14.3%,20.3%)	8.8% (6.4%,11.1%)
	2004-2008	27.3% (23.4%,31.3%)	22.2% (18.5%,26.0%)	13.0% (9.7%,16.3%)
	2009-2013	31.9% (27.6%,36.3%)	26.6% (22.3%,30.9%)	
Both sexes	1993-1998	23.8% (21.7%,25.9%)	16.5% (14.6%,18.3%)	9.8% (8.2%,11.4%)
	1999-2003	23.7% (21.4%,25.9%)	17.0% (14.9%,19.0%)	9.0% (7.3%,10.6%)
	2004-2008	28.4% (25.7%,31.2%)	21.9% (19.3%,24.5%)	13.4% (11.1%,15.8%)
	2009-2013	35.1% (32.0%,38.1%)	27.9% (24.8%,30.9%)	

Source: Northern Ireland Cancer Registry, <http://www.qub.ac.uk/research-centres/nicr/CancerStatistics/OnlineStatistics/UnknownPrimary/> , accessed Sept 2015

Risk: access to health care

Australia

	Age-standardised incidence rate (95% CI)
Indigenous status	
Non-Indigenous	12.4 (12.1-12.8)
Indigenous	24.5 (19.7-30.0)
Residential remoteness	
Major cities	13.1 (12.8-13.3)
Inner regional	14.4 (13.9-14.8)
Outer regional	14.9 (14.2-15.7)
Remote & very remote	18.6 (16.6-20.9)

Source: Cancer in Australia 2010, Australian Institute of Health and Welfare,
<http://www.aihw.gov.au/publication-detail/?id=6442472459>, accessed Sept 2015

Socio-economic deprivation

	Australia ASR (95% CI)	Northern Ireland ASR (95% CI)
Socioeconomic deprivation		
1 st quintile (most deprived)	15.4 (14.9-16.0)	22.0 (19.4-24.7)
2 nd quintile	14.4 (13.9-14.9)	19.3 (17.0-21.7)
3 rd quintile	13.8 (13.3-14.3)	17.5 (15.3-19.7)
4 th quintile	12.6 (12.1-13.1)	15.8 (13.7-17.9)
5 th quintile (least deprived)	11.7 (11.3-12.2)	14.5 (12.6-16.5)

Sources: Cancer in Australia 2010, Australian Institute of Health and Welfare, <http://www.aihw.gov.au/publication-detail/?id=6442472459>, accessed Sept 2015
Northern Ireland Cancer Registry, <http://www.qub.ac.uk/research-centres/nicr/CancerStatistics/OnlineStatistics/UnknownPrimary/>, accessed Sept 2015

Health service use

UK, NCIN Routes to diagnosis project¹

Emergency presentation

CUP	57%
All cancers	23%

Australian DVA clients, 3 months prior to CUP²

Emergency dept OR 2.10 (1.16-3.80)

¹ http://www.ncin.org.uk/publications/data_briefings/routes_to_diagnosis_cancer_of_unknown_primary

² Vajdic et al. Cancer Epidemiology 2015;39:585-92.

Co-morbidity

Risk of CUP relative to general population (SIR):

Autoimmune disease 1.27 (1.22-1.32)

Hemminki 2015

Diabetes 1.71 (1.55-1.88)

Hemminki 2015

HIV 2.2 (1.6-3.0)

Engels 2008

Dialysis 2.71 (2.12-3.40)

Vajdic 2006

Kidney transplantation 5.79 (4.55-7.25)

Vajdic 2006

Co-morbidity

Australian Department of Veterans' Affairs clients

1 year prior to CUP, hospitalised for

Renal failure	OR 2.10 (1.16-3.80)
Weight loss	OR 3.25 (1.55-6.82)
Liver disease	OR 3.64 (1.31-10.1)

3 months prior to CUP, treated for

Hypertension	OR 1.45 (1.09-1.94)
Pain	OR 1.72 (1.25-2.37)
Congestive heart failure	OR 1.87 (1.21-2.89)
Mental ill-health	OR 2.56 (1.20-5.44)

