Adenocarcinoma of the oesophagus: incidence and survival rates in New South Wales, 1972–2005

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ABSTRACT

Objective: To investigate trends in the incidence of adenocarcinoma (AC) of the oesophagus in New South Wales, factors associated with a diagnosis of AC, and factors associated with survival of patients with AC.

Design and setting: We examined all cases of invasive oesophageal cancer recorded in the NSW Central Cancer Registry from 1972 to 2005. The Accessibility/Remoteness Index of Australia was used to assess geographical remoteness and the Index of Relative Socio-Economic Disadvantage to assess socioeconomic status.

Main outcome measures: Incidence of AC; factors associated with diagnosis of AC and survival of patients with AC.

Results: The overall incidence of oesophageal AC in NSW increased in both males and females (annual percentage change, 4.2% [95% CL, 2.7%, 5.8%] in males [1988–2005] and 4.3% [95% CL, 1.8%, 7.0%] in females [1983–2005]). A diagnosis of AC was significantly associated with being male (adjusted odds ratio [AOR], 4.37 [95% CL, 3.84, 4.98]; $P < 0.001$); a younger age at diagnosis (P trend < 0.001); having distant rather than localised disease spread (AOR, 2.12 [95% CL, 1.82, 2.48]; $P < 0.001$); higher socioeconomic status (P trend < 0.001); and living in an inner regional area (AOR, 1.26 [95% CL, 1.11, 1.43]; $P < 0.001$) or outer regional area (AOR, 1.19 [95% CL, 1.00, 1.41]; $P = 0.05$) compared with a major city. Early diagnosis of AC was associated with substantial improvement in survival outcomes: patients with metastatic disease at diagnosis had a three times greater risk of dying than those with localised AC at diagnosis.

Conclusion: The incidence of AC is increasing in NSW. Possible contributing factors include increasing obesity, which is associated with increased incidence of gastro-oesophageal reflux disease. Survival may be improved by diagnosis at an earlier stage and changes in modifiable risk factors (eg, smoking, diet, exercise).

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The most common malignant tumours of the oesophagus are primary oesophageal tumours.[1] Of these, over 90% are squamous cell carcinomas (SCCs) and adenocarcinomas (ACs) of the oesophagus and gastro-oesophageal junction. Although SCC is the most prevalent type of oesophageal cancer throughout the world, its incidence has stabilised over the past 20–30 years. By contrast, the incidence of AC of the oesophagus and gastro-oesophageal junction has dramatically increased in the United States, Europe and Australia, particularly in men.[2-7] Unfortunately, symptoms often manifest late in the course of the disease, leading to diagnosis at a fairly advanced stage and thus a poor prognosis.

An association between alcohol and tobacco intake and SCC and AC is well established, although the mechanism is unclear.[3,8-10] Barrett's oesophagus, which is a consequence of chronic gastro-oesophageal reflux disease (GORD), is an important risk factor for AC of the oesophagus.[3,8,10,11] GORD is also an independent risk factor for AC of the oesophagus.[12]

The aim of our study was to investigate trends in the incidence of AC of the oesophagus in New South Wales, factors associated with a diagnosis of AC, and factors associated with survival of patients with AC.

METHODS

Data source

We examined all cases of invasive oesophageal cancer recorded in the NSW Central Cancer Registry (NSW CCR) from 1972 to 2005. Cases were selected based on the *International classification of diseases for oncology*, 3rd edition, topography codes C15.0–C15.9 for the period 1972–2005 and were divided into morphology codes for AC, SCC and other oesophageal cancers. The NSW CCR receives notifications of cancer in NSW residents from public and private hospitals, departments of radiation oncology, nursing homes, pathology laboratories, hospital outpatient departments and day-procedure centres as a statutory requirement.

Abbreviations

ABS	Australian Bureau of Statistics
AC	Adenocarcinoma
ARIA+	Accessibility/Remoteness Index of Australia
GORD	Gastro-oesophageal reflux disease
IRSD	Index of Relative Socio-Economic Disadvantage
LGA	Local government area
NSW CCR	New South Wales Central Cancer Registry
SCC	Squamous cell carcinoma

Degree of spread of cancer

The NSW CCR is run according to the rules of the International Association of Cancer Registries,[13] and is the only Australian cancer registry to record degree of spread at first diagnosis for all solid malignant tumours.[14] For each case, the degree of spread is assigned by the NSW CCR to one of four stages: localised, regional, distant (metastatic) or unknown. Degree of spread is defined as the maximum extent of disease, based on all diagnostic and therapeutic evidence received within 4 months of diagnosis. It follows the international coding guidelines for summary stage adopted by several international groups, including the World Health Organization and the International Association of Cancer Registries.[13]

