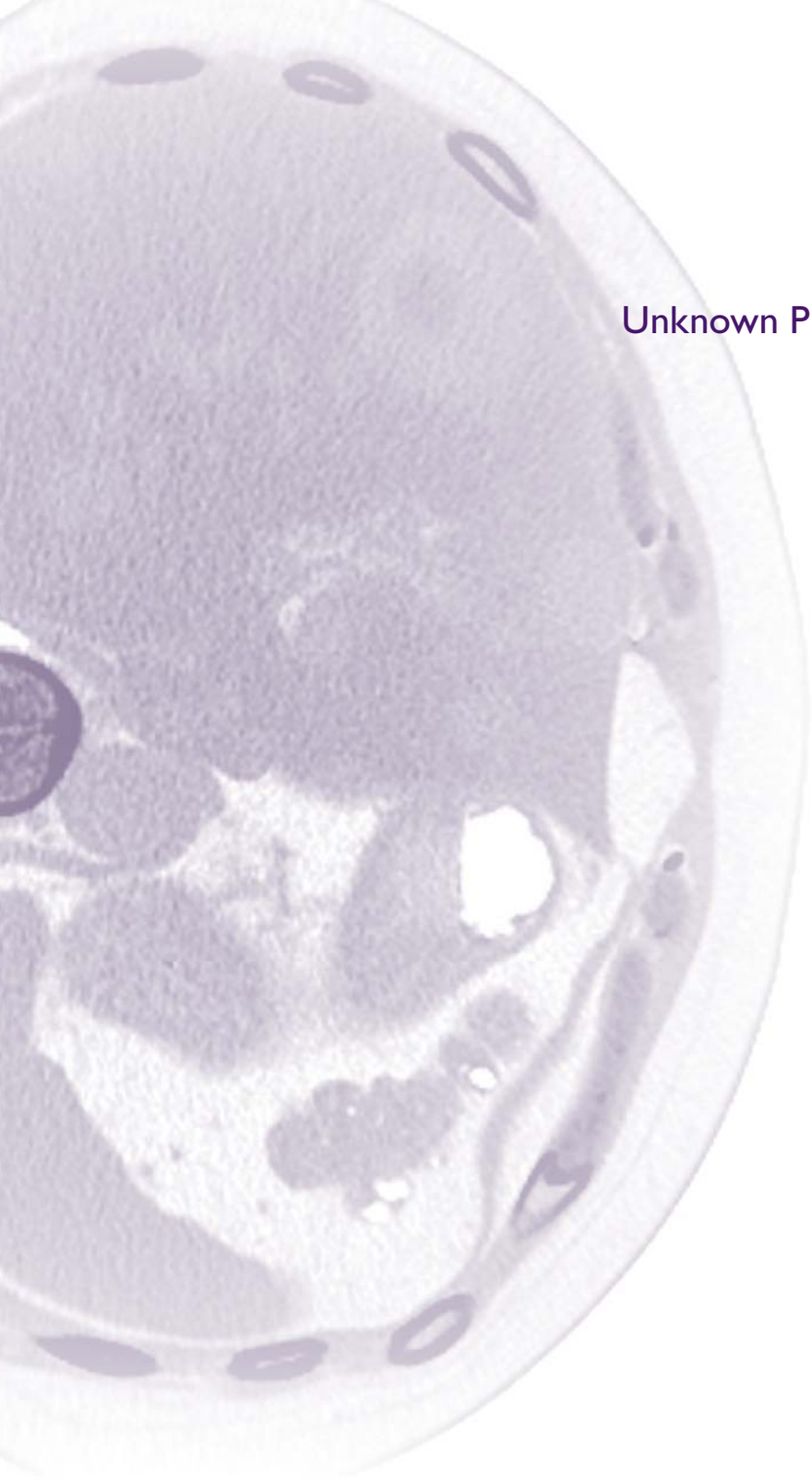

Cancer Institute NSW Monograph

Unknown Primary Cancer in New South Wales

May 2008

Elizabeth Tracey, Parisa Glass, David Roder,
David Currow, Paul Jelfs, James Bishop

The NSW Government agency dedicated to the control and cure of cancer through prevention, detection, innovation, research and information.

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Foreword from the Minister

In 2006 the NSW Government endorsed the *NSW Cancer Plan 2007–2010*. This plan provides an overall blueprint to make a substantial impact on the control and care of cancer in NSW.

One of the commitments in the *NSW Cancer Plan* was to make important cancer data more accessible to the public and others interested in this disease. This latest monograph from the Cancer Institute NSW provides a tangible outcome from that commitment.

Cancer without a primary site for the cancer at diagnosis is surprisingly common. It represents 4% of all cancers, but sadly 8% of cancer deaths. It is therefore an important cancer to understand so more effective strategies to control this cancer can be devised.

This report provides a comprehensive overview of this cancer, drawing on the extensive data available within the NSW Central Cancer Registry. It is hoped that making this information available will enable new opportunities for research and better treatment programs for this important group of patients.

I commend this report to you.

The Hon. Verity Firth MP

Minister for Climate Change and the Environment
Minister for Women
Minister for Science and Medical Research
Minister Assisting the Minister for Health (Cancer)

Chief Cancer Officer's report

Cancers of unknown primary site (CUP) represented around 4% of all new cases in New South Wales (NSW) in 2005. However, CUP was the third most common cause of cancer death after lung cancer and bowel cancer in NSW, representing 8% of all cancer deaths in 2005. Cancer registries reporting the incidence of CUP use this classification to monitor quality of reporting. Over use of this category can be interpreted as reflecting poor quality reporting and poor clinical follow up of cases. However, in clinical medicine, CUP has remained poorly defined and it is unclear whether this classification simply represents poorly documented clinical disease at presentation where a primary is not detected as above or a special pathological entity with distinctive features or a combination of these two possibilities.

This report clearly demonstrates that cancers of unknown primary differ from metastatic cancer for some key types of cancer. This suggests that at least some CUPs could represent a new type of cancer or a distinct genetic make-up, possibly from stem cells or other cells as yet undefined.

This report, *Unknown Primary Cancer in New South Wales,* documents some new observations about this cluster of cancers. The outcomes for around 14,500 cases were reviewed.

Overall, the prognosis is worse for CUP patients than patients presenting with metastatic cancer with an obvious primary site of cancer especially in the subgroup of adenocarcinoma CUP. However, squamous cell CUP patients do considerably better than those who have squamous cell cancers with a known primary site.

There are other differences noted between CUP and metastatic cancers, such as a higher proportion females and older individuals with CUP.

This report is one of the largest reported series of CUP and provides valuable insight into these cancers. It appears likely that in specific types of CUP where the outlook differs from other metastatic cancers, differences in the genetic make-up are also likely and warrant further research.

Professor Jim Bishop MD MMed MBBS FRACP FRCPA

Chief Cancer Officer
CEO, Cancer Institute NSW

Acknowledgements

This report was made possible through the collaboration of many people and organisations. We would particularly like to thank the Cancer Registry staff for their hard work in processing and coding the data. Survival matching was also undertaken for interstate records by the Australian Institute of Health and Welfare (AIHW). We would also like to thank Professors David Roder and David Currow for reviewing this report.

We appreciate the cooperation of medical records personnel in the supply of cancer notifications and the assistance of statutory notifiers, clinicians and pathologists. Also, the assistance of the Principal Registrar of Births, Deaths and Marriages (NSW) and the Australian Bureau of Statistics in their work to supply population and death data.

The NSW Central Cancer Registry is managed and funded by the Cancer Institute NSW under a Memorandum of Understanding with the NSW Department of Health Department.

Executive Summary

In 2005, there were 1,401 new cases of cancer of ill-defined or unknown primary site (CUP) in NSW (715 male, 686 female), accounting for 3.7% of all cancers in males and 4.6% in females. There were 940 cancer deaths from CUP (446 males and 494 females), which is 6.9% of male cancer deaths and 8.5% of female cancer deaths. Males were 1.3 times more likely to be diagnosed and 1.4 times more likely to die from CUP than females.

Cancers of unknown primary sites are routinely recorded in population-based cancer registries and in descriptive reports of registry data. They have traditionally been considered metastatic cancers where the primary site of origin had not been confirmed. Yet, cancers of unknown primary site are increasingly recognised as distinct clinical and pathological entities, characterised by rapid progression and atypical metastatic spread.[1] Registries commonly refer to the proportions of cancers in this category as indicators of data quality.

Historically, the simplest clinical definition has included all patients who present with histologically confirmed metastatic carcinoma in whom a complete medical history, careful physical examination and chest x-ray did not identify the primary site.[2] In recent times, more sophisticated diagnostic tools, such as: blood biochemistry; stool occult blood testing; urinalysis; histopathogical review of all biopsy material using immunohistochemistry and CT of the abdomen and pelvis; mammography; and sometime PET scan are considered to help define this group of patients.[3]

Cancer of ill-defined or unknown primary site includes the following: the digestive tract (ICD-10 C26), respiratory system and intrathoracic organs (C39), retroperitoneum and peritoneum (C48), ill-defined sites (C76) and unknown primary site (C80).

Trends in rates by histological grouping

The difference in rates between unknown primary on its own and ill-defined with the unknown primary is the proportion referred to as ill-defined.

From 1973 to 1977, there was a higher proportion of ill-defined cancer (22%) as a proportion of total unknown and ill-defined cancer. This proportion declined to 5% in 1980 and remained at this level until 1994, then increased to 15% in 2001.

- The increase in the two years from 2002 to 2003 is largely due to myeloproliferative disorders and myelodysplasias. These conditions were considered not to be invasive cancer prior to the introduction of ICD–03. These have now been removed and are considered a separate category.
- Other and unspecified specific carcinomas, followed by adenocarcinoma and squamous cell carcinoma, are the major histological groups that comprise unknown primary cancer.
- The change in rates for unspecified cancer follows the same trend as known primary cancer. Other specified cancers have not changed over time and are less than 1% of unknown primary cancers.

Differences in age-specific rates

Rates rose with increasing age in both sexes for both unknown and known primary cancers. For cancers of unknown primary site, rates increased for ages 45–49 in both males and females, with slightly higher rates in males aged 60 years and older.

For cancers with a known primary site, rates in males increased for ages 40–44 years. In females, rates exceeded males between the ages of 25–29 and 50–54 years. Thereafter, rates in males were double those in females.

- More females than males between the ages of 30–34 to 50–54 years were likely to be diagnosed with adenocarcinoma of unknown primary. Whereas from 55 years onwards, rates were similar in both sexes. In those with a known primary site, rates were higher in females up to 55–59, thereafter rates were higher in males.

- Rates for squamous cell carcinoma of unknown primary were similar for both males and females until 60–64 years and older; thereafter rates were slightly higher in males. By contrast, rates in those with a known primary cancer were higher in males than females for all ages.
- Specified types of cancer in known and unknown primary cancer cases were similar, with rates higher in females until 55–59. Thereafter rates were higher in males.
- Rates of unspecified neoplasms in both unknown and known primary sites were higher in males than for females for all ages until 70–74 years of age. Thereafter, rates were higher in females.

Trends in age-standardised rates by stage: known primary

Rates for localised stage of known primary tumours as a proportion of total cancers increased from 35% in 1972 to 41% in 1990. Thereafter, rates for localised cancer increased from 45% to 48% of total cancers in 1999–2003. Regional stage has declined in males from 21% of known primary tumours in 1973 to 15% in 2003, and remained consistent at 25% in females for the same time period. Rates for distant stage declined from 18% to 12% of known primary tumours in males and remained at 12% in females.

Trends in age-standardised rates by stage: unknown primary

Rates for the proportion of unknown stage and localised decreased for the time period 1992 to 1999 in all persons and in males. Since then, rates have been steadily increasing for the proportion of unknown stage and regional stage to 20% and 10% respectively of total unknown primary cancers in 2003.

There is very little difference between the pattern of presentation for unknown stage in both males and females. The majority of unknown primary cancers in all persons are late stage (distant metastases) at diagnosis. In 1973, 90% of total unknown primary cases had distant metastases, this proportion declined to 70% in 2003.

Differences by Area Health Service

A breakdown of standardised incidence ratios by Area Health Service of residence for unknown primary cancer in males, females and persons was undertaken to see if there were geographical differences in incidence rates.

Rates were significantly lower for unknown primary cancer in male residents of Northern Sydney and Central Coast Area Health Service; while rates in were significantly higher than NSW as a whole for males resident in Hunter New England and Greater Western Area Health Services. There is no significant difference in rates by Area Health Service for females.

Modelling of unknown primary cancer cases compared to known primary cancer all stages (1999–2003)

Between 1999 and 2003, there were 7,008 cancers of unknown and ill-defined site. Of these, 6,460 (92%) were true unknown primary cancers (C80), compared with 133,252 known primary cancers of known primary site. Logistic regression analysis indicates that the likelihood of diagnosis of unknown primary cases were:

- higher in females than males
- higher in those aged more than 75 years or older at diagnosis, compared to younger age groups
- more likely to be diagnosed with squamous cell carcinoma than adenocarcinoma
- three times more likely to be diagnosed with unspecified cancer than adenocarcinoma
- almost two times more likely to be diagnosed with unspecified than adenocarcinoma, but less likely to be diagnosed with a specific cancer than adenocarcinoma
- seven times more likely to be diagnosed with a regional lymph nodes involvement than localised
- 75 times more likely to be diagnosed with distant metastases and 13 times more likely to be diagnosed with unknown stage at diagnoses than localised
- more likely to have been diagnosed by clinical or cytological means than to be histologically verified at diagnosis.

The final multivariate model showed exactly the same results for the longer time period from 1980 to 2003 as the analysis on those diagnosed between 1999 and 2003.

Those diagnosed with late stage unknown primary cancer (distant metastases) have 80% (95%CI 70% to 92%) greater chance of dying in the first year after diagnosis, compared to the same stage in those with a known primary tumour.

Survival for all stages (1980–2003)

Known primary

Of the 285,616 with a known primary cancer diagnosed between 1980 and 2003: 129,437 (45%) had localised stage; 60,276 (22%) regional; 36,717 (12%) had distant metastases; and 59,186 (21%) were classified as unknown stage.

The median survival time for those diagnosed with a known primary cancer in this time period was:

- localised stage: 274 months
- regional stage: 42 months
- distant metastases: five months
- unknown stage: 56 months.

Overall, the median survival of known primary cancer is 107 months (95%CI 105–110).

For unknown primary cancers diagnosed between 1980 and 2003, 89% were diagnosed with distant metastases, 4% with regional lymph nodes and 7% with unknown stage. The median survival time was three months for distant metastases, 22 months for regional and six months for unknown stage.

Unknown primary

Of the 14,640 unknown primary cancers diagnosed in 1980–2003, 1,791 (1,144 dead from another cause and 647 alive) were censored. For the 12,849 who died from an unknown primary cancer, the median survival time was three months.

Unknown versus known primary

At 12-months post-diagnosis, 75% of people with a known primary site had survived, whereas only 19% of people with an unknown primary site had survived.

Seventy-five per cent of people with known cancers had died by 277 months (95% CI 274–282 months), while 75% of people with an unknown primary site had died by nine months (95% CI eight–nine months).

Survival for distant metastatic disease

All further analyses of survival were conducted with distant metastatic disease at diagnosis (36,717 with a known primary site versus 13,165 cancers of unknown primary site).

The relative risk of dying from cancer of unknown primary site compared to cancers where the primary site is known is:

- higher in males compared to females
- higher in those 75 years and older than the youngest age group
- lower if of high socioeconomic status (SES) compared to the lowest SES group
- lower if diagnosed with adenocarcinoma, squamous cell carcinoma and specified cancer; and higher for unspecified carcinoma and mesothelioma than unspecified cancer
- higher if the unknown primary cancer is cytologically and clinically verified than histological verification
- higher in earlier diagnostic time periods than more recent diagnosis periods.

Among metastatic cases, the risk of death for cancers of unknown primary site is 23% (95% CI 19–26%) higher than for cancers where the primary site is known while controlling for age, sex, socioeconomic status and histological type.

Introduction

Cancers of unknown primary (CUP) sites are routinely recorded in population-based cancer registries and in descriptive reports of registry data. They are metastatic cancers where the primary site of origin had not been discovered. While registries commonly refer to the proportions of cancers in this category as indicators of data quality, comparatively little emphasis has been placed on them in epidemiological analyses.

Yet, cancers of unknown primary site are increasingly recognised as distinct clinical and pathological entities, characterised by rapid progression and atypical metastatic spread[1] and cytogenic abnormalities detected, especially deletions of chromosome 1p.[4]

Patients with these cancers generally have advanced symptoms, often with malaise, weight loss, fatigue and weakness. Although subsets of these cancers are responsive to platinum-based chemotherapies and other systemic and localised treatments, these cancers generally have a very poor prognosis, with median survivals of around four months reported in a number of case series.[5–8]

While considerable effort has been directed at finding the primary sites of these cancers, this has had little effect on clinical outcomes. Accordingly, exhaustive searches for the primary lesion has been discouraged to avoid unnecessary patient duress and waste of clinical resources.[4]

Common primary sites associated with unknown primaries include the lung and pancreas, which are renowned for poor outcomes. Other common sites include breast, prostate, liver and large bowel.[1,4,6,9]

Risk factors

Since the exact type of a cancer of ill-defined and unknown primary site is not known, it is difficult to identify the risk factors. Smoking is probably an important risk factor since more than half of CUP patients have a history of smoking.* Other cancers of unknown primary site are eventually found to have started in the stomach, colon, or rectum, with known dietary risk factor association.

Diagnosis of unknown primary

Even though CUPs are commonly characterised with rapid progression and atypical metastatic spread,[1] clinically an accurate diagnosis of site of origin is of considerable interest because treatment and survival are influenced by the type of primary cancer. The success of most cancer treatments is directly dependent on correct diagnosis and staging of the cancer.

Historically, the simplest clinical definition has included all patients who present with histologically confirmed metastatic carcinoma in whom a complete medical history, careful physical examination and chest x-ray did not identify the primary site.[2]

In recent times, a diagnostic tools for investigation of unknown primaries may include: complete history, physical examination, complete blood count, routine chemistries, stool Hemoccult test, radiography, endoscopy, CT, MRI, tumour markers, mammography and more recent advances using position emission tomography.[4,10–15] At this stage, careful gross and histological examinations are the most important tools in determining the primary sites.[16] Metastatic cancers of unknown origin remain to be poorly diagnosed with relatively poor prognosis, depending on the type, site and stage of the disease.[4,10,17–23]

It has been suggested that diagnostic evaluation should be focused on distinguishing treatable from untreatable unknown primaries to provide the most appropriate treatment for best chance of response.[4] In this case, the role of genotype, phenotype and the biological behaviours of unknown primaries could become an important topic for review.[9,24]

* Tracey E, Baker D, Chen W, Stavrou E, Bishop J. Cancer in New South Wales: Incidence, Mortality and Prevalence, 2005. Sydney: Cancer Institute NSW, December 2007.

Over the past decade, the diagnosis of many diseases has improved due to advancements in medical technology. However, the diagnosis of unknown primary carcinomas remains a challenge for cancer medicine. The most extreme examples occur in the 15–25% of patients in whom the diagnosis of the primary site cannot be determined, even at post-mortem examination.[24]

A retrospective review of 657 consecutive patients with CUP (270 additional patients were excluded as a result of identification of a primary malignancy, a non-carcinoma cell type, or no malignancy) reported several variables of significant prognostic importance identified by multivariate analysis.[26]

Lymph node involvement and neuroendocrine histology were associated with longer survival, male sex, increasing number of involved organ sites, adenocarcinoma histology, and hepatic involvement was unfavourable prognostic factors. Adrenal involvement has also been noted to be a poor prognostic finding.[1,27]

Classification of unknown primary cancer

There are differences between cancer registries in what is included in the category of ill-defined and unknown primary site. This category has long been considered an indicator of quality for a registry, based on the premise that insufficient information has been gathered to determine the diagnosis of a primary.

According to Parkin et al (1994) *'The proportion of cases with missing information for indicator variables such as age and cancer site is an indicator of validity in a cancer registry. Thus the percentage of cases registered with an unknown or primary site is clearly related to the quality of the diagnostic information and may result from careless or incomplete record keeping'*.[28] These researchers also suggest that a high percentage arbitrarily set at 10% might indicate inadequate diagnostic services, low utilisation of available services or poor documentation of results.[29]

Unfortunately, this view fails to consider that unknown primary may be a true entity even after considerable examination, including autopsy, has been undertaken to detect a true cancer.