Lifestyle factors

- European Prospective Investigation into Cancer and Nutrition (EPIC) cohort
- 476,940 aged 35-70 years enrolled 1992-2000
 - n=651 incident CUP (C809)
 - 273 adenocarcinoma
 - 140 carcinoma
 - 210 “malignant neoplasm”
 - 28 undifferentiated tumours

	All CUP (n=651)		CUP with survival ≤1yr (n=494)	
	Adjusted HR (95%CI)*	Fully adjusted HR (95%CI)**	Adjusted HR (95%CI)*	Fully adjusted HR (95%CI)**
Smoking				
Never smoked	1.00	1.00	1.00	1.00
Current smoker, 1-15/day	1.86 (1.44-2.40)	1.81 (1.39-2.34)	2.20 (1.65-2.93)	2.10 (1.57-2.80)
Current smoker, 16-25/day	3.46 (2.63-4.56)	3.25 (2.46-4.30)	3.94 (2.88-5.39)	3.61 (2.63-4.95)
Current smoker, 26+/day	4.05 (2.49-6.58)	3.66 (2.24-5.97)	5.80 (3.53-9.54)	5.12 (3.09-8.47)
Former smoker, quit ≤10 yrs	1.39 (1.04-1.87)	1.34 (0.99-1.80)	1.53 (1.10-2.14)	1.14 (0.88-1.47)
Former smoker, quit >10 yrs	1.10 (0.88-1.38)	1.08 (0.86-1.36)	1.16 (0.90-1.50)	1.52 (0.97-2.40)

* Adjusted by age, sex, study centre

** Also adjusted by education level, BMI, waist circumference, avg lifetime alcohol consumption

	All CUP (n=651)		CUP with survival ≤1yr (n=494)	
	Adjusted HR (95%CI)*	Fully adjusted HR (95%CI)**	Adjusted HR (95%CI)*	Fully adjusted HR (95%CI)**
Waist circumference				
Quartile 1 (low)	1.00	1.00	1.00	1.00
Quartile 2	0.90 (0.70-1.16)	0.91 (0.71-1.16)	0.87 (0.66-1.15)	0.87 (0.66-1.15)
Quartile 3	1.03 (0.81-1.31)	1.02 (0.80-1.30)	0.97 (0.74-1.27)	0.95 (0.73-1.25)
Quartile 4 (high)	1.34 (1.06-1.71)	1.29 (1.02-1.65)	1.41 (1.08-1.84)	1.34 (1.03-1.75)
<i>P linear trend</i>	<i><0.01</i>	<i>0.01</i>	<i><0.01</i>	<i>0.02</i>
Highest education level				
≤Primary school	1.00	1.00	1.00	1.00
Technical school	1.01 (0.82-1.25)	1.06 (0.86-1.31)	0.99 (0.78-1.25)	1.04 (0.82-1.32)
Secondary school	0.79 (0.59-1.06)	0.82 (0.61-1.10)	0.78 (0.56-1.09)	0.82 (0.58-1.14)
Further education	0.75 (0.58-0.98)	0.81 (0.62-1.06)	0.68 (0.50-0.92)	0.75 (0.55-1.01)

* Adjusted by age, sex, study centre

** Also adjusted by education level, BMI, waist circumference, smoking intensity, avg lifetime alcohol consumption

Lifestyle factors

- 3 Swedish biobanks linked to cancer registries
- N=475 incident CUP, 1992-2000
- Smoking
 - ever vs never OR 1.82 (1.48-2.26)
- BMI
 - ≥ 20 vs < 20 OR 0.77 (0.50-1.18)

Conclusions

- Incidence and mortality rates halved, CUP profile changing
- Survival rates modestly improved
- Risk factors emerging for all CUP
 - Elderly
 - Males
 - Smoking
 - Major illness
 - Waist circumference
 - Less education/socio-economic deprivation

Current and future steps

- Standardise CUP classification and reporting
- Identify risk factors for CUP subtypes
 - Educate high-risk groups
 - Prevention
 - Clues to biology and possibly treatment
- Education regarding the signs and symptoms of cancer → early diagnosis
- Ensure equality of access to diagnostic investigations, where clinically justified

Thank you!

Acknowledgements

Cancer Research UK

Northern Ireland Cancer Registry

United States Surveillance, Epidemiology and
End Results (SEER) Program

Australian Institute of Health and Welfare