Geographical classification

Cases in the sample were assigned to geographical remoteness categories using the Accessibility/Remoteness Index of Australia (ARIA+).[15] Each case was first allocated to a local government area (LGA) based on the patient's residential address at the time of diagnosis. ARIA+ categories were then applied via LGA classifications. LGAs were defined according to 2001 census information from the Australian Bureau of Statistics (ABS).[15]

1 Factors associated with a diagnosis of adenocarcinoma and other cancers of the oesophagus in New South Wales residents, 1972–2005

Variable	Adenocarcinoma ($n = 2445$)	SCC and other cancers ($n = 6518$)	Crude odds ratio	Adjusted odds ratio* (95% CL)	P
Sex					< 0.001†
Female	418 (17.1%)	2988 (45.8%)	1.00	1.00	
Male	2027 (82.9%)	3530 (54.2%)	4.20	4.37 (3.84, 4.98)	
Age group (years) at diagnosis					< 0.001†
0–39	30 (1.2%)	42 (0.6%)	1.00	1.00	
40–49	124 (5.1%)	212 (3.3%)	0.79	0.72 (0.39, 1.30)	0.27
50–59	378 (15.5%)	959 (14.7%)	0.56	0.52 (0.30, 0.92)	0.02
60–69	673 (27.5%)	1941 (29.8%)	0.47	0.47 (0.27, 0.81)	0.007
70–79	780 (31.9%)	2010 (30.8%)	0.53	0.56 (0.33, 0.98)	0.04
⩾ 80	460 (18.8%)	1354 (20.8%)	0.45	0.62 (0.36, 1.09)	0.10
Degree of cancer spread					< 0.001†
Localised	700 (28.6%)	2352 (36.1%)	1.00	1.00	
Regional	639 (26.1%)	1493 (22.9%)	1.45	1.60 (1.38, 1.85)	< 0.001
Distant	595 (24.3%)	792 (12.2%)	2.47	2.12 (1.82, 2.48)	< 0.001
Unknown	511 (20.9%)	1881 (28.9%)	0.90	0.94 (0.81, 1.08)	0.37
ARIA+ category‡					< 0.001†
Major cities	1062 (47.2%)	3225 (54.5%)	1.00	1.00	
Inner regional	839 (37.3%)	1863 (31.5%)	1.37	1.26 (1.11, 1.43)	< 0.001
Outer regional	322 (14.3%)	730 (12.3%)	1.34	1.19 (1.00, 1.41)	0.05
Remote/very remote	25 (1.1%)	96 (1.6%)	0.79	0.71 (0.44, 1.14)	0.16
IRSD quintile‡§					< 0.001†
1	519 (21.2%)	1200 (18.4%)	1.00	1.00	
2	477 (19.5%)	1335 (20.5%)	0.83	0.71 (0.60, 0.84)	< 0.001
3	507 (20.7%)	1232 (18.9%)	0.97	0.79 (0.67, 0.95)	0.01
4	515 (21.1%)	1376 (21.1%)	0.86	0.68 (0.58, 0.81)	< 0.001
5	426 (17.4%)	1375 (21.1%)	0.74	0.65 (0.54, 0.77)	< 0.001
Year of diagnosis			1.07	1.07 (1.07, 1.08)	< 0.001†

ARIA+ = Accessibility/Remoteness Index of Australia. IRSD = Index of Relative Socio-Economic Disadvantage. * Adjusted odds ratios were estimated using a logistic regression model with independent variables sex, age group at diagnosis, degree of cancer spread, ARIA+ category, IRSD quintile and year of diagnosis. † Overall P value. ‡ Data were missing in some categories. § Quintile 1, least disadvantaged; quintile 5, most disadvantaged. ◆

Socioeconomic status

Socioeconomic status of patients was estimated using the Index of Relative Socio-Economic Disadvantage (IRSD), one of four Socio-Economic Indexes for Areas created by the ABS.[16] The IRSD score for each LGA was taken from 2001 census information and categorised into population-weighted quintiles.