Based on mainly non-registry or hospital-based studies, the majority of CUPs are classified as metastatic adenocarcinomas, followed by squamous cell carcinomas and undifferentiated neoplasms, with lung and pancreas as the common diagnosed sites of primary cancer.

The incidence rate, symptoms and metastatic pattern among unknown primaries are thought to be different to cancers with a known primary but similar histology,[30,31] suggesting that populations presenting with unknown primaries are distinctly different, thus requiring a more specialised form of treatment. These studies support the view that unknown primary cancers are a unique entity rather than a cancer in which the primary site has not yet been located. Presented in Appendix 1 is a typical example, which illustrates that an unknown primary cancer can have extensive investigation without identification of a primary site.

Purpose

1. Provide a descriptive overview of unknown primary cancers in NSW.
2. Describe trends in incidence by major histological category and stage at diagnosis.
3. Consider the characteristics of people diagnosed with CUP compared to those with a known cancer site by: age; sex; stage at diagnosis; major morphological grouping; method of diagnosis; socioeconomic status; and index of geographical remoteness.
4. Undertake predictive modelling of characteristics of unknown primary cancer versus known primary tumours, while controlling for sex, age, histological grouping, period of diagnosis and survival time.
5. Compare survival between known versus unknown primary cancer for people diagnosed with distant metastases controlling for sex, age, socioeconomic status and index of remoteness, histology and period of diagnosis.
6. Investigate how cancer of ill-defined and unknown primary site should be reported and to consider the data quality implications.
7. Refine further questions of interest that may need to be followed up through other studies.

The purpose of this study is to describe trends in incidence and mortality rates for CUPs in the NSW population. Distinctive features of their epidemiological profiles are explored, together with trends in case survival.

Cancer of unknown primary in NSW

In 2005, there were 1,401 new cases of cancers of ill-defined or unknown primary site (CUP) in NSW (715 male, 686 female), accounting for 3.7% of all cancers in males and 4.6% in females. There were 940 cancer deaths from CUP (446 males and 494 females), which is 6.9% of male cancer deaths and 8.5% of female cancer deaths. Males were 1.3 more likely to be diagnosed and 1.4 times more likely to die from CUP than females.

CUP ranked seventh in males and fifth in females for incidence and its mortality ranked fourth in males and females. Incidence rates (adjusted for age) were 21.7 new cases per 100,000 in males and 16.6 in females and mortality rates were 13.8 deaths per 100,000 in males and 11.7 in females.

Incidence and mortality rates for CUP were generally higher in males than in females. In both sexes they increased sharply from 50 to 54 years of age. In 2005, the median age at diagnosis of CUP was 73 years in males and 75 years in females.

Table 1 Numbers of new cases of cancer ill-defined or unknown primary site and sex, 2005.

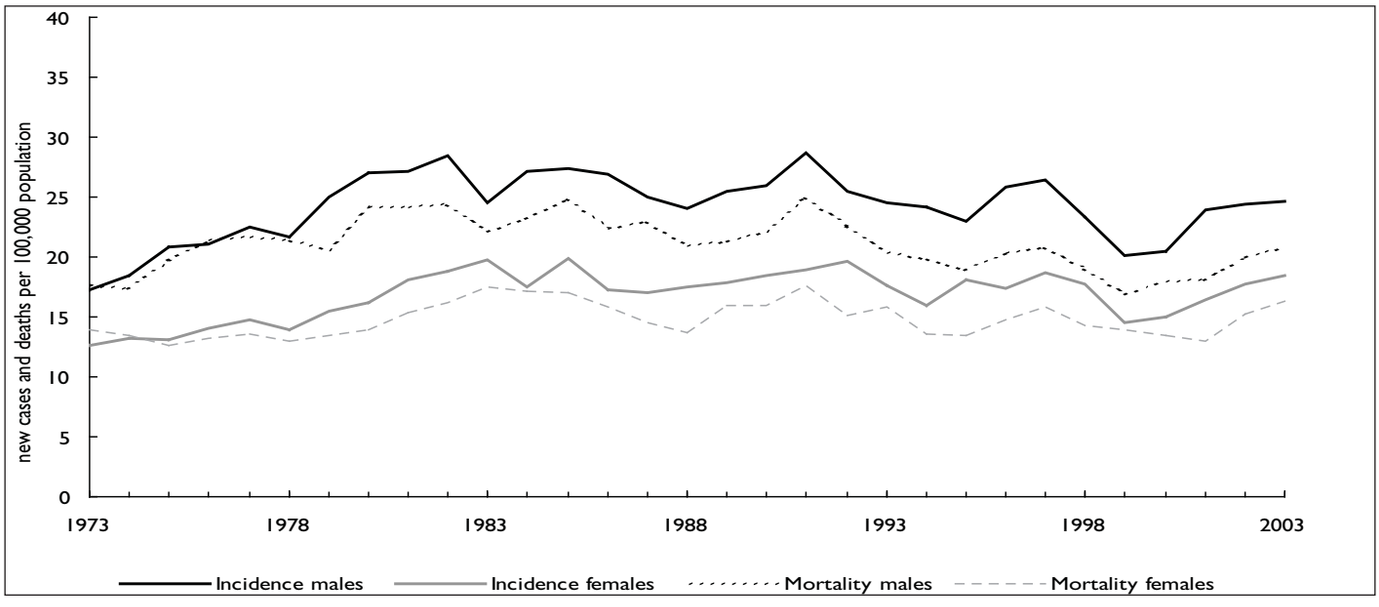
Age	0–34	35–44	45–54	55–64	65–74	75–84	85+	Total
Males	8	22	49	131	185	223	97	715
Females	8	19	55	97	141	222	144	686

Males were 1.3 times more likely to be diagnosed with and 1.4 times more likely to die from CUP than females. In both sexes rates increased sharply from 50 to 54 years of age.

The pattern of CUP incidence rates over time is very similar in both males and females in NSW. The same pattern is seen with mortality rates. Rates are uniformly higher in males than females.

In the most recent period, 1996 to 2005, the age-standardised incidence rates of CUP did not change significantly but have fluctuated; whereas mortality rates declined by 22% in males but did not significantly change in females. Incidence and mortality rates closely mirror one another, largely due to poor survival, and have shown a downward tendency since 1993.

Figure 1 Trends in incidence and mortality rates for unknown primary cancer, 1973–2003, NSW.



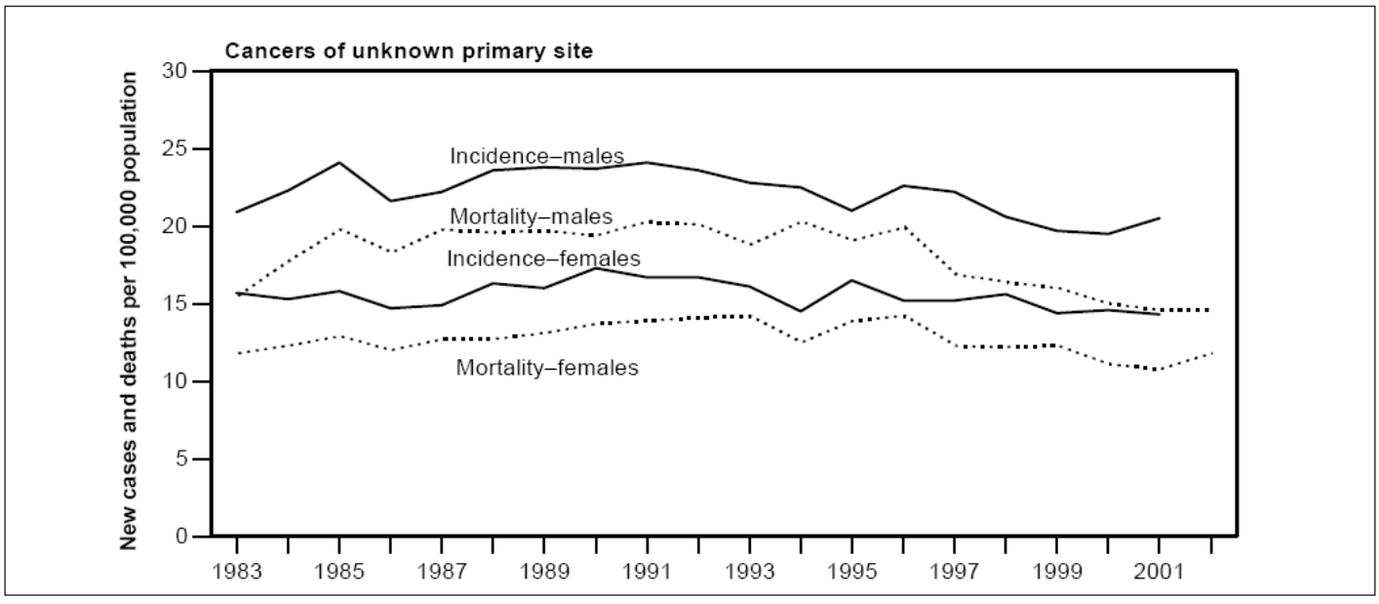
National comparisons

Nationally, ill-defined and unknown primary cancers were responsible for 3,304 cases, or 3.7% of total cancers, and 6.7% of all cancer deaths in 2001.[32] Between 1983 and 2001, incidence rates were fairly consistent at 17 per 100,000 in persons (20 per 100,000 in males and 14 per 100,000 in females). Between 1991 and 2001, incidence rates declined in males and females by 1.9% per annum. In the same time period, mortality rates declined by 3.4% in males and 2.5% in females per annum respectively. Variations in cause-of-death definitions used by the Australian Bureau of Statistics and those used by NSW could account for the differences in trends in death rates seen in NSW and Australia.

Rates of unknown primary cancer vary by state and territory for the period 1997–2001. In order: Northern Territory 25 per 100,000; ACT 21 per 100,000; Tasmania, South Australia and Queensland 17 per 100,000; and Victoria and NSW 15 and 19 per 100,000 respectively.

Pattern of CUP incidence and mortality rates is very similar for males and females in NSW and Australia. Rates are uniformly higher in males than females.

Figure 2 Trends in incidence and mortality rates for unknown primary cancer, 1973–2001, Australia (AIHW).



Survival

The five-year relative survival experienced from 1999 to 2003 in NSW was 16% for males and 14% for females diagnosed with CUP.

Survival five years post-diagnosis declined with extent of disease at diagnosis. Survival was 45.1% for localised disease, 38.9% for regional spread, 11.7% for distant metastases and 15.6% for cancers of unknown spread. The majority of cases (72%) for the time period 1999–2003 presented with distant spread of cancer at diagnosis.

Unadjusted five-year relative survival remained relatively constant with improvement in survival in the latest time period. Five-year survival ranged from 8.6% in those diagnosed in 1980–1983 to 10.9% in 1984–1988, 10.5% in 1989–1993, 11.5% in 1994–1998 and 15.7% in the latest time period 1999–2003.[33]

In Australia during 1992–1997, relative survival one year after diagnosis was 23.3% for males and 22.5% for females. Five-year relative survival was 13.4% for males and 11.5% for females. Relative survival 10 years after diagnosis was 12.8% for males and 10.7% for females in 1987–1991: the most recent period for which 10-year relative survival data are available.[34]

International comparisons

NSW incidence rates for indefinite and unspecified sites (13.8 and 9.7 new cases per 100,000 population 'World' standard in males and females respectively) were similar to rates for Denmark (13.2 males, 11.9 females) and New Zealand (14.0 males, 12.2 females). Higher rates occurred in the UK (15.6 males, 11.9 females) and Scotland (16.9 males, 13.2 females). Rates in the USA were lower than NSW for SEER (Survival and End Results Program) (white) males and females with 8.3 and 6.9 new cases per 100,000 respectively. NSW rates were similar to SEER black rates (11.6 in males and 9.5 in females).[35]

1. **Materials** and methods

Data sources and definitions

The NSW Central Cancer Registry data were used for trend analysis for all cases diagnosed between 1972 and 2003, and for survival analysis of those diagnosed from 1980 to 1995 followed to the end of 2001. Population data was the June Estimated Resident Population (ERP) by year. Australian 2001 standard population was used for age standardisation. Indices of socioeconomic status and Accessibility/Remoteness Index of Australia (ARIA) were from Australian Bureau of Statistics Indices, which is based on characteristics of a Local Government Area (LGA). These indices were based on 1996 LGA boundaries.

In this analysis, unknown primary cancer is defined as C80.9 only. Cancers considered to be ill defined – ill-defined sites of digestive tract (ICD–10 C26), within respiratory system and intrathoracic organs (C39), retroperitoneum and peritoneum (C48), ill-defined sites (C76) – were excluded so that there could be a consistent definition of unknown primary cancers.

Where comparison is made with a known primary site, only solid tumours were included for analysis. Lymphohaematopoetic cancers were excluded because there is no staging information on these cancers. In addition non-melanoma skin cancers are not collected or registered by the NSW Central Cancer Registry. Rates were considered by year of diagnosis and by histological group for cancers of known tumour type, compared to unknown primary cancer.

Statistical analyses

SAS (Statistical Analysis Software) version nine was used to calculate proportions using chi-squared analysis. For each of the explanatory variables, chi-squared analysis was undertaken. The percentage of the variable of interest in people with unknown primary cancer is compared to people with known solid primary tumour. Univariate logistic regression between the outcome variable of unknown primary versus known primary and each of the potential explanatory variables of sex, age, ARIA, SES, stage at diagnosis, histological cancer type and method of diagnosis for the time period 1999–2003 was undertaken.

Multivariate stepwise logistic regression was used to determine a final model and the resulting odds ratios were converted to relative risks by undertaking multivariate Poisson regression analysis. Cause-specific survival analysis was undertaken using Kaplan Meier product limit method using proc LIFE TEST in SAS. Cause-specific survival for unknown primary cancers and known primary cancers stratified by stage at diagnosis, sex, age, period of diagnosis, morphological grouping, SES, ARIA and method of diagnosis were considered.

Cause-specific survival is defined as the interval from the date of diagnosis to the date of death for the cancer of interest (unknown primary cancer or known primary cancer).

Cases were censored if the patient died of a non-cancer death, another cancer or the person was alive at the end of 2001. Cause-specific survival excludes death certificate only cases and people diagnosed at autopsy because they were diagnosed and died at the same time. Multivariate modelling was undertaken using Cox proportional hazards modelling.

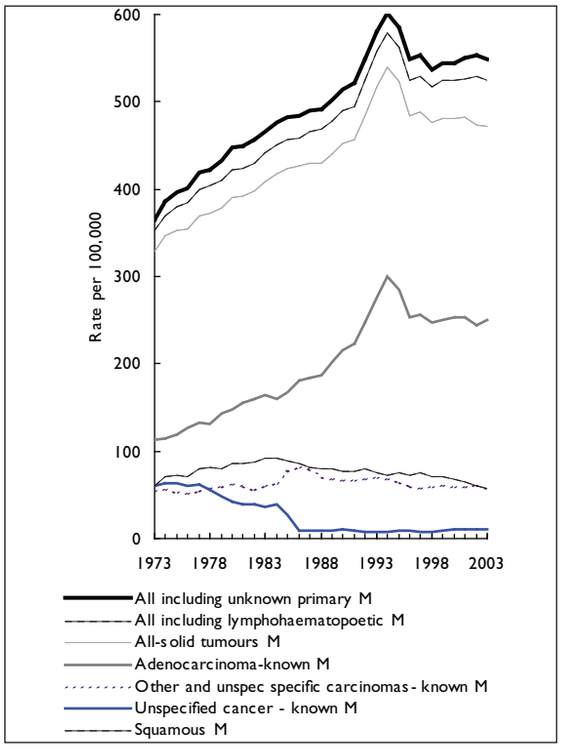
2. **Descriptive** overview

Trends by histological group

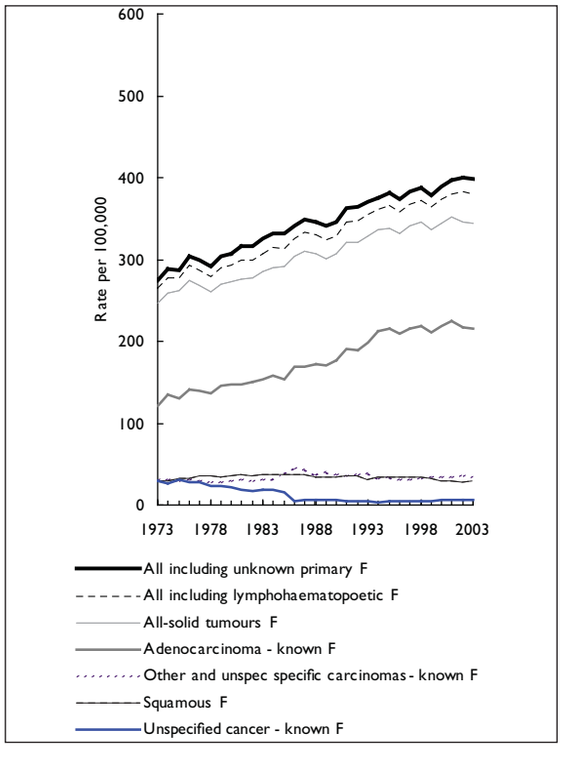
Trends are displayed below by major histological grouping for males and females for all cancers (including unknown primary), cancers excluding unknown primary and solid tumours only. A further breakdown in rates is provided for the major histological groups of adenocarcinoma, squamous cell carcinoma, unspecified cancer and unspecified carcinoma for known and unknown primary sites.

Observing the pattern in trends by major histological group provides an understanding of which histological group is contributing the most to overall trends. Rates in both males and females are most strongly influenced by changes in rates for adenocarcinoma. This is not surprising as adenocarcinoma was responsible for 31% of known primary site in males in 1973, increasing to 56% in 1994. Thereafter, rates were 52% of known primary site in males. In females, adenocarcinoma was responsible for 49% of known primary site in females, increasing to 63% of known primary site in 1994. Thereafter, rates remained at this level until 2003.

Figure 3 Age-standardised incidence rates in males and females by histological category 1973–2003.



Male



Female

It is important to consider changes in registry practice or notification. Pathology reports have been received by the registry since it commenced in 1972, but mandatory reporting of all pathology laboratories did not begin until 1986. Rates of unspecified cancer in both males and females have declined since 1986, which may be due to the increase in the notification of pathology reports to the registry since that time. Other specified cancers have not changed over time (Figure 3).

Trends by histological group: known primary cancers in males

Adenocarcinoma in males displays the same pattern as all known primary cancers, with rates commencing at 100 per 100,000 in 1972 and increasing to 300 per 100,000 in 1994. Thereafter, rates of adenocarcinoma dropped to 250 per 100,000 in 1997 and then remained at this rate until 2003.

- The difference in rates between all cancers and all cancers including haematopoietic is the proportion of unknown primary cancers as displayed in Figure 3. This difference ranges from 15 per 100,000 in 1992 to 26 per 100,000 from 1980 to 1986. Thereafter rates declined to 22 per 100,000.
- Squamous cell carcinoma commenced at 60 per 100,000 in 1972, reached a peak of 92 per 100,000 in 1984 and then declined to 57 per 100,000. Squamous cell carcinomas were responsible for 20% of solid tumours until 1986, declining to 15% in 1999 and 12% in 2003. A drop in lung cancers in males was the major reason for a drop in squamous cell carcinoma rates during this time period.
- Specific carcinomas started at 60 per 100,000, reached a peak in 1986 with 80 per 100,000 and declined to 60 per 100,000 since then. Most interesting is the proportion unspecified cancer has declined; which started at 54 per 100,000 in 1972, declined to 9.7 per 100,000 in 1986 and remained at this level until 2003.

Unknown primary cancer as a proportion of total cancers in males was 4% until 1976 increased to 5% until 1979 and 6% from 1980–84, after which it declined to 5% in 1991 and 4% from 1992 onwards.