Death from cancer and non-cancer-related causes

Information on cancer deaths is routinely received by the NSW CCR from the NSW Registry of Births, Deaths and Marriages, from hospitals and from the ABS. Further linkage of death information from the National Death Index to the NSW CCR was conducted to obtain information on people with oesophageal cancer who died of a non-cancer-related cause. Information on deaths from cancer-related causes was considered complete up to the end of 2005, but for deaths from non-cancer-related or unknown causes, information was complete only up to the end of 2004. Thus, to avoid potential bias in our analysis, we used 31 December 2004 as the censoring date for all-cause survival in people diagnosed with oesophageal cancer.

Statistical analysis

Age-standardised rates of cancer incidence and survival were calculated using the 2001 Australian population as the standard. Population estimates for NSW as a whole, as well as the standard Australian population and LGA populations, were obtained from the ABS (estimated residential population) and accessed via the Health Outcomes Indicator Statistical Toolbox, a population data access and analysis facility available through NSW Health. Trend analyses were performed using the Joinpoint Regression Program provided by the US National Cancer Institute (http://srab.cancer.gov/joinpoint).

Factors associated with diagnosis of AC were examined using logistic regression and reported as crude (univariate) and adjusted odds ratios (ORs), with statistical significance reported at the $P < 0.5$ (two-tailed) level.

Survival analysis was undertaken to examine factors associated with death from any cause. A Cox proportional hazards regression model was used, with statistical significance reported at the $P < 0.10$ (two-tailed) level.

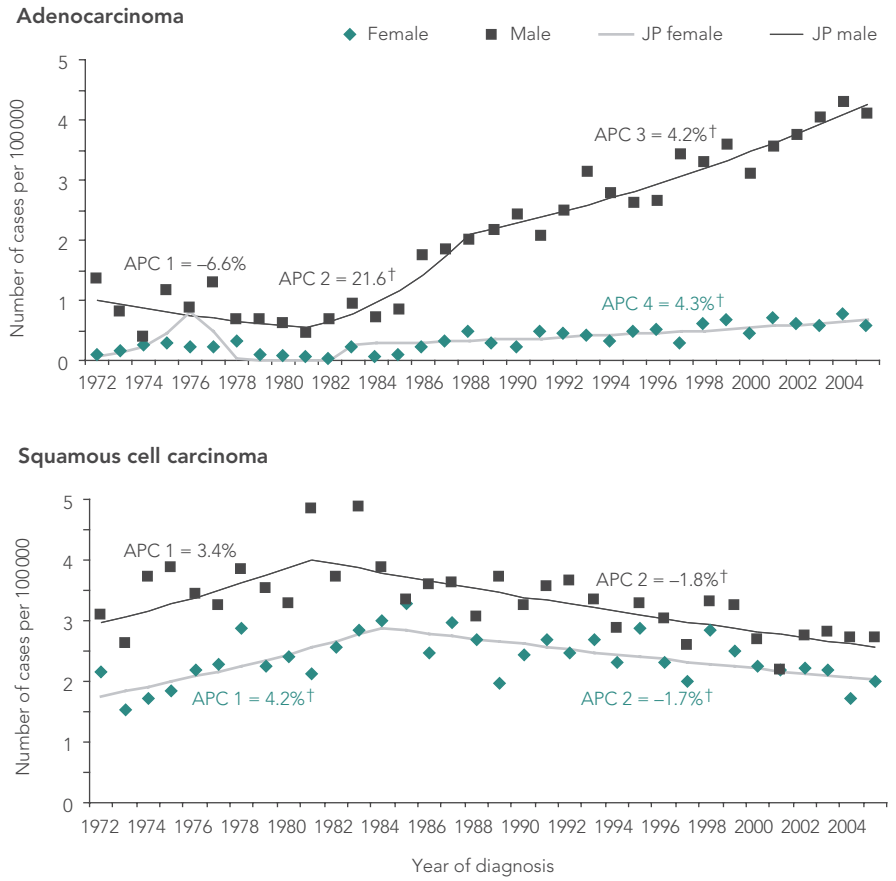
All statistical analysis was performed using SAS software, version 9 (SAS Institute Inc, Cary, NC).