Trends by histological group: known primary cancers in females

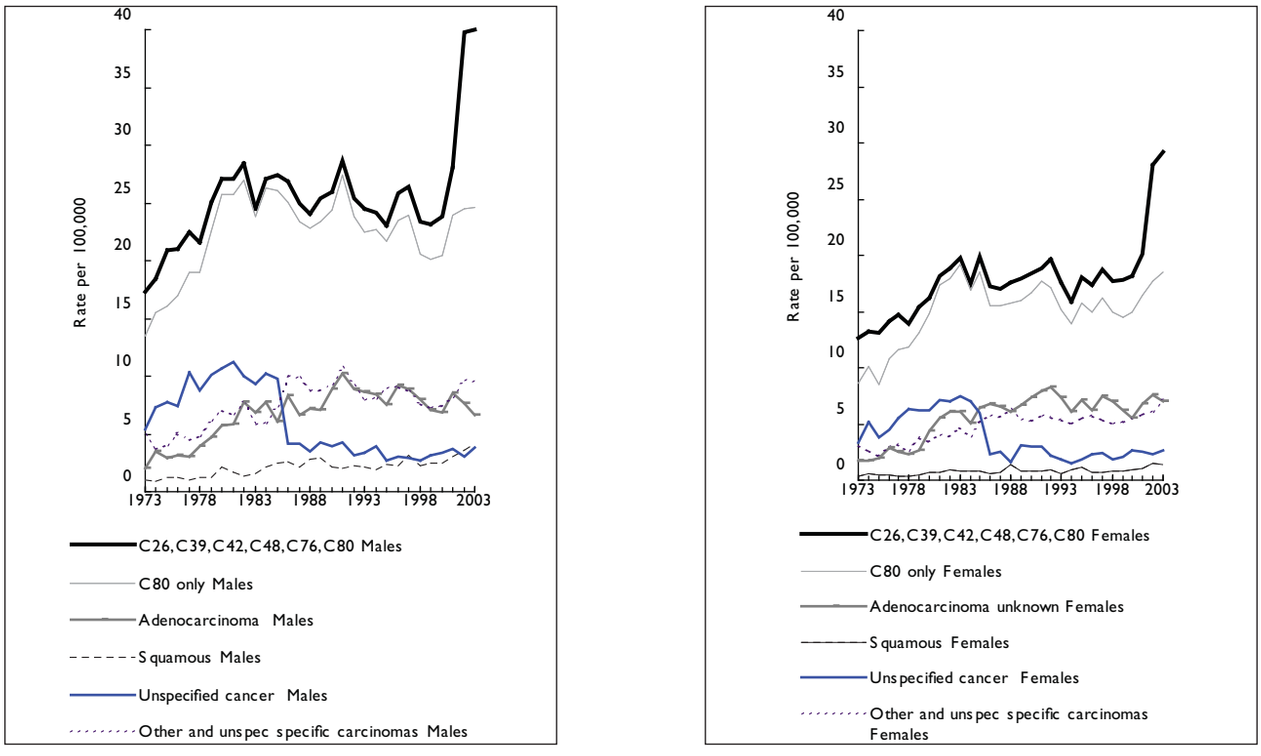
The difference in rates between all cancers and known tumours including haematopoietic is the proportion of unknown primary cancers as displayed in Figure 3. Unknown primary cancers increased from 10 per 100,000 new cases in 1982 to 18 per 100,000 in 1993 and then fluctuated between 15 and 18 new cases per 100,000 after that.

As a proportion of total cancers: unknown primary cancers in females were 4% until 1979 then increased to 5% in 1980 and 6% between 1980 and 1984. Thereafter, rates declined to 5% in 1991 and then 4% from 1993 onwards. There was a similar pattern in males.

- Adenocarcinoma in females shows the same pattern as overall cancers of known primary site, with rates commencing at 123 per 100,000 in 1972 and increasing to 224 per 100,000 in 2001. Thereafter, rates of adenocarcinoma declined to 215 per 100,000 in 2003. Adenocarcinoma was responsible for 49% of solid tumours in females in 1972, increasing to 63% of solid tumours in 1994 and remaining at this level until 2003.
- Squamous cell carcinoma remained relatively constant over the time period at 32 per 100,000 or 11% of solid tumours.
- Specific carcinomas commenced at 60 per 100,000, reached a peak in 1986 of 80 per 100,000 and declined to 60 per 100,000 thereafter.
- Unspecified cancer was 27 per 100,000 in 1973 then declined to 15.8 per 100,000 in 1985 and 5.2 per 100,000 in 1986 then remained at this level until 2003.
- Unspecified cancer declined from 11% of total solid tumours in 1972 to 2% in 1986 and remained at that level until 2003.

Trends by histological group: unknown primary cancers

Figure 4 Age-standardised incidence rates in males and females by histological category in those with unknown primary cancer 1973–2003.



From 1973 to 1977 there was a higher proportion of ill-defined cancer (22%) as a proportion of total unknown and ill-defined cancer. This proportion declined to 5% in 1980 and remained at this level until 1994 then increased to 15% in 2001.

- The pattern of rates for males and females for unknown primary cancer by histological type is very similar.
- The analysis on trends focused on unknown primary cancer and considered major histological categories and how these rates have changed over time. In addition, changes in rates for each histological category as a proportion of total unknown primary were considered.
- Other and unspecified specific carcinomas, followed by adenocarcinoma and squamous cell carcinoma were (in order of volume) the major histological groups that comprise unknown primary cancer in males and females.
- The change in rates for unspecified cancer followed the same trend as known primary cancer. Unspecified cancers of unknown primary type commenced at 5.6 per 100,000 in 1973, increased to 9.7 per 100,000 in 1986, declined to 4.0 per 100,000 and then remained at this level. Other specified cancers have not changed over time and are less than 1% of unknown primary cancers (Figure 4).

Trends by histological group: unknown primary cancers in males

Rates for unknown primary cancer (C80) in males increased from 13.4 new cases per 100,000 in 1972 to 26 per 100,000 in 2003.

- Adenocarcinoma rates in males began at 2.69 per 100,000 in 1972, increased to 8.3 per 100,000 in 1986 and remained at this rate until 2003. Adenocarcinoma was responsible for 18% of unknown primary cancer in males in 1972, increasing to 39% in 1993 then declining to 30% in 2003.
- Squamous cell carcinoma started at 1.31 per 100,000 in 1972, reached a peak of 2.57 per 100,000 in 1986 and remained constant until 2003. Squamous cell carcinomas were responsible for 9% of unknown primary cancers in 1972, increasing to 13% in 2003.
- The major histological group that comprised unknown primary cancers was other and unspecified specific carcinomas with 10 per 100,000 from 1972 to 2003. Other and unspecified specific carcinomas were responsible for 40% of unknown primary cancer from 1972 onwards.

Trends by histological group: unknown primary cancers in females

In females, unknown primary cancer rates increased from 8.6 new cases per 100,000 in 1972 to 19 per 100,000 in 1982, where they have remained.

- Adenocarcinoma in females shows a similar pattern to all CUPs with rates commencing at 1.71 per 100,000 in 1973, increasing to 8.3 per 100,000 in 1992 and declining slightly to 7.0 per 100,000 in 2003. Adenocarcinoma was responsible for 20% of unknown primary cancer in females, increasing to 49% in 1993 and then dropping to 38%.
- Squamous cell carcinoma started at 0.4 per 100,000 in 1972 reached a peak of 1.33 per 100,000 in 2003 and then remained constant. These cancers were responsible for 5% of CUPs in 1972, increasing to 7% in 2003.
- Unspecified cancers started at 3.4 in 1972 increased to 7 per 100,000 in 1981, then declined to 2.3 in 1986 and remained at this level until 2003. These cancers were responsible for 53% of all CUPs in females in 1972, declining to 18% in 2003.
- Other and unspecified carcinomas increased from 3.0 per 100,000 in 1972 to 7.0 per 100,000 in 2003. These cancers were responsible for 34% and 37% of cancers of unknown primary site in 1972 and 2003 respectively.

Patterns of rates broken down by histological subtype were similar for both males and females with unknown primary cancer.

Trends in age-specific rates by histological group

Incidence rates rose with increasing age in both sexes for both unknown and known primary cancers. Age-specific rates by histological grouping for those with an unknown primary cancer compared to a known primary cancer (Figure 5).

Cancers with a known primary site:

- Incidence rates for females exceeded those in males between the ages of 25–29 and 50–54 years and were double in males compared to females after that.
  - Adenocarcinoma rates were higher in females compared to males from ages 10–59, after 60 years of age rates were higher in males.
  - Rates of squamous cell carcinoma were higher in males than females for all ages, largely because rates of oesophagus and lung cancer were higher in males (Figure 5).

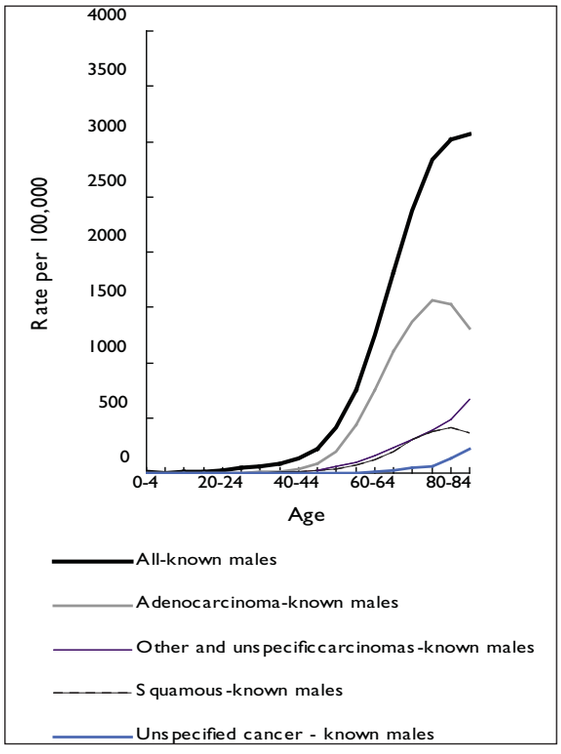
Cancers of unknown primary site:

- Incidence rates in males and females increased from ages 45 to 49, with slightly higher rates in males aged 60 years and older.
  - Adenocarcinoma rates were higher in females than males between 30 and 54 years of age; however, from 55 years onwards rates were the same in both males and females.
  - Squamous cell carcinoma rates were similar in both males and females until 60–64 years, thereafter rates were higher in males (Figure 6).

Rates for specified types of cancer in both known and unknown primary cancers were similar, with rates higher in females to the age of 55–59. Thereafter rates were higher in males. For unspecified neoplasms in both unknown and known primary sites rates were higher in males than females to the age of 70–74, thereafter rates were higher in females.

The pattern of rates for adenocarcinoma and squamous cell carcinoma was different in males and females where the primary site was known. This reflects trends for major cancer types, like breast, prostate and colorectal. By contrast, the pattern of rates for adenocarcinoma and squamous cell where the primary site was unknown was the same in males and females. This supports the view that unknown primary is a specific disease, rather than just the absence of a primary site.

Figure 5 Age-specific incidence rates in males and females by histological category in those with known primary cancer 1973–2003.



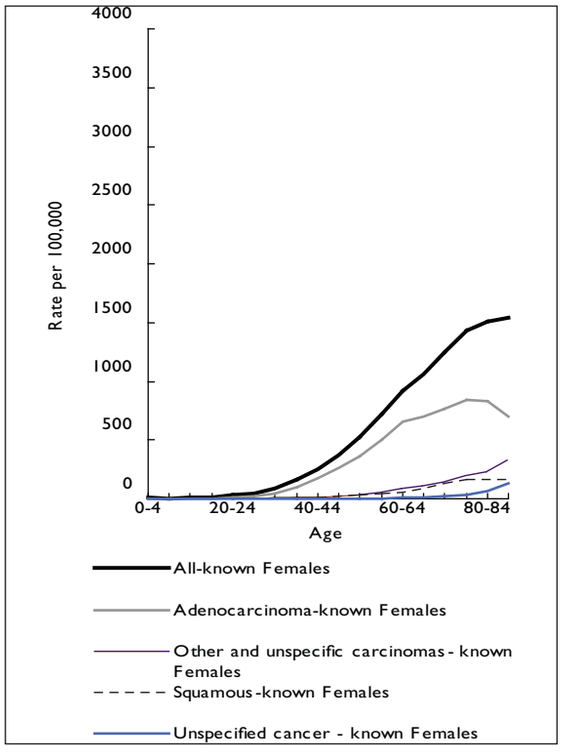
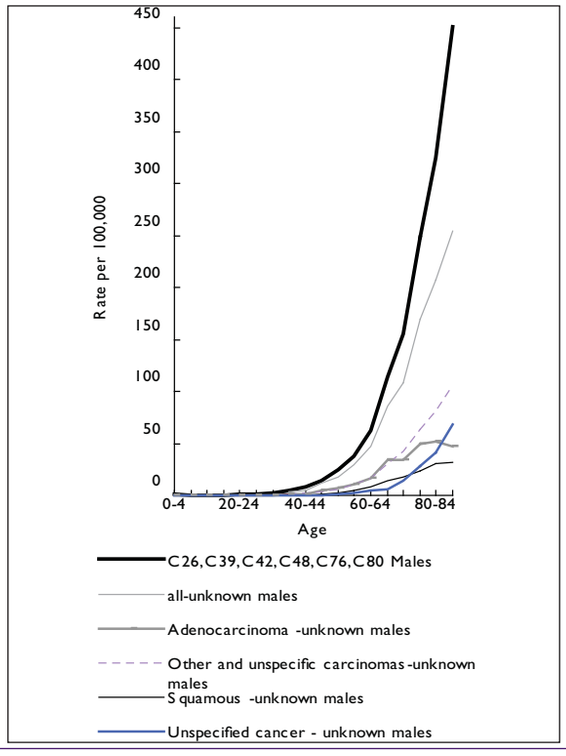
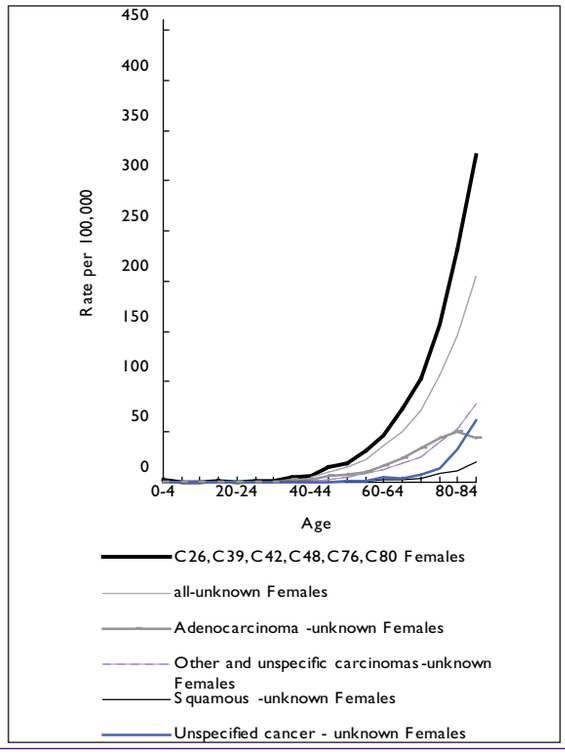


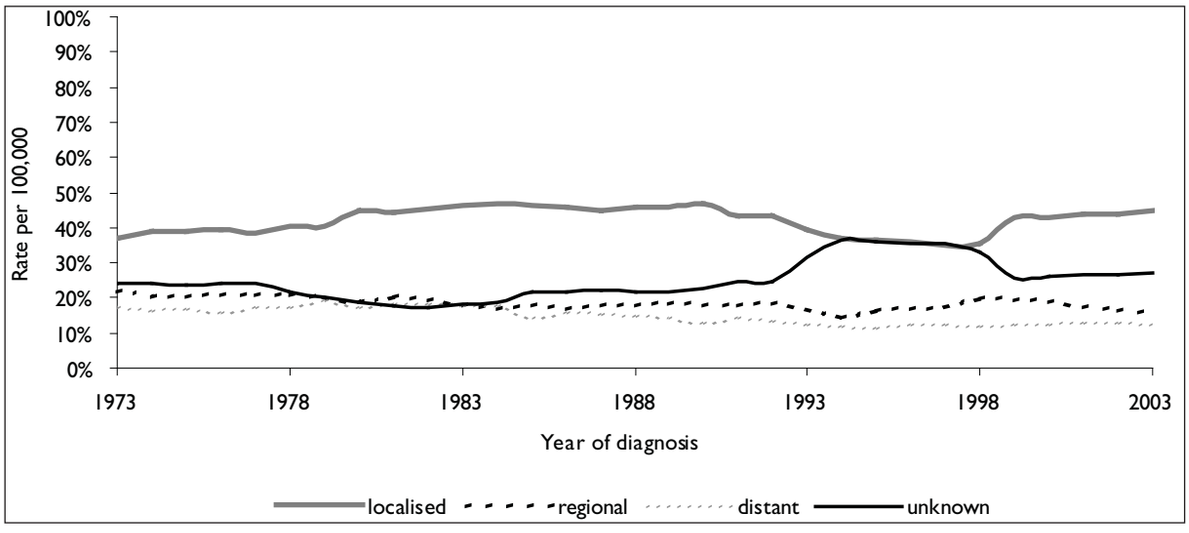
Figure 6 Age-specific incidence rates in males and females by histological category in those with unknown primary cancer 1973–2003.





Trends in stage at diagnosis

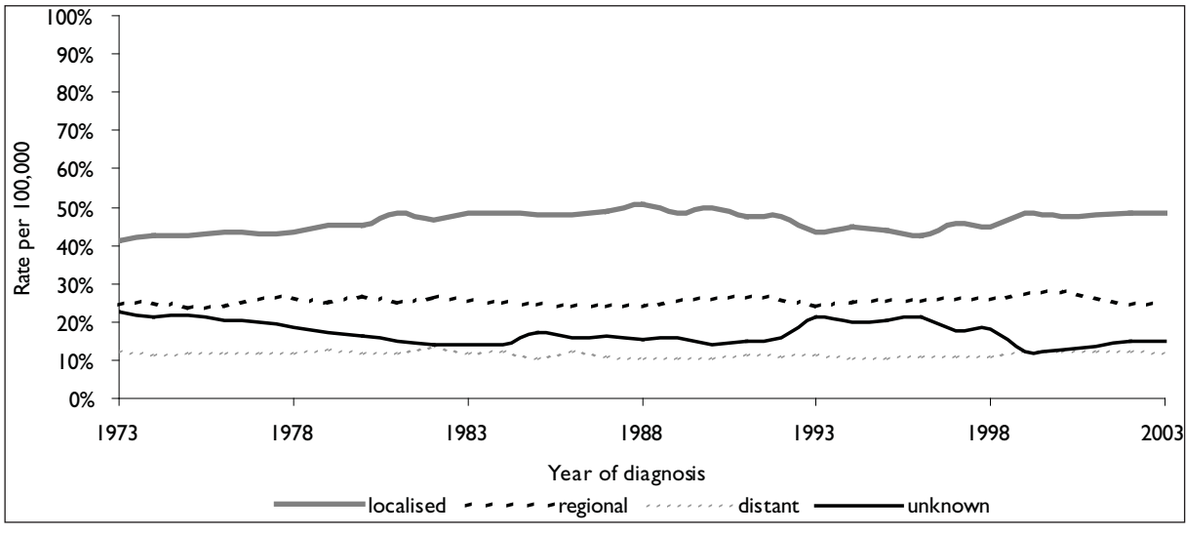
Figure 7 Males: trends in age-standardised rates for known primary cancers by stage at diagnosis 1973–2003.



In males, rates for localised known primary cancer increased from 35% of total cancers in 1972 to 47% in 1990, declining to 35% in 1998 and increasing to 45% in 2003. Regional known primary cancer has remained constant at 20% in that time period. Distant known primary cancer has declined from 18% to 12% of total cancers from 1973 to 2003.

The proportion of unknown stage increased and at the same time the localised stage decreased. A possible explanation is that there was an increase in biopsy rates during this time for prostate cancer, enabling a diagnosis but not a stage to be determined (Figure 7). Alternatively, there has been differences in the coding of localised and unknown extent of diseases as a result of electronic notification being introduced to the NSW Central Cancer Registry.

Figure 8 Females: trends in age-standardised rates for known primary cancers by stage at diagnosis.



In females, rates of localised known primary cancers increased from 41% of total cancers in 1973 to 50% in 1990, declined to 43% in 1996, after which time it increased to 48% in 1999 and remained at that level until 2003 (Figure 8).

The rate of regional extent of disease at diagnosis has remained constant at 26% since 1973. Distant extent of disease at diagnosis has remained constant at 12% of total cancers.

As observed before in males, the proportion of unknown extent of disease increased at the same time localised decreased.

Figure 9 Persons: trends in age-standardised rates for known primary cancers by stage at diagnosis.

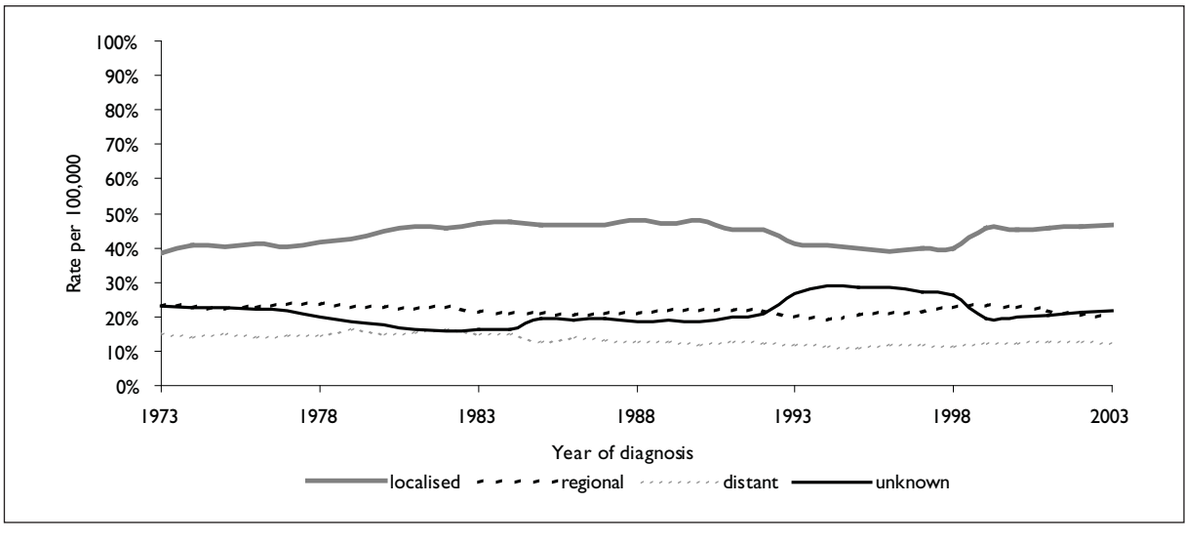


Figure 10 Males: trends in age-standardised rates for unknown primary cancers by stage at diagnosis.

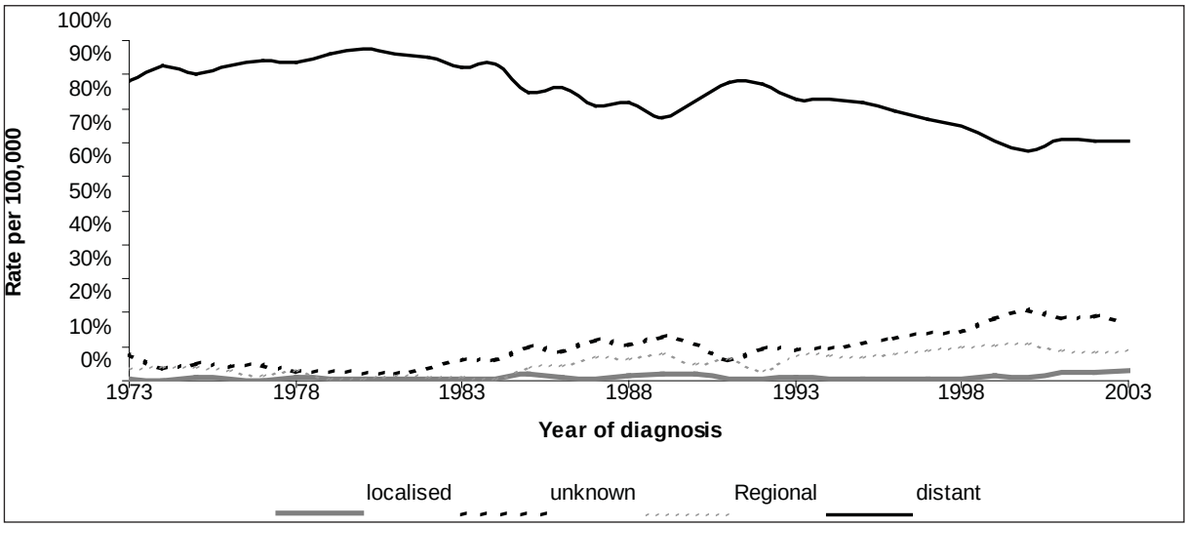


Figure 11 Females: trends in age-standardised rates for unknown primary cancers by stage at diagnosis.

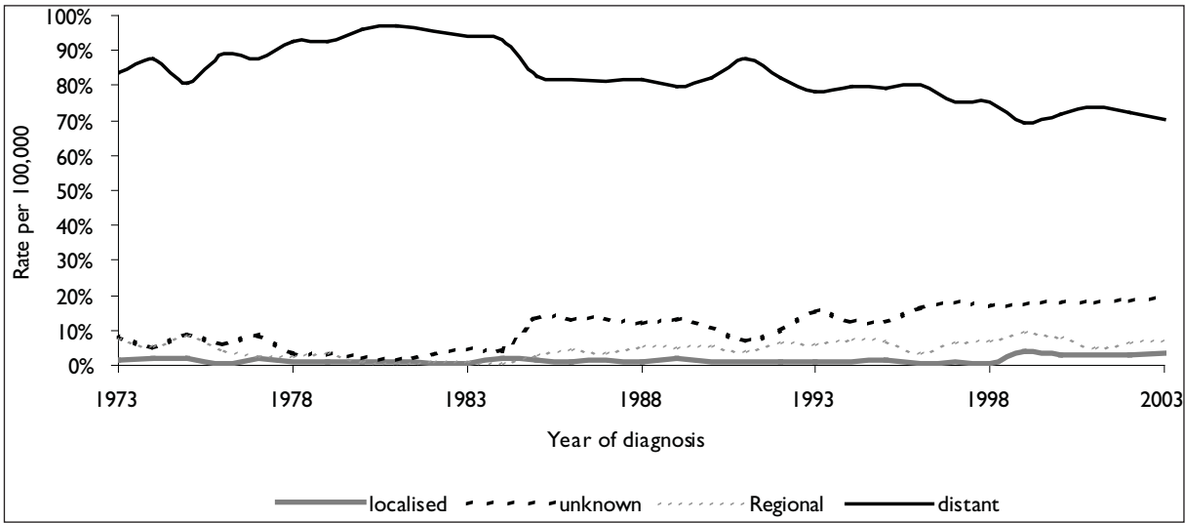
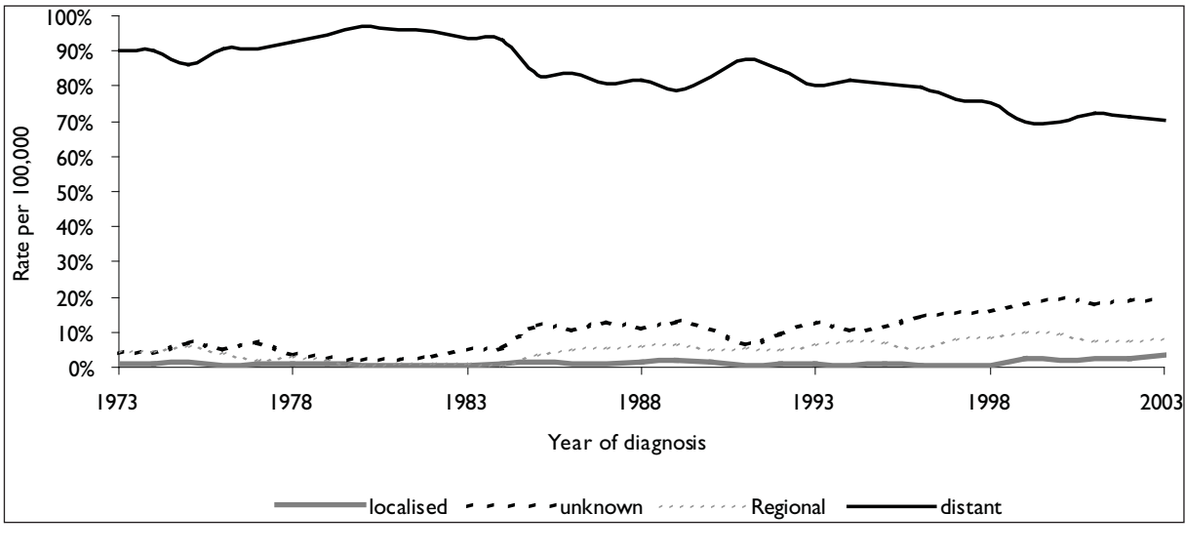


Figure 12 Persons: trends in age-standardised rates for unknown primary cancers by stage at diagnosis.



The pattern of presentation of stage at diagnosis for unknown primary in males (Figure 10) and females (Figure 11) and all persons (Figure 12) is very consistent.

In males, the majority of unknown primary cancers (90%) were distant metastases in 1973. This proportion declined to 77% in 1989 and 70% in 2003. As the proportion with distant metastases declined, the proportion of regional stage increased from 3% of total unknown primary to 11% respectively. The proportion with unknown stage increased from 7% in 1973 to 21% in 2003.

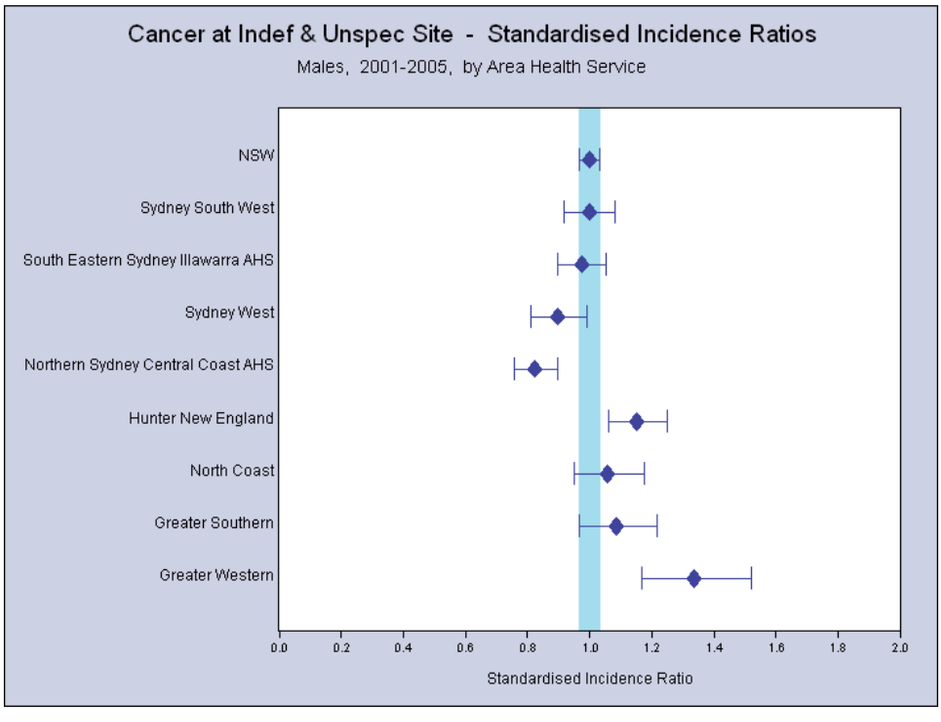
The majority of total unknown primary cancers (85%) in females were distant metastases in 1973, this proportion declined to 80% in 1989 and 70% in 2003. As the proportion with distant metastases declined, the proportion with regional stage

increased from 3% of total unknown primary to 11%. The proportion with unknown stage also increases from 5% in 1973 to 19% in 2003.

A possible reason for changes by extent of disease more specifically the increase in the proportion of unknown stage for unknown primary cancers has been the introduction of pathology reporting in 1986 to the NSW Central Cancer Registry. This improvement enabled more comprehensive reporting of a diagnosis of cancer. However, where there was insufficient information or investigation on the pathology report due to perhaps age or other co-morbid conditions, the extent of disease for an unknown primary cancer remained unknown.

Variation by Area Health Service

Figure 13 NSW males: standardised incidence ratios for unknown primary cancer by Area Health Service of residence and distant metastases 2001–2005.



A breakdown of standardised incidence ratios by Area Health Service all persons (Figure 15) diagnosed with unknown primary cancer with distant metastases indicate that Northern Sydney Central Coast has significantly lower rates of unknown primary cancer, while Hunter New England and Greater Western had significantly higher rates. This was due to differences in rates in males only (Figure 13).

Rates were in higher in females resident in Greater Western Area Health Service (Figure 14).

Figure 14 NSW females: standardised incidence ratios for unknown primary cancer by Area Health Service of residence and distant metastases 2001–2005.

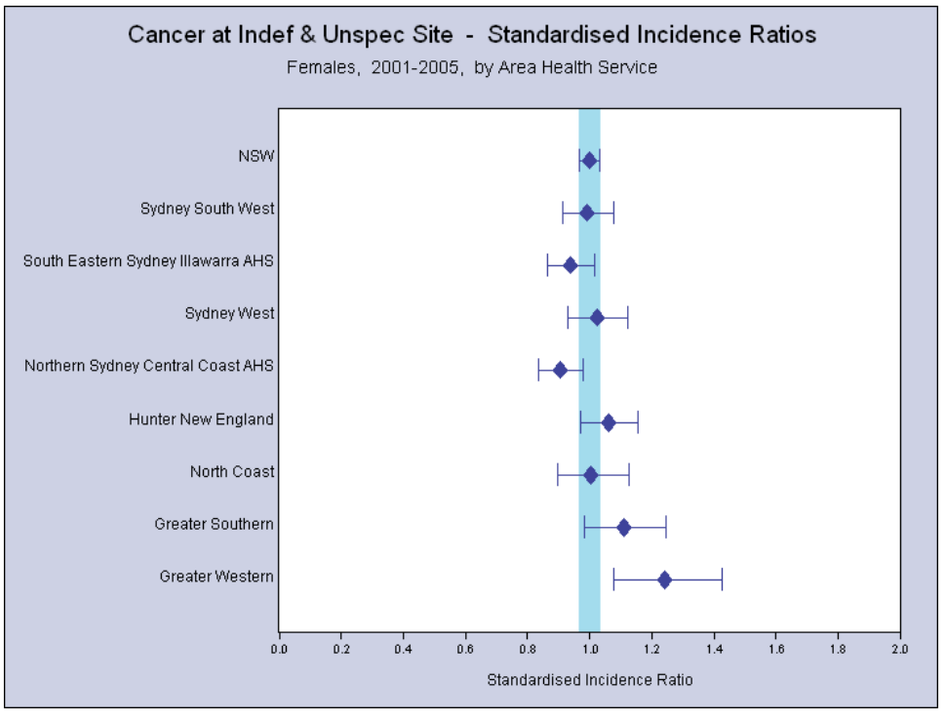
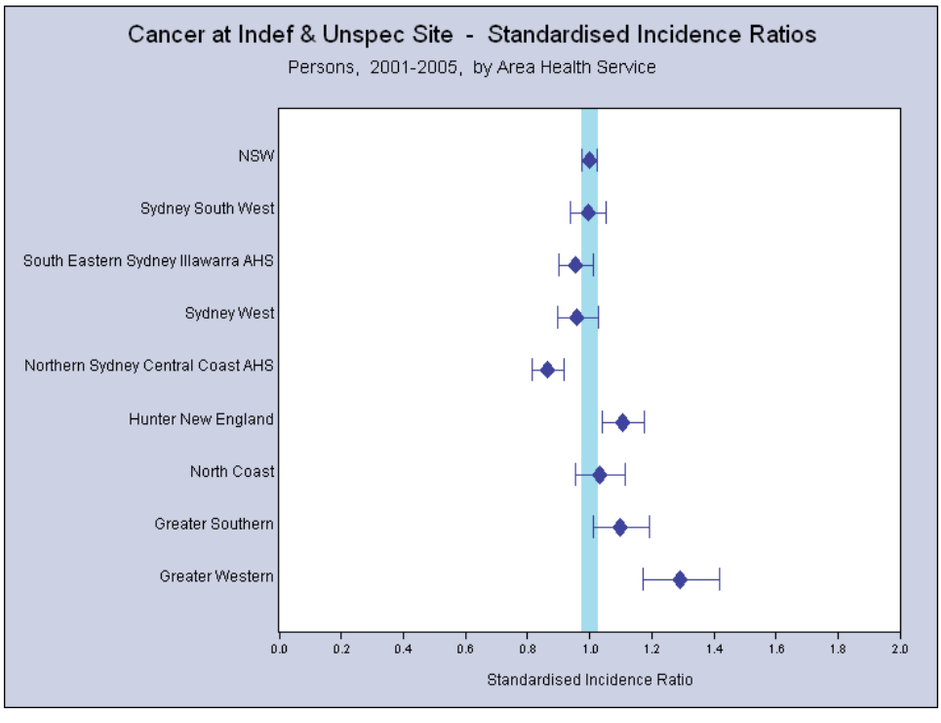


Figure 15 NSW persons: standardised incidence ratios for unknown primary cancer by Area Health Service of residence and distant metastases 2001–2005.



Descriptive overview of unknown and known primary cancer diagnosed between 1999 and 2003

Between 1999 and 2003 there were 7,008 cancers of unknown and ill-defined site. Of these, 6,460 (92%) were true unknown primary (C80.9). These were compared with 133,252 solid tumours of known primary site. Table 2 illustrates the following:

- There was a lower proportion of males with unknown primary cancer compared to a known primary cancer (52% versus 55%) and a higher proportion of females with unknown primary cancer (48% versus 45%).
- There was a higher proportion of unknown primary cancer in those aged over 75 years (47%), compared to known primary cancers in the same age group (30%).
- The proportion living in highly-accessible areas is similar.
- There is a lower proportion of persons with high SES and unknown primary cancer than known primary cancer (17% compared to 20%).

There is a lower proportion of localised and regional stage and a much higher proportion of people with unknown primary cancer at diagnosis presenting with distant metastases compared to known primary cancer (73% compared to 12%).

The histological subtype of unknown primary cancer compared to a known primary cancer indicates:

- a lower proportion of adenocarcinoma (36% compared to 48%)
- a lower proportion of squamous cell carcinoma (10.8% compared to 11.4%)
- a lower proportion of specified cancer (1% compared to 17%)
- a higher proportion of unspecified cancer (15% compared to 2%) and unspecified carcinoma (37% compared to 11%)
- no mesothelioma found in those diagnosed with unknown primary cancer.

Diagnosis

Diagnosis includes a combination of all tests done on cancer patients and notified to the registry over a three-month period. Histological diagnosis is an examination of solid tissue or fragments of tissue in which a diagnosis is determined by a pathologist. Cytology is the examination of cells from fluid that have been obtained using a fine needle aspiration. A clinical diagnosis may include, but is not limited to, methods such as x-ray, CT or PET scan.

Patients with unknown primary cancer at diagnosis compared to a known primary cancer were more likely to:

- be diagnosed using cytological methods (15% compared to 3%) or clinical methods at diagnosis (23% compared to 6%)
- have a higher proportion of histological verification if notified by a hospital (21% compared to 14%)
- have a higher death certificate only notification (4% compared to 1%)
- be less likely to have a pathology report sent to registry and independently verified by the NSW Central Cancer Registry coder (37% to 75%).

Table 2 Descriptive overview of unknown primary cancer versus known primary cancer in NSW residents, 1999–2003.

	Unknown primary	%	Known primary	%	Chi–squared
Sex					
Male	3,357	52	72,622	55	
Female	3,103	48	60,630	45	15.94 1df p<0.0001
Age groups					
15–49	424	7	18,474	14	
50–64	1,286	20	37,618	28	
65–74	1,731	27	36,776	28	
75 plus	3,015	47	39,842	30	959.4 3df p<0.0001
ARIA					
Highly Accessible	5,115	79	107,920	81	
Accessible	1,158	18	21,369	16	
Moderately Accessible	148	2.29	3,231	2.4	
Remote	36	0.5	635	0.5	
Very Remote	3	0.05	97	0.07	18.02 4df p<0.0001
Socioeconomic index					
First Quintile (Low Ses)	1,462	22	28,860	22	
Second Quintile	1,374	21	27,100	20	
Third Quintile	1,300	20	25,049	19	
Fourth Quintile	1,250	19	25,633	19	
Fifth Quintile (High Sees)	1,072	17	26,610	20	67.6 4df p<0.0001
Stage at diagnosis					
Localised	103	1.2	59,997	45	
Regional	476	7	27,998	21	
Distant	4,777	74	16,347	12	
Unknown	1,104	17	28,910	21	18,827.9 3df p<0.0001
Histological groupings					
Adenocarcinoma	2,327	36	76,121	58	
Squamous	692	11	15,068	11	
Specified Carcinoma	52	1	22,242	17	
Unspecified Cancer	967	15	2,508	2	
Unspecified Carcinoma	2,370	37	14,994	11	
Mesothelioma	–	0	919	0.7	8,939.1 5df p<0.0001
Method of diagnosis					
Cytology	945	15	3,451	3	
Clinical	1,485	23	8,183	6	
Histologically Verified Externally	2,076	21	18,888	14	
Death Certificate Only	284	4	1,501	1	
Histologically verified registry	2,391	37	100,508	75	7282 (6df) p<0.0001
Total	**6,460**		**133,292**		

Poisson regression modeling was then undertaken for each of the explanatory variables individually, before undertaking and determining the final model (Table 4).