RESULTS

Over the period 1972–2005, 2445 cases of AC and 6518 cases of SCC and other oesophageal cancers were recorded in the NSW CCR (Box 1). Age-standardised incidence rates of AC increased significantly for both males and females (Box 2). In males, the annual percentage change in AC age-standardised incidence between 1972 and 1981 (estimated) was not significant (−6.6% [95% CL, −13.4%, 0.8%]); between 1981 and 1988 (estimated), there was a sharp increase in AC incidence (annual percentage change, 21.6% [95% CL, 10.8%, 33.5%]; $P < 0.001$); and from 1988 (estimated) AC incidence increased significantly, though at a lower rate (annual percentage change, 4.2% [95% CL, 2.7%, 5.8%]; $P < 0.001$). In females, the age-standardised incidence of AC increased significantly from 1983 (estimated), with an annual percentage change of 4.3% (95% CL, 1.8%, 7.0%) between 1983 and 2005.

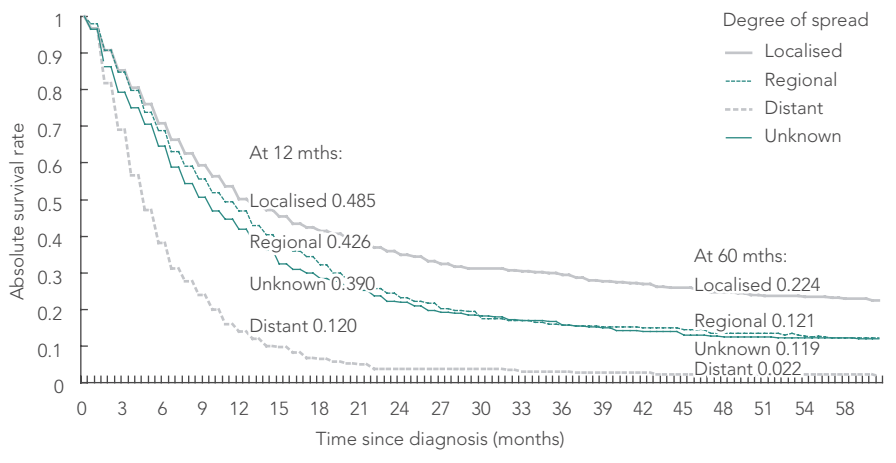
By contrast, age-standardised incidence rates of SCC rose in the 1970s but began to

2 Age-standardised incidence and joinpoint analysis of oesophageal adenocarcinoma and squamous cell carcinoma in New South Wales residents, by sex, 1972–2005*



APC = annual percentage change (joinpoint analysis). JP = joinpoint analysis. * *International classification of diseases for oncology*, 3rd edition, morphology codes 814–826, 831–832, 848, 849, 857 (for adenocarcinoma) and 805–808 (for squamous cell carcinoma). † Significant at $P < 0.05$ level. ◆

3 Kaplan–Meier curve:* all-cause survival in New South Wales residents with oesophageal adenocarcinoma, by degree of cancer spread at diagnosis



* Product limit method. ◆

fall again in the 1980s. In males, a significant fall in SCC incidence began in 1981 (estimated), with an annual percentage change of –1.8% occurring annually since that year (95% CL, –2.4%, –1.2%; $P = 0.007$). In females, there has been an annual percentage change of –1.7% (95% CL, –2.5%, –0.8%; $P = 0.03$) since 1984 (estimated).

A diagnosis of AC rather than SCC or other cancers was associated with being male (adjusted OR [AOR], 4.37 [95% CL, 3.84, 4.98]; $P < 0.001$); having a younger age at diagnosis (P trend < 0.001); progressive year of diagnosis (P trend < 0.001); having higher socioeconomic status (P trend < 0.001); living in an inner regional area (AOR, 1.26 [95% CL, 1.11, 1.43]; $P < 0.001$) or an outer regional area (AOR, 1.19 [95% CL, 1.00, 1.41]; $P = 0.05$) compared with a major city; and having regional disease spread (AOR, 1.60 [95% CL, 1.38, 1.85]; $P < 0.001$) or distant (metastatic) disease spread (AOR, 2.12 [95% CL, 1.82, 2.48]; $P < 0.001$) rather than localised disease (Box 1).

One-year absolute survival proportions for patients diagnosed with AC between 1972 and 2004 were 48.5% (95% CL, 44.5%, 52.4%) for localised cancer; 42.6% (95% CL, 38.6%, 46.6%) for cancer with regional spread; and 12.0% (95% CL, 9.3%, 15.1%) for cancer with distant spread (Box 3).

Proportional regression analysis (Box 4) showed that the adjusted hazard ratio (AHR) for poor all-cause survival was three times higher in AC patients with distant cancer spread than in patients with localised disease (AHR, 3.10 [95% CL, 2.70, 3.56]; $P < 0.001$). Increasing age at diagnosis ($P < 0.001$), earlier period of diagnosis ($P < 0.001$), and living in a regional area rather than a major city (P trend $= 0.09$) were also associated with poorer survival. There was no association between sex or socioeconomic status and absolute survival in patients with AC.

DISCUSSION

The incidence of oesophageal AC has increased in NSW since 1972, in line with trends in Australia as a whole[7] and throughout the Western world.[3-6] A falling prevalence of *Helicobacter pylori* infection may contribute to the increasing incidence of GORD, and hence AC. Another possible factor contributing to the increase in AC is the rise in obesity/body mass index with age that has occurred in recent times.[8,9,17,18] It has been suggested that increased abdominal pressure due to obesity can cause

4 Factors associated with all-cause survival in New South Wales residents with oesophageal adenocarcinoma, 1972–2004

Variable	Died ($n = 1895$)	Survived* ($n = 378$)	Crude hazard ratio	Adjusted hazard ratio† (95% CL)	*P*
Sex					0.52‡
Female	332 (17.5%)	59 (15.6%)	1.00	1.00	
Male	1563 (82.5%)	319 (84.4%)	0.91	1.04 (0.92, 1.19)	
Age group (years) at diagnosis					< 0.001‡
0–39	20 (1.1%)	9 (2.4%)	1.00	1.00	
40–49	99 (5.2%)	23 (6.1%)	1.29	1.29 (0.78, 2.12)	0.32
50–59	272 (14.4%)	80 (21.2%)	1.29	1.42 (0.89, 2.27)	0.14
60–69	501 (26.4%)	131 (34.7%)	1.49	1.63 (1.03, 2.59)	0.03
70–79	633 (33.4%)	91 (24.1%)	1.77	1.99 (1.26, 3.15)	0.003
⩾ 80	370 (19.5%)	44 (11.6%)	2.27	3.01 (1.88, 4.82)	< 0.001
Degree of cancer spread					< 0.001‡
Localised	478 (25.2%)	165 (43.7%)	1.00	1.00	
Regional	509 (26.9%)	92 (24.3%)	1.26	1.38 (1.21, 1.58)	< 0.001
Distant	498 (26.3%)	44 (11.6%)	2.70	3.10 (2.70, 3.56)	< 0.001
Unknown	410 (21.6%)	77 (20.4%)	1.35	1.30 (1.13, 1.49)	< 0.001
ARIA+ category					0.09‡
Major cities	838 (44.2%)	154 (40.7%)	1.00	1.00	
Inner regional	638 (33.7%)	131 (34.7%)	1.02	1.09 (0.98, 1.22)	0.11
Outer regional	246 (13.0%)	59 (15.6%)	1.00	1.13 (0.97, 1.32)	0.11
Remote/very remote	18 (0.9%)	4 (1.1%)	0.91	0.71 (0.44, 1.14)	0.15
IRSD quintile§					0.52‡
1	396 (20.9%)	87 (23.1%)	1.00	1.00	
2	382 (20.2%)	66 (17.5%)	1.12	1.13 (0.98, 1.32)	0.10
3	394 (20.8%)	81 (21.5%)	1.00	1.04 (0.89, 1.21)	0.65
4	388 (20.5%)	84 (22.3%)	1.09	1.10 (0.94, 1.27)	0.24
5	335 (17.7%)	59 (15.6%)	1.03	1.07 (0.91, 1.25)	0.42
Period of diagnosis					< 0.001‡
2000–2004	509 (26.9%)	260 (68.8%)	1.00	1.00	
1990–1999	874 (46.1%)	99 (26.2%)	1.49	1.27 (1.13, 1.42)	< 0.001
1980–1989	348 (18.4%)	10 (2.6%)	1.37	1.52 (1.32, 1.76)	< 0.001
1972–1979	164 (8.7%)	9 (2.4%)	1.18	1.68 (1.39, 2.03)	< 0.001

ARIA+ = Accessibility/Remoteness Index of Australia. IRSD = Index of Relative Socio-Economic Disadvantage. * As at 31 December 2004. † Adjusted hazard ratios were estimated using a Cox proportional hazards regression model with independent variables sex, age group at diagnosis, degree of cancer spread, ARIA+ category, IRSD quintile, and period of diagnosis. ‡ Overall *P* value. § Quintile 1, least disadvantaged; quintile 5, most disadvantaged. ◆