The univariate analysis pointed to a lower likelihood of unknown primary cancer in the more accessible areas (ARIA) and in high SES areas, but these variables were not predictive in the multivariable logistic regression and as such were not retained.

The final multivariate regression model included the following.

Compared with people with a known tumour at diagnosis those with an unknown primary cancer were:

- less likely to be male (RR 0.86 95% CI 0.82,0.90) than female
- more likely to be aged over 75 years or older at diagnosis (RR 1.2 95% CI 1.15,1.28) than the youngest age category
- more likely to be diagnosed with squamous cell carcinoma (RR 1.7 95% CI 1.6,1.9)
- three times more likely to be diagnosed with unspecified cancer (RR 3.4 95% CI 3.06,3.6)
- almost twice as likely to be diagnosed with unspecified carcinoma (RR 1.8 95% CI 1.7,2.0)
- less likely to be diagnosed with a specific cancer (RR 0.16 95% CI 0.12,0.22) than adenocarcinoma
- seven times more likely to be diagnosed with regional lymph nodes involvement (RR 7.8 95% CI 6.3,9.6)
- 75 times more likely to be diagnosed with distant metastases (RR 74.8 95% CI 61.4,91.0)
- 13 times more likely to be diagnosed with unknown stage at diagnoses (RR 13.2 95% CI 10.8, 16.2) than localised
- more likely to have been diagnosed using cytology (RR 1.36 95% CI 1.18, 1.57) and less likely to be histologically verified at diagnosis (RR 0.65 95% CI 0.57, 0.74).

Table 3 Descriptive overview of unknown primary cancer versus known primary cancers in NSW residents 1999–2003, with distant stage at diagnosis.

	Unknown primary	%	Known primary	%	Chi-squared
Sex					
Male	2,447	51	8,876	54	
Female	2,329	49	7,329	46	15.94 1df P<0.0001
Age groups					
15–49	312	7	1,631	10	
50–64	1,023	21	4,557	28	
65–74	1,306	27	4,752	29	
75 plus	2135	45	5,343	32	243.4 3df p<0.0001
ARIA					
Highly Accessible	3,810	80	13,229	81	
Accessible	838	18	2,479	16	
Moderately Accessible	97	2.0	386	2.4	
Remote	29	0.6	104	0.6	
Very Remote	2	0.04	15	0.09	17.3 4df p<0.0017
Socioeconomic index					
First Quintile (Low Ses)	1075	22	3781	23	
Second Quintile	996	21	3320	20	
Third Quintile	951	20	3054	19	
Fourth Quintile	942	19	3194	20	
Fifth Quintile (High Ses)	812	17	2934	18	5.96 4df p<0.0001
Histological groupings					
Adenocarcinoma	1983	42	8793	54	
Squamous	362	7.6	1249	8	
Specified Carcinoma	26	0.55	1105	7	
Unspecified Cancer	584	12.3	559	3	
Unspecified Carcinoma	1790	38	4335	27	
Mesothelioma	–	0	110	0.7	1087 5df p<0.0001
Method of diagnosis					
Cytology	734	15	1170	2.6	
Clinical	988	21	1932	6.1	
Histologically Verified Externally	999	21	3581	14	
Death Certificate Only	124	2.6	165	1.13	
Histologically Verified Registry	1922	40.2	9408	75	763 (6df) p<0.0001

Table 4 Final multivariate models of unknown primary cancer versus known primary cancers in NSW residents 1999–2003, for all stages, with distant stage at diagnosis and histologically verified only.

Explanatory variables	Relative risk	Lower CI	Upper CI	P value
Sex – female	**1.00**			
Sex – male (all stages)	0.86	0.82	0.91	P<0.0001
Sex– male (metastatic only)	0.86	0.80	0.93	P<0.0001
Sex– male (metastatic only –histologically verified)	0.93	0.86	1.0	P=0.068
Age less than 75	**1.00**			
Age over 75 (all stages)	1.22	1.16	1.30	P<0.0001
Age over 75 (metastatic only)	1.38	1.29	1.48	P<0.0001
Age over 75 (metastatic only –histologically verified)	1.41	1.30	1.52	P<0.0001
Adenocarcinoma	**1.00**			
Squamous cell (all stages)	1.80	1.68	1.92	P<0.0001
Squamous cell (metastatic only)	1.32	1.16	1.51	P<0.0001
Squamous cell (metastatic only –histologically verified)	1.37	1.20	1.56	P<0.0001
Specific cancer (all stages)	0.17	0.13	0.22	P<0.0001
Specific cancer (metastatic only)	0.11	0.08	0.16	P<0.0001
Specific cancer (metastatic only –histologically verified)	0.11	0.08	0.17	P<0.0001
Unspecified neoplasm (all stages)	3.4	3.1	3.7	
Unspecified neoplasm (metastatic only)	3.9	3.34	4.54	P<0.0001
Unspecified neoplasm (metastatic only –histologically verified)	5.96	4.56	7.72	P<0.0001
Unspecified and specified carcinoma (all stages)	1.9	1.8	2.0	P<0.0001
Unspecified and specified carcinoma (metastatic only)	1.68	1.55	1.82	P<0.0001
Unspecified and specified carcinoma(metastatic only –histologically verified)	1.83	1.69	2.00	P<0.0001
Mesothelioma	0.001			0.9263
Clinically verified	**1.00**			
Cytologically verified at diagnosis (all stages)	1.37	1.19	1.60	P<0.0001
Cytologically verified at diagnosis (distant only)	1.83	1.60	2.09	P<0.0001
Histologically verified at diagnosis (all stages)	0.65	0.57	0.75	P<0.0001
Histologically verified at diagnosis	0.78	0.70	0.86	P<0.0001
Extent of disease				
Localised stage	1.00			P<0.0001
Regional stage	7.83	6.33	9.7	P<0.0001
Distant metastases	74.81	61.45	91.09	P<0.0001
Unknown at diagnosis	13.26	10.82	16.26	P<0.0001

The final multivariate regression model for the time period between 1999 and 2003 included the following:

- All cases of unknown and known primary regardless of stage (all stages).
- Those cases with a distant metastases only for unknown primary cancer (4,631) compared to those with a known primary tumour (16,563), referred to as metastatic only.
- A further analysis comparing cases with a distant metastases and an unknown primary cancer (3,513) to those with a known primary tumour (14,462) who were histologically or cytologically verified only (Table 4).

The multivariate regression models included the following:

- less likely to be male
- more likely to be aged over 75 years or older at diagnosis than younger
- more likely to be diagnosed with squamous cell carcinoma than adenocarcinoma
- three times as likely to be diagnosed with unspecified cancer than adenocarcinoma
- almost twice as likely to be diagnosed with unspecified and specific carcinoma than adenocarcinoma
- more likely to be cytologically diagnosed and less likely to be histologically verified at diagnosis (Table 4).

Additional variables: time to death and period of diagnosis to the model

In order to consider the proportion dying by time period as an explanatory variable in the model it is necessary to consider the time period from 1980 to 1995 and allow at least five years follow-up to the end of 2001.

In addition, cases diagnosed at autopsy, or notified through a death certificate only, were excluded. Restricting the diagnosis from 1980 onwards was required since death information was not recorded by the Australian Bureau of Statistics in the same level of details prior to the 1980s.

It is important to exclude death certificate only or a person diagnosed at autopsy, since coding practices have not been consistent in determining a date of diagnosis and hence survival time. Prior to 1996, if the death certificate stated that a person had cancer for five years, then the date of diagnosis was changed to reflect this. From 1996 onwards, this practice changed so that the date of diagnosis was equal to date of death on the death certificate. In addition, survival cannot be calculated appropriately if death certificate cases or cases diagnosed at autopsy are included as they have a survival time of zero.

Table 5 NSW cases of unknown primary cancer and known primary cancer by stage and the number of years from diagnosis to death.

Type of cancer	Stage	1	2	3	4	5	6+ years	Total	
Known primary	Localised	17988	9466	6881	5601	4814	84687	129437	45%
		14%	7%	5%	4%	4%	65%	100%	
	Regional	18270	8318	4839	3177	2243	23429	60276	21%
		30%	14%	8%	5%	4%	39%	100%	
	Distant	26759	4321	1631	804	495	2707	36717	13%
		73%	12%	4%	2%	1%	7%	100%	
	Unknown	20300	7185	4136	2884	2297	22384	59186	21%
		34%	12%	7%	5%	4%	38%	100%	
	Total	**83317**	**29290**	**17487**	**12466**	**9849**	**133207**	**285616**	
Unknown primary	Localised	29	10	2	1	1	12	55	0%
	Regional	278	62	34	21	18	166	579	4%
		48%	11%	6%	4%	3%	29%	100%	
	Distant	11182	827	249	121	71	715	13165	90%
		85%	6%	2%	1%	1%	5%	100%	
	Unknown	559	64	31	20	21	146	841	6%
		66%	8%	4%	2%	2%	17%	100%	
	Total	**12048**	**963**	**316**	**163**	**111**	**1039**	**14640**	

There were 305,857 cases of cancer diagnosed between 1980 and 1995. Of these, 5,601 cases (4,775 known primary cancers and 825 unknown primary cancers) were excluded because they were death certificate only, leaving 300,256 cases. The impact on the total number of known primaries was to remove 2% of known and 5% of total unknown primaries.

The majority of these cases, 285,616 (95%), were cancers with a known primary site, while 14,640 (5%) had an unknown primary site. Of those with known primary cancer, 45% had localised cancer at diagnosis, 21% had regional metastases, 13% had distant metastases and 21% were unknown stage. For those with an unknown primary cancer, 90% had distant metastases, 4% had regional metastases and 6% had an unknown stage.

For those with a known primary cancer, the proportion that died within the first year were 14% localised, 30% regional, and 34% of an unknown stage, while 73% of those with distant metastases died within the first year of diagnosis (Table 5).

Unknown primary cancer cases compared to those with a known primary had a higher proportion that died within the first year for all stage categories. Approximately 85% of CUPs with distance metastases died within the first year of diagnosis, compared to 73% of those with a known tumour with distant metastases. Of the remaining 15% of cases of unknown primary cancer, 10% died within two to five years, with the remaining 5% dying within six years.

Table 6 Final multivariate model for unknown primary cancer compared to solid primary tumours in NSW residents 1980–1995, with distant metastasis at diagnosis.

Explanatory variable	Relative risk	Upper CI	Lower CI	P value
Sex – female	1.00			
Sex – male	0.78	072	0.80	P<0.0001
Age less than 75 years	1.00			
Age 75 years and older	1.08	1.25	1.14	P<0.0001
Adenocarcinoma	1.00			
Squamous	0.92	0.84	1.006	P<0.0049
Specified carcinoma	0.06	0.04	0.10	
Unspecified neoplasm	4.37	3.40	5.61	P<0.0001
Unspecified and specified carcinoma	1.35	1.28	1.43	P<0.0001
Mesothelioma				
Dying in later years	1.00			
Dying in the first year	1.80	1.69	1.92	P<0.0001
1980 – 1985				
1986–1990	0.87	0.82	0.93	NS
1991–1995	0.91	0.86	97	NS

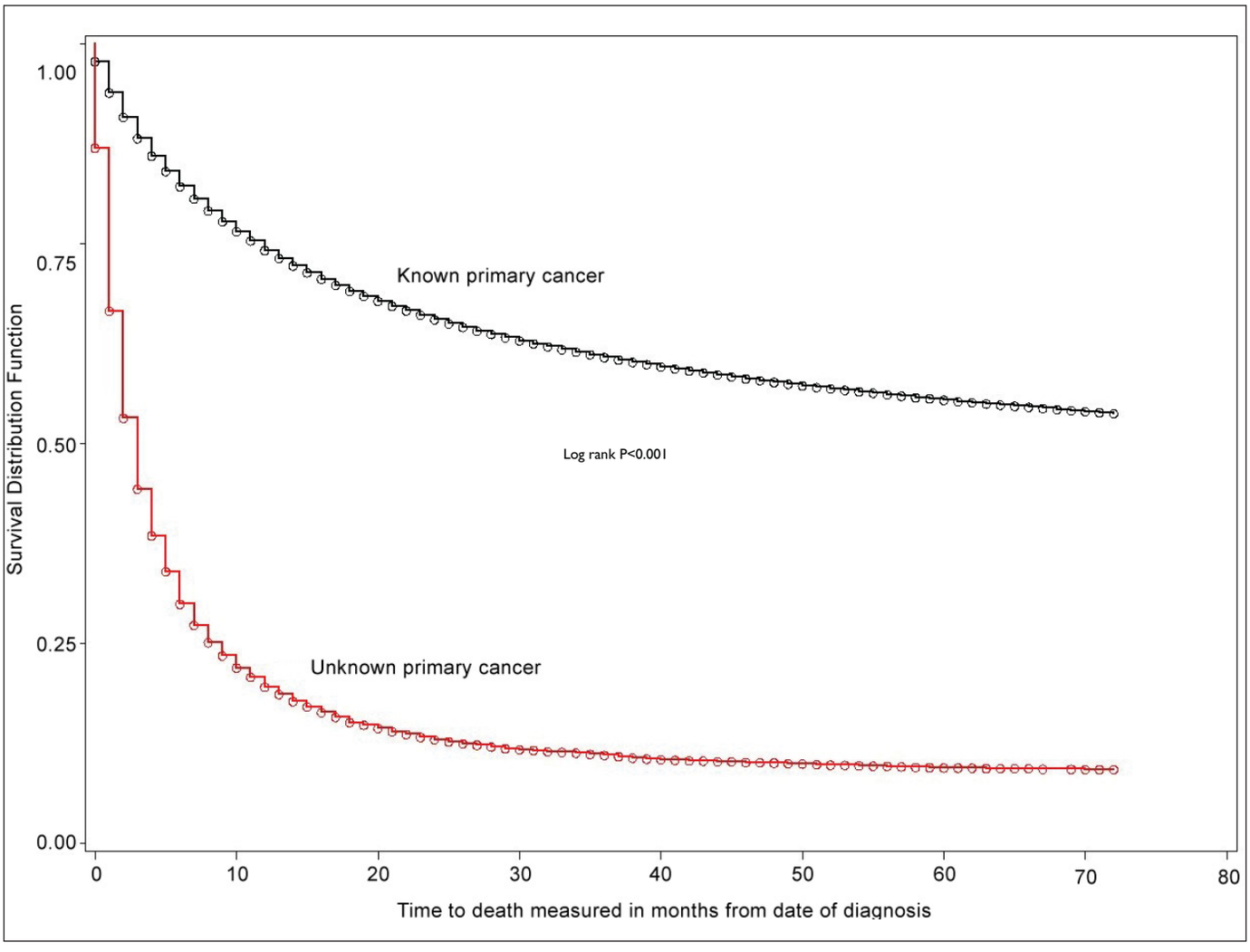
The final model includes the additional explanatory variables of time to death and period of diagnosis (Table 6). The final multivariate regression model for the time period 1980–1995 compared 8,684 cases of unknown primary cancer to 29,565 cases with a known primary cancer that had been histologically verified (Table 6).

People diagnosed with known tumour at diagnosis compared to those diagnosed with unknown primary cancer were (1980–1995):

- less likely to be male than female
- more likely to be aged over 75 years or older at diagnosis than younger
- more likely to be diagnosed with squamous cell carcinoma than adenocarcinoma
- three times more likely to be diagnosed with unspecified cancer than adenocarcinoma
- almost two times more likely to be diagnosed with unspecified and specific carcinoma than adenocarcinoma
- more likely to be cytologically diagnosed and less likely to be histologically verified at diagnosis than clinically verified.

3. **Survival** for unknown primary cancers

Figure 16 Kaplan Meier survival curve of all cases diagnosed with known or unknown primary cancer for the time period 1980–1995.



This section is comprised of unadjusted Kaplan Meier survival curves and proportional hazards regression analysis. In the following analyses, survival time is the outcome of interest, with each factor e.g. sex, age, socioeconomic status, ARIA, histological type and period of diagnosed, considered separately, and then together in a model that best explains factors that can influence survival time.

There were a total of 300,256 cases diagnosed between 1980 and 1995. Of these, 285,616 had a known primary site and 14,640 had an unknown primary site.

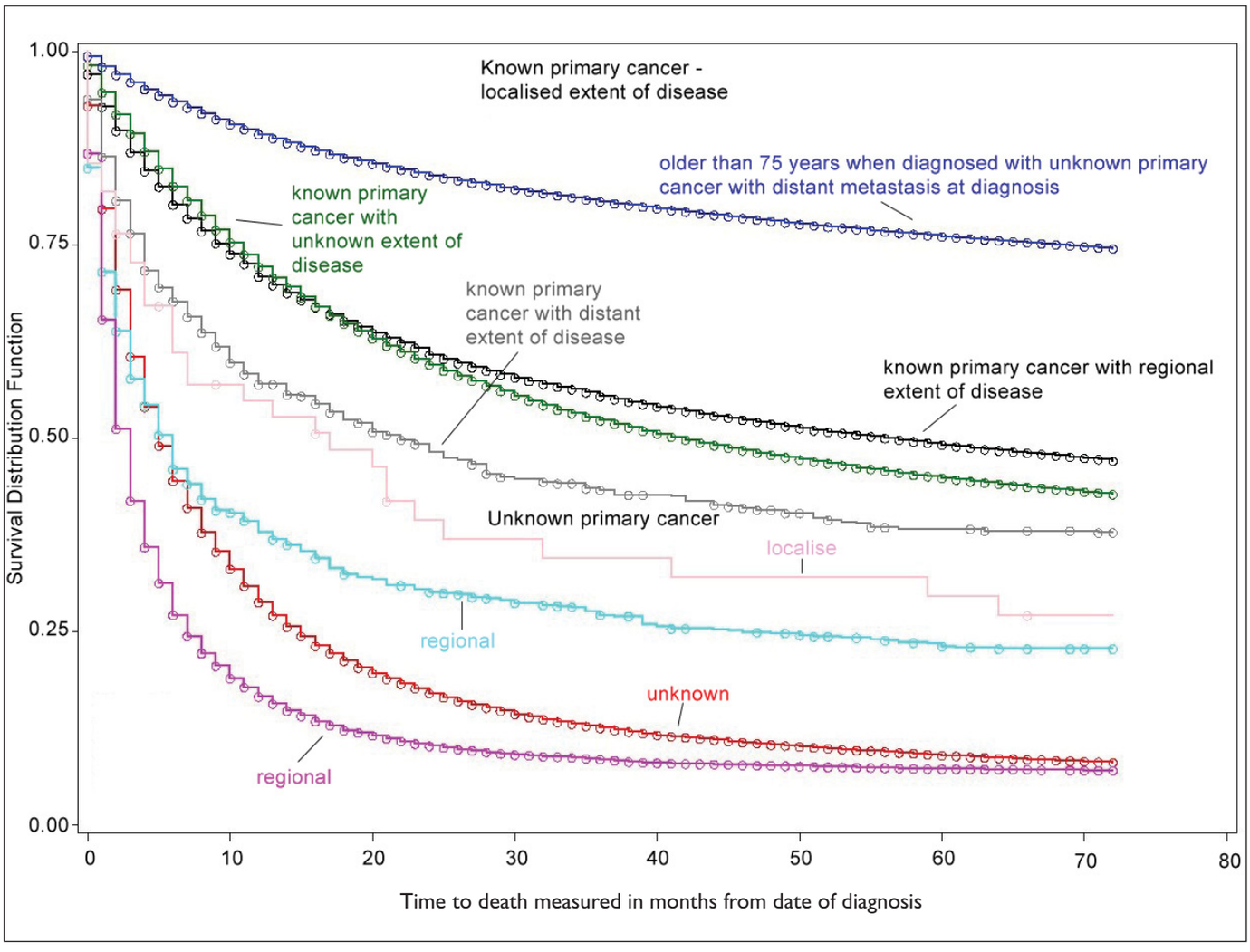
Approximately half (147,115 or 51%) of the known primary site cancers were censored because they either died from another cancer (59,514 or 20%) or were still alive at the end of five years (87,601 or 31%).