GORD. Furthermore, the effect of obesity and reflux has been shown to be synergistic — that is, the mechanism of association between obesity and AC is not necessarily only via GORD.[8]

Rates of obesity and excessive alcohol consumption have been reported to be higher in rural than metropolitan areas.[18-20] These may be contributing factors to the higher odds of being diagnosed with oesophageal AC in regional areas. Lack of access to specialists in regional areas may also correlate with the increased incidence of AC in rural communities. Programs of "open-access" endoscopy, allowing general practitioners to refer patients directly for diagnostic endoscopy (in accordance with American Society for Gastrointestinal Endoscopy guidelines) without an initial gastrointestinal examination, have been advocated to reduce costs and waiting times for remote and rural patients.[21]

The higher incidence of oesophageal AC in males may reflect the fact that men are less likely than women to consult a GP when they experience early warning signs of AC (such as dysphagia and weight loss).[22]

Unfortunately, survival of patients with oesophageal cancer is poor, especially those with metastatic disease. Over 21% of patients with AC in our study had metastatic disease at diagnosis, a significantly higher proportion than in those with SCC and other cancers. Nevertheless, early diagnosis of AC was associated with substantial improvement in survival: patients with localised AC at diagnosis had survival rates three times higher than those with metastatic cancer at diagnosis. Survival from AC has also improved over time, despite the proportion of distant metastases increasing in the past decade. This may reflect improvements in diagnostic and imaging techniques, resulting in earlier and more appropriate interventions.

Some authors have recommended surveillance of patients with Barrett's oesophagus who are suitable for undergoing oesophagectomy, as it is cost-effective with regard to long-term outcome, with the interval between endoscopy procedures dependent on the presence or absence of dysplasia.[23] However, other studies of surveillance of Barrett's oesophagus have produced mixed results.[24-26] Endoscopic surveillance can monitor the progression of metaplasia to low-grade dysplasia, high-grade dysplasia or AC.[27] The cost-effectiveness of undergoing such a process in NSW needs to be evaluated.

As a preventive measure against oesophageal AC, education about good lifestyle practises (eg, healthy diet, reduced alcohol and tobacco use and greater physical activity) should be promoted, particularly in regional communities.

Our study had a number of limitations. As cancer data were not linked to information on behavioural risk factors, we could only speculate that the increase in oesophageal cancer, particularly AC, was associated with increases in body mass index and obesity in the NSW population.[18,28] Similarly, without linkage to disease registers or other data sources, it could only be speculated that the increase in AC was related to an increase in GORD. However, cohort studies overseas and in Australia have demonstrated a link between behavioural and environmental risk factors and oesophageal AC.[8,9]

A further limitation of our study was that ARIA+ and IRSD scores were assigned to LGA boundaries defined according to 2001 census information. Although year of diagnosis was included in the modelling to

account for changes over time, boundary changes could not be accounted for, as scores would be calculated based on populations that differed with respect to accessibility and socioeconomic status. Thus there was the potential for misclassification bias, particularly in areas that were considered "regional" 20–30 years ago but are now part of a "major city". However, although other geographical classifications have been used by the ABS in the past, remoteness classification based on standard geographical classification did not exist before 2001.[29] Furthermore, as a historical database, it is important that consistent numerator and denominator populations be applied to the NSW CCR. Reporting based on 2001 geographic boundaries is consistent with using the 2001 Australian population as the standard population.

Finally, the NSW CCR is yet to be evaluated for validity and completeness, but this will be done in the near future. Nevertheless, two measures of data quality are already available: the proportion of cases with histological verification and the proportion with a death certificate only.[2] The proportion of cases with histological verification in the NSW CCR has improved from 69% in 1972 to 87% in 2005, and has consistently been over 80% since 1980. Such percentages are only slightly lower than those of cancer registries in Denmark and the US.[2] Similarly, the proportion of cases with a death certificate only has been comparable to that of other registries at < 2% since 1972 (with the exception of the period 1983–1990, when active follow-up of cases was reduced due to lack of resources).

CONCLUSION

Although there has been some improvement in recent times, survival for patients with AC of the oesophagus is poor, particularly those diagnosed with metastatic disease. This suggests that any improvement in survival is most likely to be gained through prevention and early intervention for modifiable risk factors, as well as early detection in people at risk of developing oesophageal cancer. Until there is more consistent evidence to support screening of high-risk populations, prevention and early intervention activities should focus on reducing tobacco and alcohol consumption and reducing body weight.

COMPETING INTERESTS

None identified.

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