Of the 14,640 unknown primary cancers, 1,791 cases (1,144 dead from another cause and 647 alive) were censored.

The median survival of the remaining 138,501 cases of known primary and 12,849 cases of unknown primary was 107 months (95%CI 105–110) and three months respectively (Figure 16).

At 12 months post-diagnosis, 75% of people with known cancer at diagnosis had survived, where as only 19% of people diagnosed with CUP had survived. Seventy-five per cent of people with known cancers had died by 277 months (95%CI 274–282), while 75% of people with CUP had died by nine months (95% CI eight–nine months).

Figure 17 Kaplan Meier survival curve of all cases diagnosed with known or unknown primary cancer for the time period 1980–1995, stratified by stage at diagnosis.



Stratification by stage at diagnosis for people with a known and unknown primary site at diagnosis enables a much greater understanding of survival.

Of the 285,616 cases with a known primary site, 129,437 (45%) were localised stage, 60,276 (21%) were regional, 36,717 (12%) were distant metastases and 59,186 (21%) were of unknown stage.

Whereas 89% of unknown primary cancers were diagnosed with distant metastases, 4% with regional lymph nodes involvement and 6% with unknown stage.

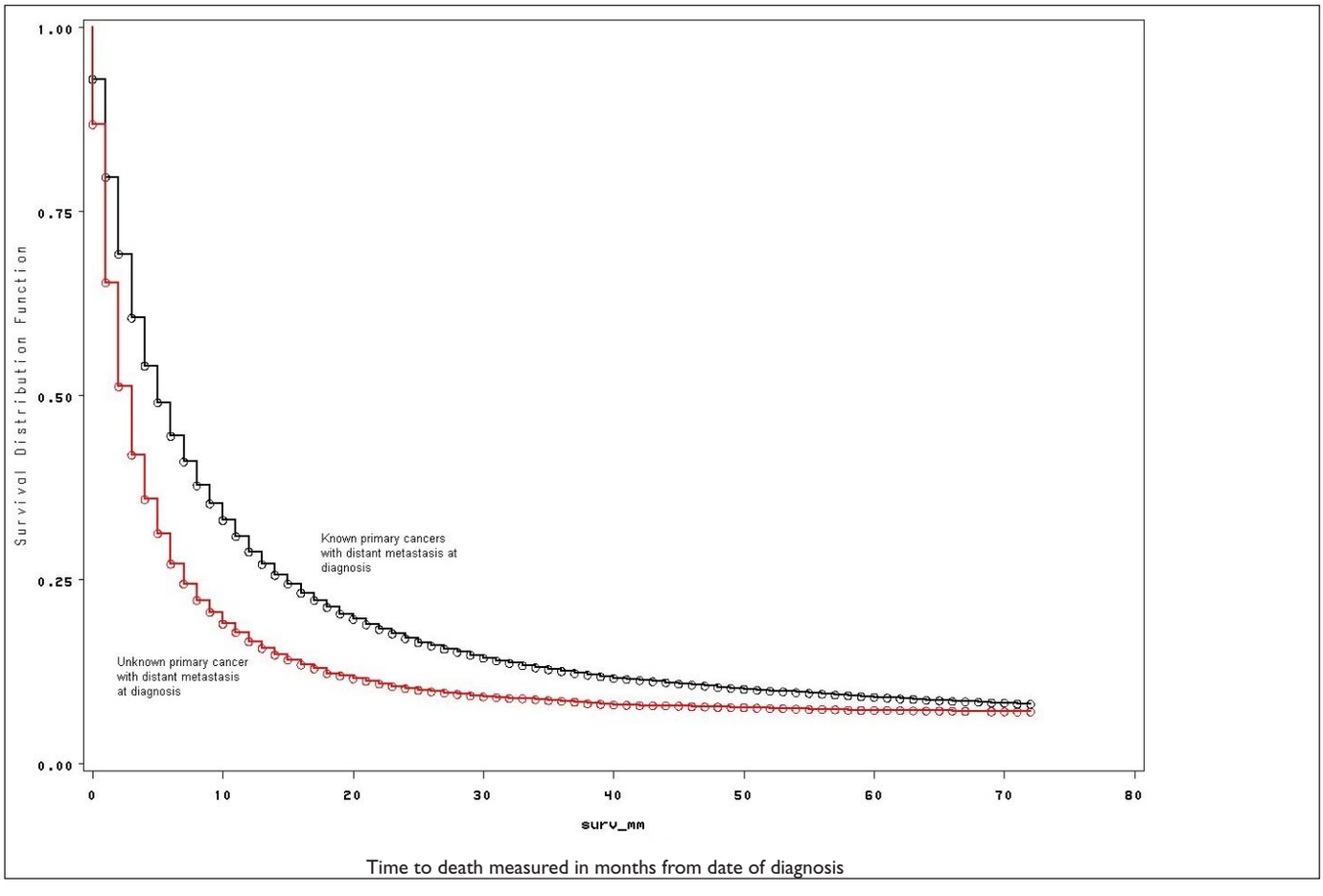
The median survival for those diagnosed with a known primary was:

- localised disease: 274 months (95% CI 267–278 months)
- regional :42 months (95% CI 41–43)
- distant metastases: five months (five–six months)
- unknown: 56 months (95% CI 54–48).

The median survival for people with unknown primary cancers was:

- regional: 22 months (17–28)
- distant metastases: three months (three–four months)
- unknown extent of disease: six months (95% CI five–six months).

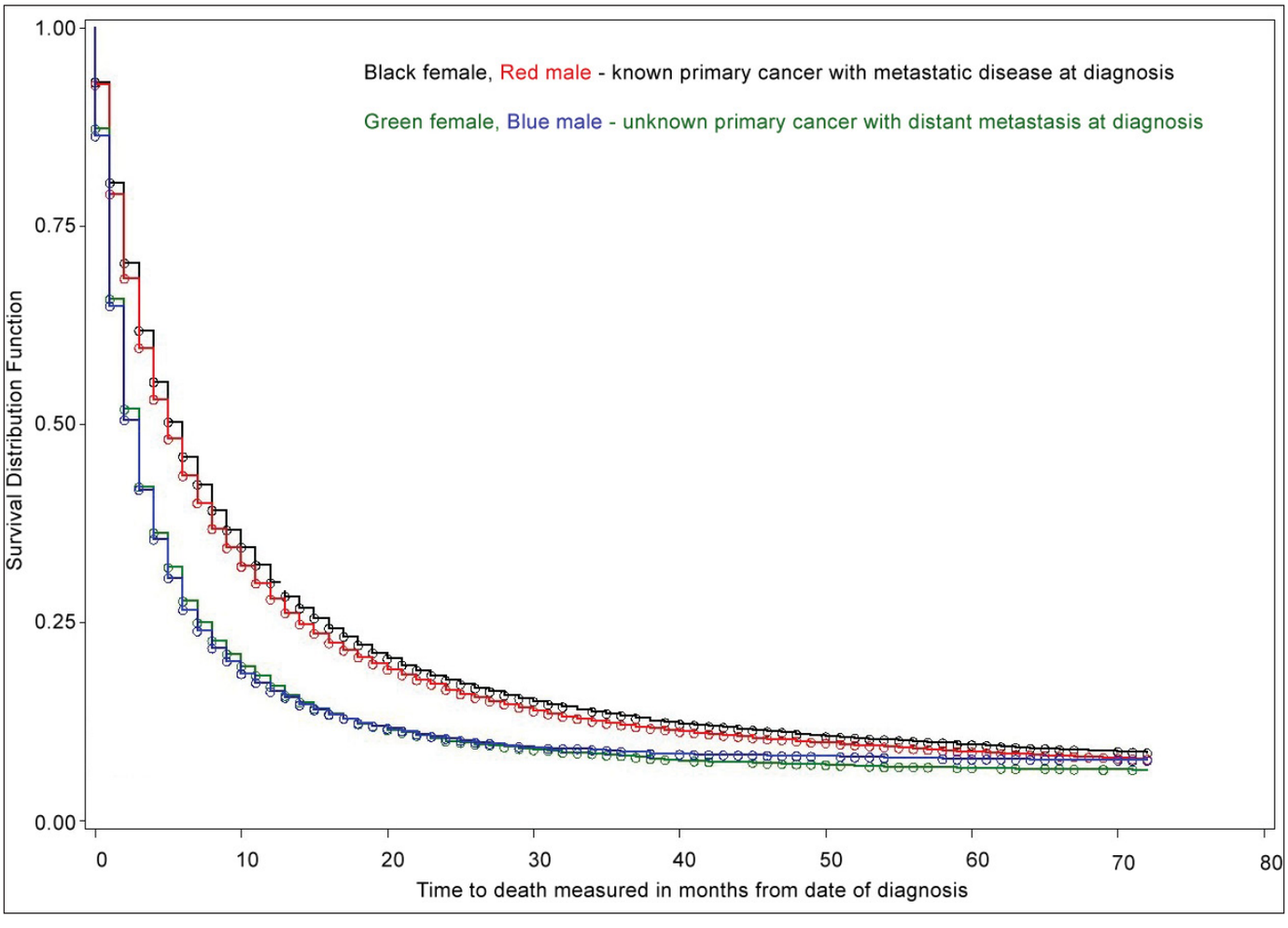
Figure 18 Kaplan Meier survival curve of cases diagnosed with known or unknown primary cancer that have distant metastases for the time period 1980–1995.



All further analyses of survival were conducted with metastatic stage at diagnosis only (36,717 known versus 13,165 unknown cancers). For both known and unknown primary cases, 10% were censored (3,654 and 1,333) since they died of another cancer (2,278 known and 895 unknown) or were still alive (1,376 known and 438 unknown).

In the remaining cases, the median survival time for those with known primary was five months versus three months for unknown cancer and 75% of those with known primary cancer had died by 15 months compared to seven months (95%CI seven–eight) for unknown cancer (Figure 18).

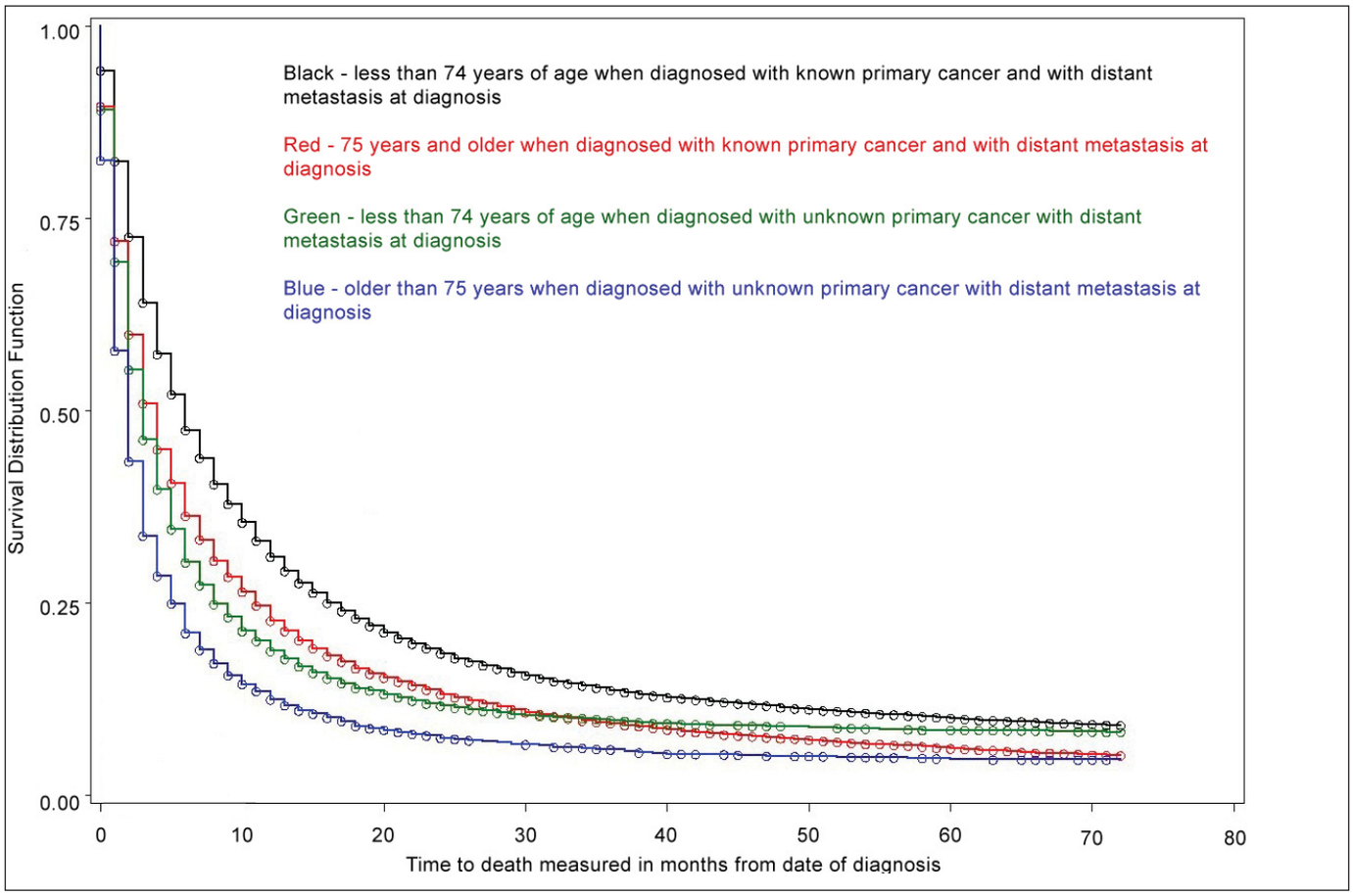
Figure 19 Kaplan Meier survival curve of cases diagnosed with known or unknown primary cancer that have distant metastases for the time period 1980–1995 stratified by sex.



Females with metastatic disease at diagnosis and a known primary cancer had slightly higher survival than males. The median survival time was six months for females (95% CI five–six months) and five months for males. Seventy-five per cent of females and males had died by 16 months (95% CI 15–16 months) and 14 months (95% CI 14–15) respectively.

For those with unknown primary cancer the median survival time for both males and females was three months (Figure 19) and 75% of both females and males had died by seven months (95% CI seven–eight months).

Figure 20 Kaplan Meier survival curves of cases diagnosed with known or unknown primary cancer that have distant metastases for the time period 1980–1995 stratified by age.

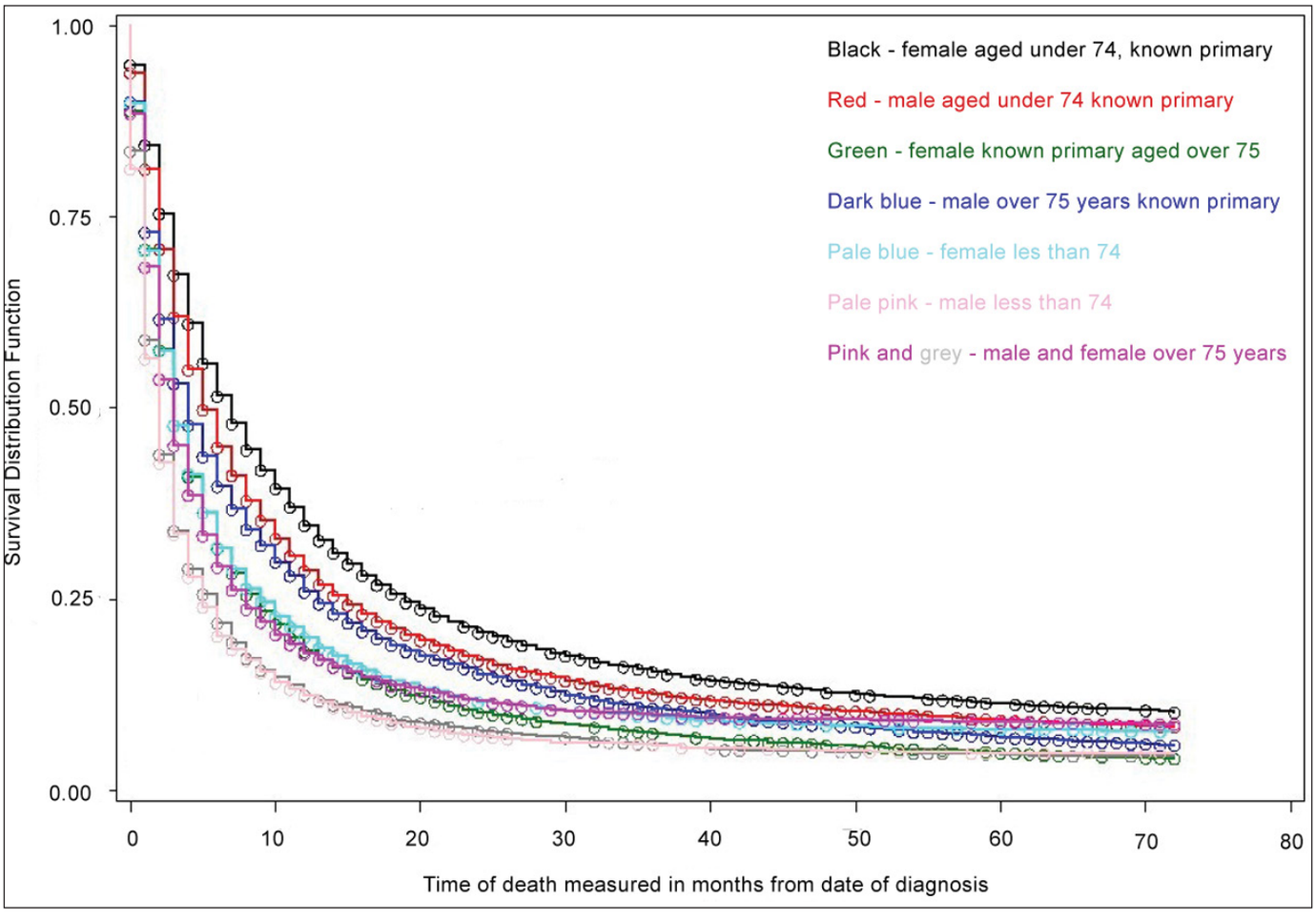


As it is shown in Figure 20, survival for those diagnosed with distance metastases was better for people aged less than 74 years if the primary tumour was known.

For those with known primary and aged 74 years and younger, the median survival time was six months. In this group, 75% had died by 16 months (16–17 months). For those aged 75 years and older, the median survival time was four months (95% CI three–four months) and 75% had died by 11 months.

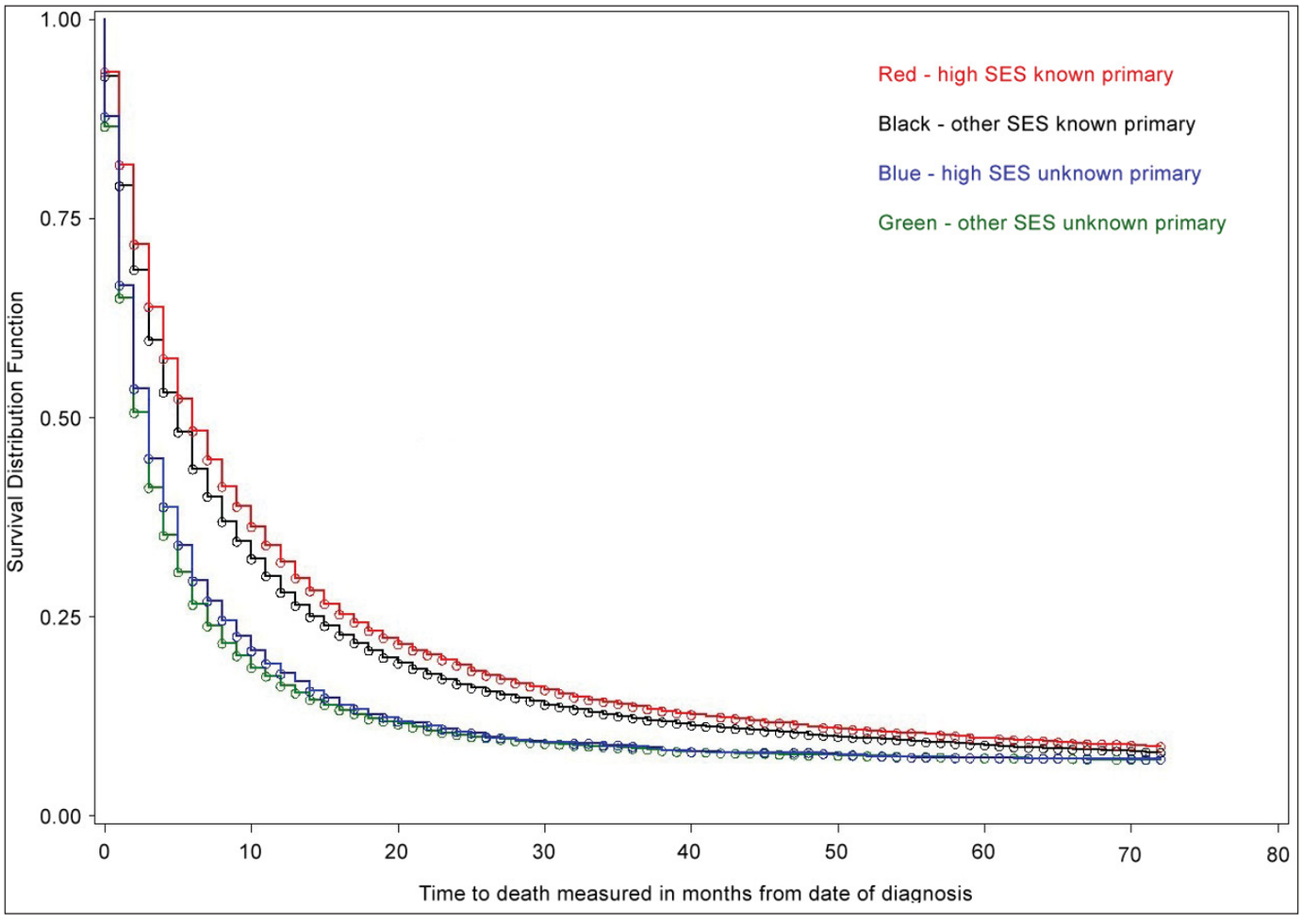
For those with unknown primary cancer and distant metastases aged less than 74, the median survival time was three months and 75% had died by eight months. For those aged 75 years and older, the median survival time was two months and 75% had died by five months.

Figure 21 Kaplan Meier survival curves of cases diagnosed with known or unknown primary cancer that have distant metastases for the time period 1980–1995, stratified by age and sex.



There was little difference in survival when stratified by age and sex. In both younger females and males (age 74 years or less) and older females and males (75 years and older), the survival was better if the patients were diagnosed with known primaries (Figure 21).

Figure 22 Kaplan Meier survival curves of cases diagnosed with known or unknown primary cancer that have distant metastases for the time period 1980–1995, stratified by socioeconomic status.

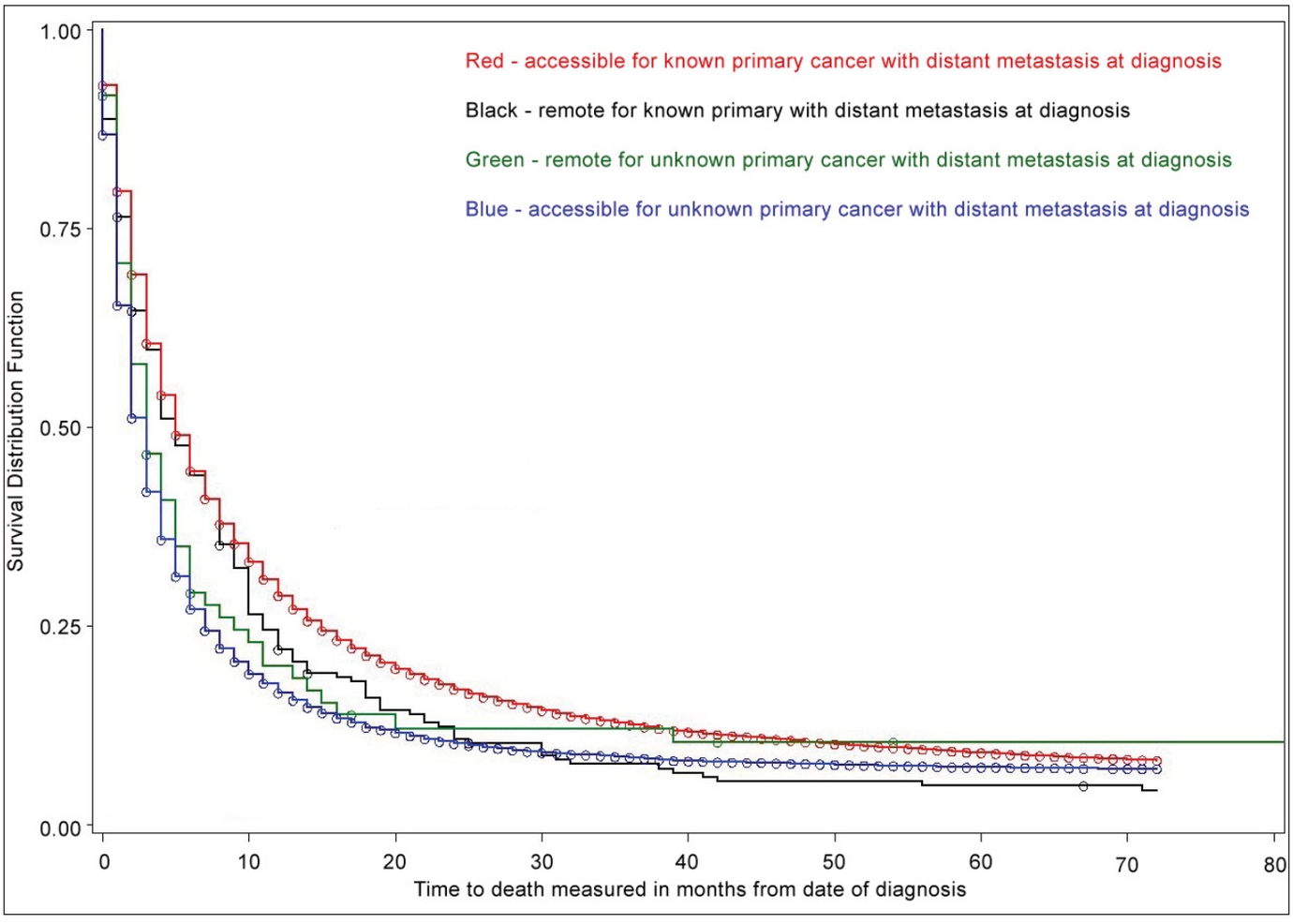


For people with distant metastases and a known primary, residing in a high SES at diagnosis translated into significantly better survival compared to all other SES groups (Figure 22).

The median survival time for those with high socioeconomic status was six months compared to five months for all other SES groups. In high SES groups, 75% had died by 17 months (95% CI 16–18 months) compared to 14 months (14–15) for all other SES groups.

High SES groups in those diagnosed with distant metastases and an unknown primary had slightly higher, but statistically non-significant, survival compared to all other SES groups. The median survival time for both groups was three months. In high SES groups 75% had died by eight months, compared to seven months for all other SES groups.

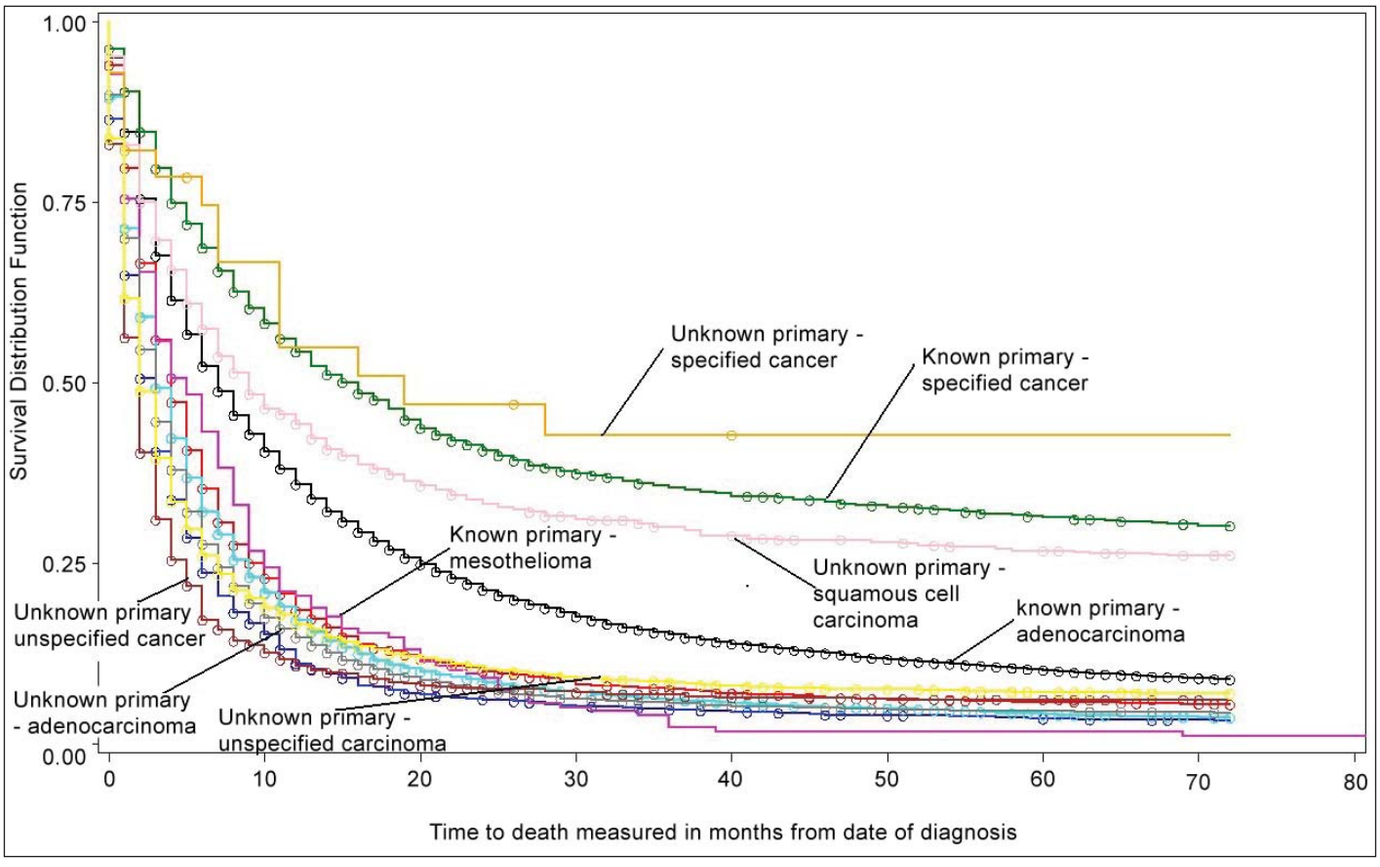
Figure 23 Kaplan Meier survival curve of cases diagnosed with known or unknown primary cancer that have distant metastases for the time period 1980–1995, stratified by ARIA (index of remoteness).



Those with distant metastases of known primary and living in accessible areas had slightly better but statistically non-significant survival compared to remote areas. The median survival time for those living in an accessible area was five months (Figure 23).

There was no difference in survival for those diagnosed with unknown primary cancer in accessible versus remote areas (Figure 23).

Figure 24 Kaplan Meier survival curve of cases diagnosed with known or unknown primary cancer that have distant metastases for the time period 1980–1995, stratified by histological grouping at diagnosis.



Histological groupings consistent with the *International Agency for Research in Cancer* were considered for both known and unknown primary cancers with distant metastases.

The hierachy of survival from highest to lowest were:

- unknown primary cancer site with a specified morphology
- known primary specified cancers
- unknown primary squamous cell carcinoma
- adenocarcinoma of known primary.

For known primary cancers the median survival times were:

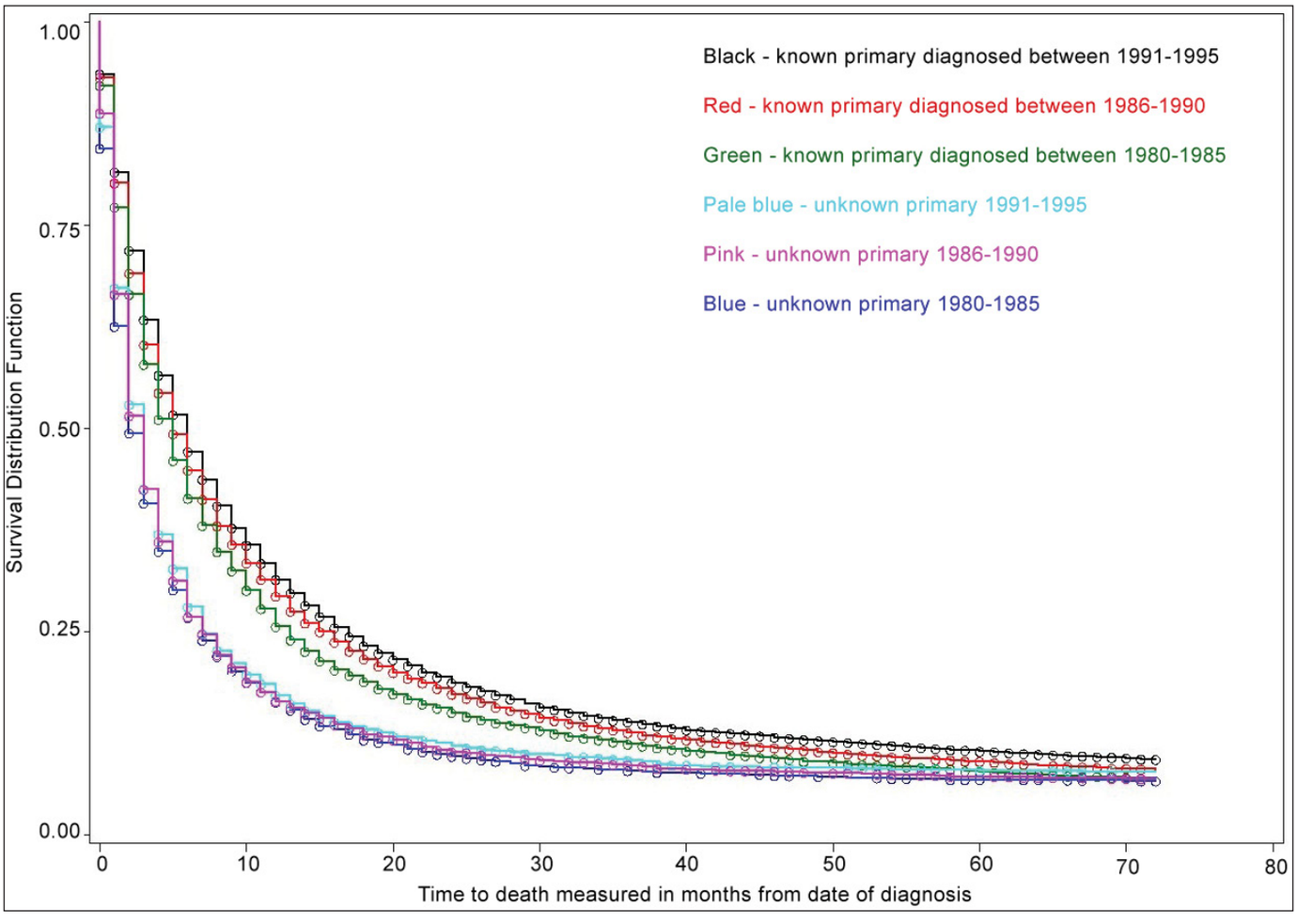
- specified cancer 16 months
- adenocarcinomas seven months

- mesothelioma five months
- squamous cell carcinomas four months
- unspecified cancer three months
- unspecified carcinoma three months.

For unknown primary tumours the median survival times were as follows:

- adenocarcinoma three months
- squamous cell carcinoma nine months
- specified cancer 19 months
- unspecified cancer and carcinoma two months.

Figure 25 Kaplan Meier survival curves of cases diagnosed with known or unknown primary cancer that have distant metastases for the time period 1980–1995, stratified by year of diagnosis.



Three time periods were examined by period of diagnosis. Survival for known primary cancers improved for each period of diagnosis. However, for unknown primary cancer there was very little difference (Figure 25).

Those diagnosed between 1990 and 1995 had a median survival of six months, compared to those diagnosed between 1980 and 1985 and from 1986 to 1990, with median survival of five months.

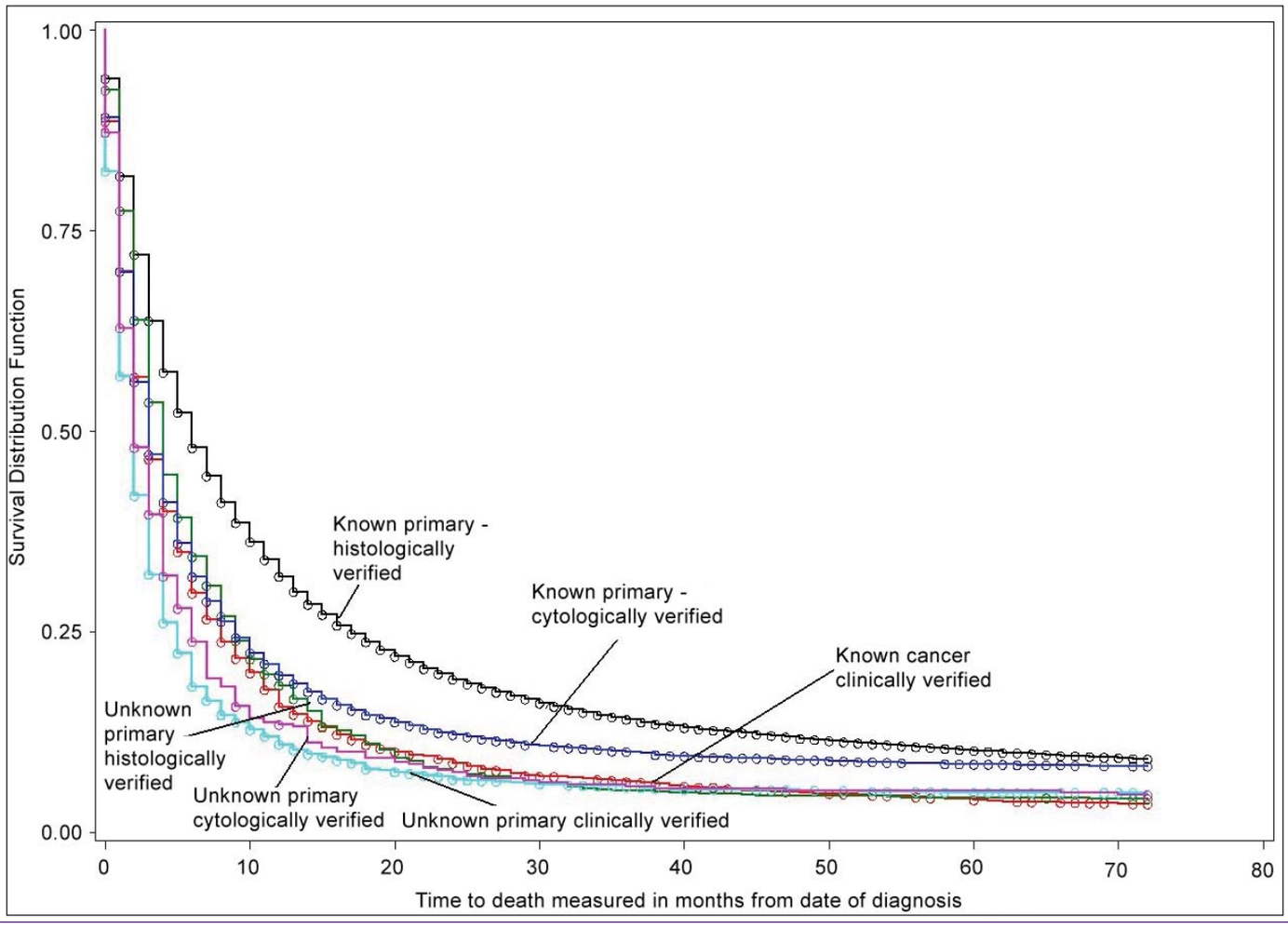
There was no difference in survival between the three time periods for those diagnosed with unknown primary cancer.

A greater understanding is obtained when 12-months survival is compared for those with known primary cancer and distant metastases. The 12-month survivals for known primary cancers in these three time series were:

- 32% in 1991–1995
- 25% in 1980–1985
- 29% in 1986–1990.

Between 1990 and 1995, 75% of those diagnosed with known primary cancers had died by 17 months (95% CI 16–18 months), compared to 15 months in 1985–1990 and 13 months in 1980–1984.

Figure 26 Kaplan Meier survival curves of cases diagnosed with known or unknown primary cancer that have distant metastases for the time period 1980–1995, stratified by method of diagnosis.



As it is shown in Figure 26, the median survival of histologically verified known primary cancers was six months and four months if they were cytologically and clinically verified. On the other hand, those with an unknown primary cancer and distant metastases had a median survival time of three months if histologically verified and two months if they were cytologically or clinically verified.

Cox proportional hazard modelling of unknown primary cancer and each of the explanatory variables

Cox proportion hazards regression modeling was undertaken for 44,882 people diagnosed with distant metastases between 1980 and 1995 and followed to the end of 2001. In that time period 10% (4,987) of the sample was censored because they died of another cancer, a non-cancer death or were still alive at the end of the period. A further analysis only considered those who were histologically or cytologically verified only (Table 11 histologically verified).

Of the remaining 38,249 persons with distant metastases, 8,624 had an unknown primary cancer and the remainder (29,625) were known primary tumours that had been verified histological or cytologically.

Table 11 shows that among metastatic cases, the risk of death for unknown primaries is 23% (95% CI 19–26%) higher than known primaries. Meanwhile, there is a higher risk of case fatality in males than females and patients aged 75 years or older. Conversely, there is a lower case fatality in high socioeconomic groups, and for those diagnosed in the later time period 1990–1995.

Compared with adenocarcinomas, the risk of death is slightly higher for squamous, unspecified neoplasm, unspecified/specified carcinoma and mesothelioma, but lower for specified cancer.

From looking at the hazard ratios, the model indicates for unknown cancer compared to someone with a known primary cancer (all other variables are held constant), the rate of death increases by 23%.

Holding all other variables constant, the death rate decreases by (123% –100%) = 23.5% in those under the age of 75. In the same age group, if the cancer is unspecified and specified, (all other variables are held constant) the death rate increases by (132% – 100%) = 32%. If the person is of high socioeconomic status, the death rate decreases by (100%–94%) =6% (Table 8).

Table 7 Cox Proportion Hazards model showing relative risks of death for unknown primary cancer and each of the explanatory variables persons with distant metastases that have been histologically verified , diagnosed between 1980–1995 and followed to the end of 2001.

Explanatory variable	Hazard Ratio	Lower HR	Upper HR	Chi squared	P value
Unknown	1.21	1.18	1.24	279.72	<0.0001
Unknown (histologically verified)	1.23	1.19	1.26	245.98	<0.0001
Male	1.03	1.01	1.05	7.87	<0.005
Male (histologically verified)	1.03	1.01	1.06	9.2	<0.0024
75 years and older	1.21	1.18	1.23	295.65	<0.0001
75 years and older (histologically verified)	1.23	1.20	1.27	268.24	<0.0001
High socio–economic status	0.95	0.92	0.92	22.05	<0.0001
High socio–economic status (histologically verified)	0.94	0.91	0.96	23.43	<.0001
Adenocarcinoma	1.00				
Squamous	1.04	0.99	1.07	3.7	<0.0537
Squamous (histologically verified)	1.04	1.00	1.08	12.25	<0.00005
Specified cancer	0.54	0.51	0.57	459.48	<0.0001
Specified cancer (histologically verified)	0.53	0.50	0.56	477.45	<0.0001
Unspecified neoplasm	1.32	1.26	1.38	161.7	<0.0001
Unspecified neoplasm (histologically verified)	1.26	1.10	1.44	11.87	<0.0006
Unspecified carcinoma versus unspecified cancer	1.32	1.29	1.357	553.09	<0.0001
Unspecified carcinoma and specified carcinoma (histologically verified)	1.32	1.29	1.36	472	<0.0001
Mesothelioma versus unspecified cancer	1.33	1.43	1.56	13.3098	<0.0003
Mesothelioma (histologically verified)	1.36	1.15	1.6	13.62	<0.0002
Clinical	1.00				
Cytology	1.08	1.02	1.15	6.6961	<0.0097
Histological	0.82	0.80	0.85	154.94	<.0001
1980–1984	1.00				
1985–1989	1.00	0.98	1.03	38.3659	<0.8899
1985–1989(histologically verified)	0.99	0.96	1.01	1.009	<.0.315
1990–1995	0.96	0.94	0.99	15.2332	<0.002
1990–1995 (histologically verified)	0.94	0.91	0.96	26.15	<.0001

It is more meaningful to look at the change in survival function, though it is not possible to obtain a graph through proportion hazards regression modelling. Instead we can use the model to produce survival curves for specific explanatory variables. Each explanatory variable will have a different survival function. The default survival is for each explanatory variable where each predictor is set equal to its mean. We can specify an explanatory variable and generate a survival function for patients with this specific covariate pattern.

For example, to graph the survival function for an unknown primary cancer patient who is aged 75 years or older, is male, with unspecified and specific carcinoma and who was living in the lowest socioeconomic group, for the time period of

diagnosis 1980–1985, an explanatory variable data set is created that is listed as a predictor in the model statement of the proportion hazards regression model. The same procedure can be undertaken for a known primary cancer patient who is male, aged less than 75 years, with adenocarcinoma at diagnosis living in the highest socioeconomic group for the most recent time period of diagnosis 1991–1995.

The result is seen below (Figure 27). The five-year cause-specific survival of an unknown primary cancer patient who is 75 years or older, is male, with unspecified and specific carcinoma, in the lowest SES group, for the time period of diagnosis 1980–1984 is 2% compared to 23% for the known primary cancer patient who is male, aged under 75 years, with adenocarcinoma at diagnosis living in the highest socioeconomic group for the most recent time period of diagnosis 1991–1995.

Figure 27 Survival function scenario 1 based on the final model for those diagnosed with known or unknown primary cancer that have distant metastases.

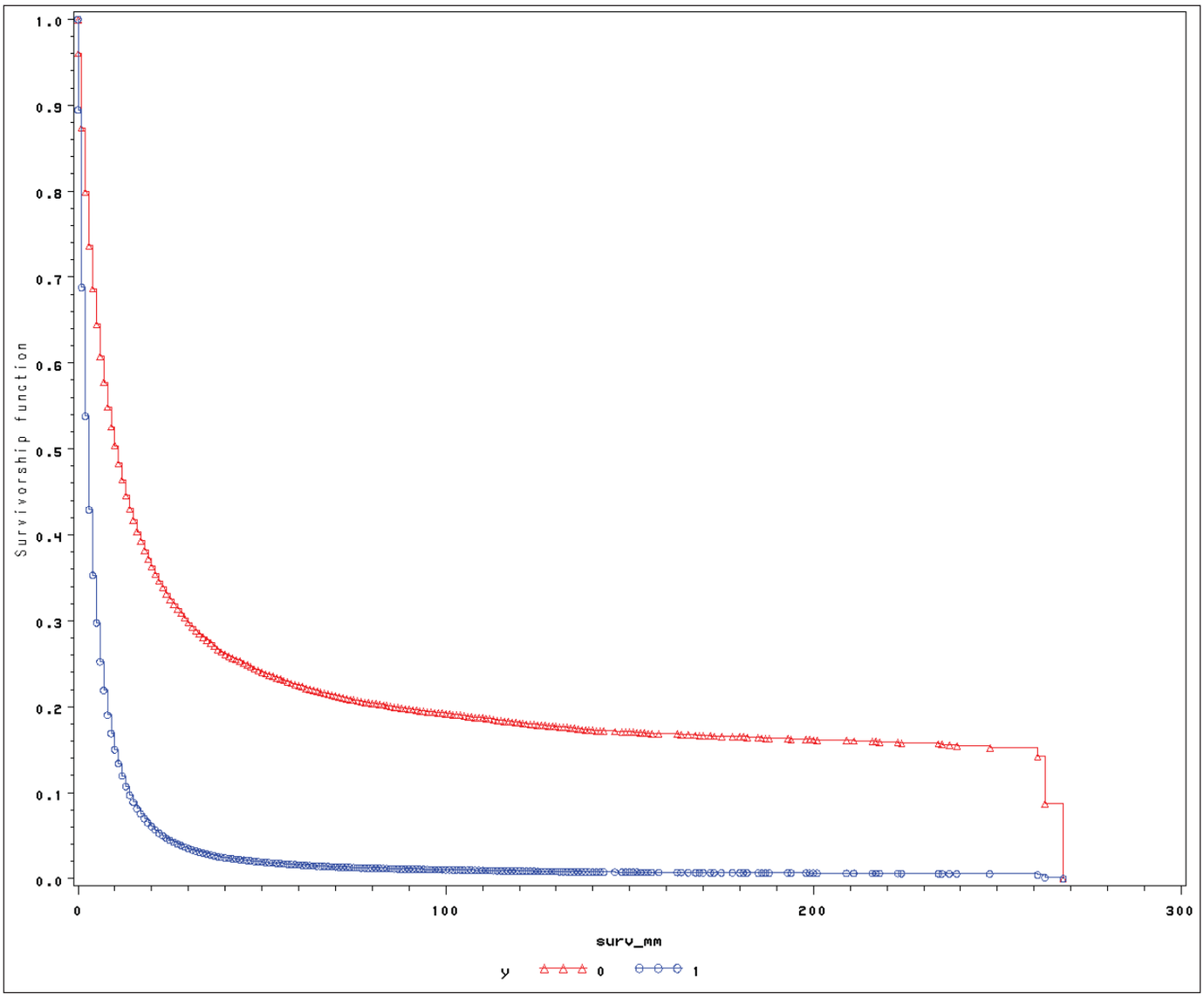
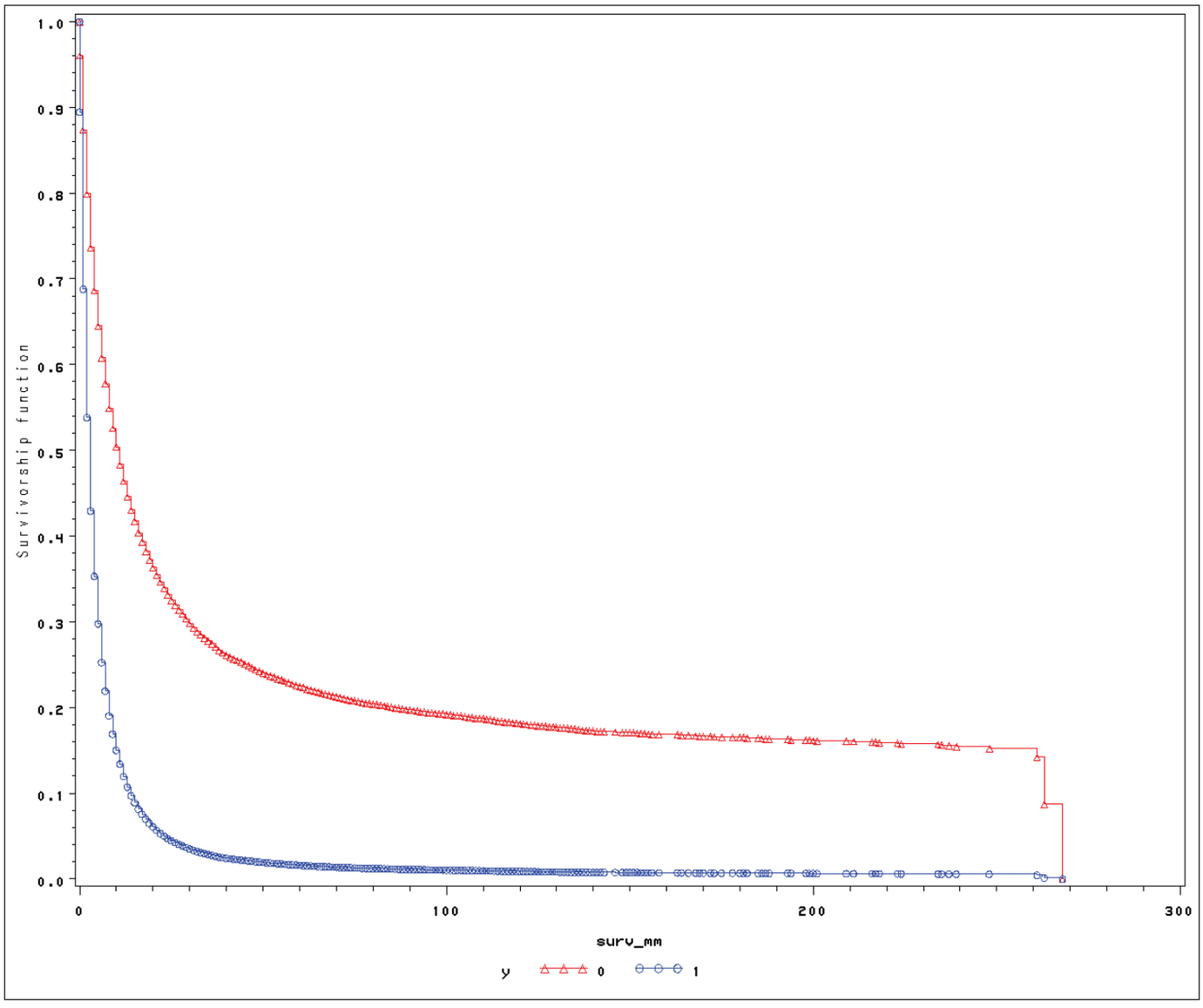


Figure 28 Survival function scenarios 2 based on the final model for those diagnosed with known or unknown primary cancer that have distant metastases.



4. **Trends** in quality indicators over time

Indices of data quality

Three commonly used indices of data quality are defined in *Cancer Incidence in Five Continents Vol VIII*[35]:

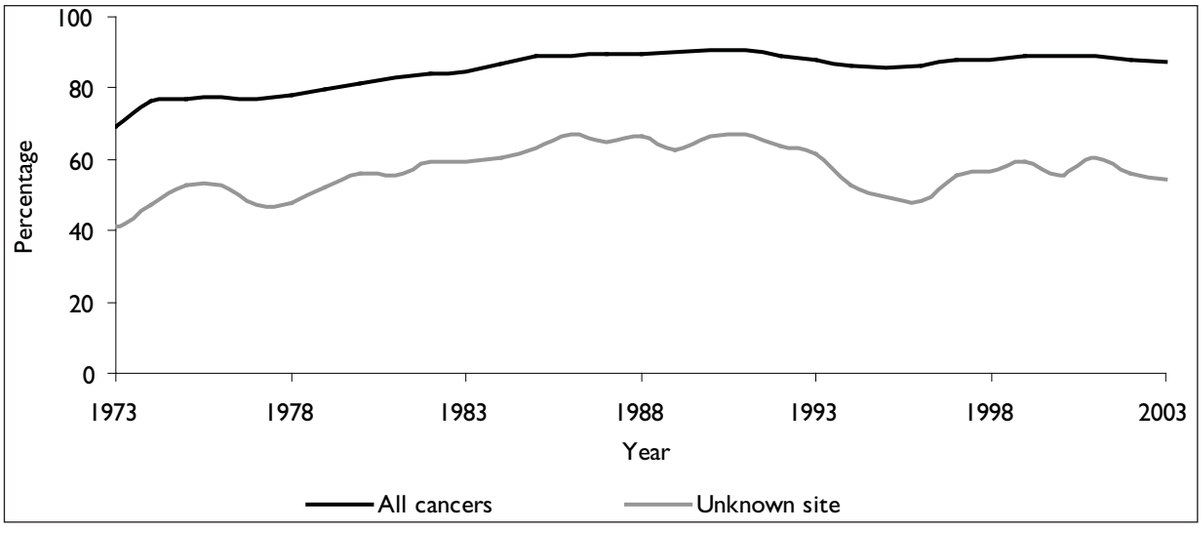
- Histological verification (**HV%**): the proportion of cases registered which had histological verification of diagnosis.
- Death certificate only (**DCO%**): the proportion of cases registered for which no information was available other than a statement on the death certificate that the deceased died from or with cancer.
- Mortality to incidence ratio (**M:I%**): comparison of the number of deaths attributed to a specific cancer in a defined population with the number of cases of the same cancer registered during the same period in the same population.

Histological verification (HV%)

An unusually low HV% suggests an incomplete histopathological verification and consequently poorer verification of diagnoses and incomplete registration of cancers. The higher the proportion of histological verification of diagnosis for cancer of sites that are less accessible, like brain and pancreas, the more confident one can be that the neoplasm existed and that it was primary rather than metastatic.[36]

The proportion of histologically verified for unknown primary cancer is on average 55% compared to 87% for all cancers. In general the proportion histologically verified has remained reasonably consistent over time (Figure 29).

Figure 29 Trends in the percentage histologically verified for known and unknown primary cancers 1973 –2003.



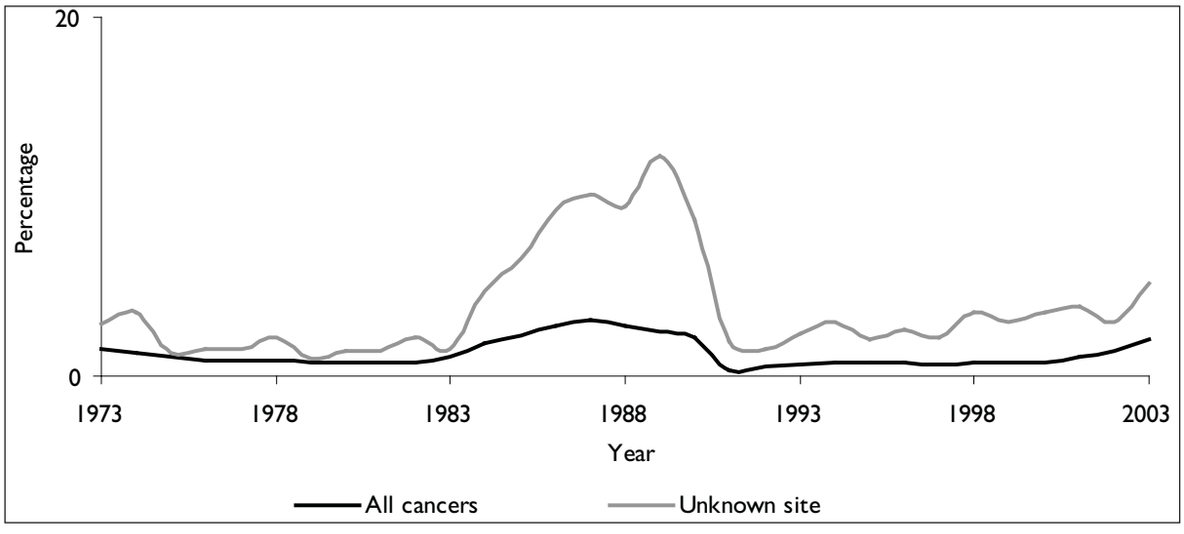
Death certificate only (DCO%)

A high DCO% suggests an incomplete incidence notification, and such diagnoses might be less accurate. The NSW Registry further investigates any cancers first notified by death certificate and confirms or rejects such cases on the basis of additional information obtained. If no further information is available, the cancer is registered as DCO on the basis of information provided on the death certificate.

For DCO cases, the date of diagnosis is the same as date of death. The proportion of DCO has remained consistent with the proportion higher in those with unknown primary cancer compared to those with known (Figure 30).

From 1983 to 1990 the proportion of DCO for unknown primary reached a peak of 12% (in 1989) largely due to less experienced coding staff who were employed for a defined time period to catch up on processing and eliminate a backlog of cancer notifications. From 1993 onwards, the proportion has been consistent at 1.4% for all cancers versus 6% for unknown primary, which is still considered to be low. Thus, the majority (94%) of cases have a source of notification that is not at death.

Figure 30 Trends in the percentage death certificate only for known and unknown primary 1973–2003.



Mortality to incidence ratio (M:I%)

If registration is complete and the incidence of the cancer in question is not changing rapidly, the mortality to incidence ratio should reflect long-term survival.

The mortality to incidence ratio is gradually declining for all cancers, which is also consistent with survival changes. For example, in 1973 40% of cancer patients survived, whereas in 2003 approximately 60% survived. As it is shown in Figure 32, 100% of unknown primary cancer cases died in 1973. This proportion gradually declined to 75% in 1993 or 72% in 2005, with 28% surviving per year until 2005.

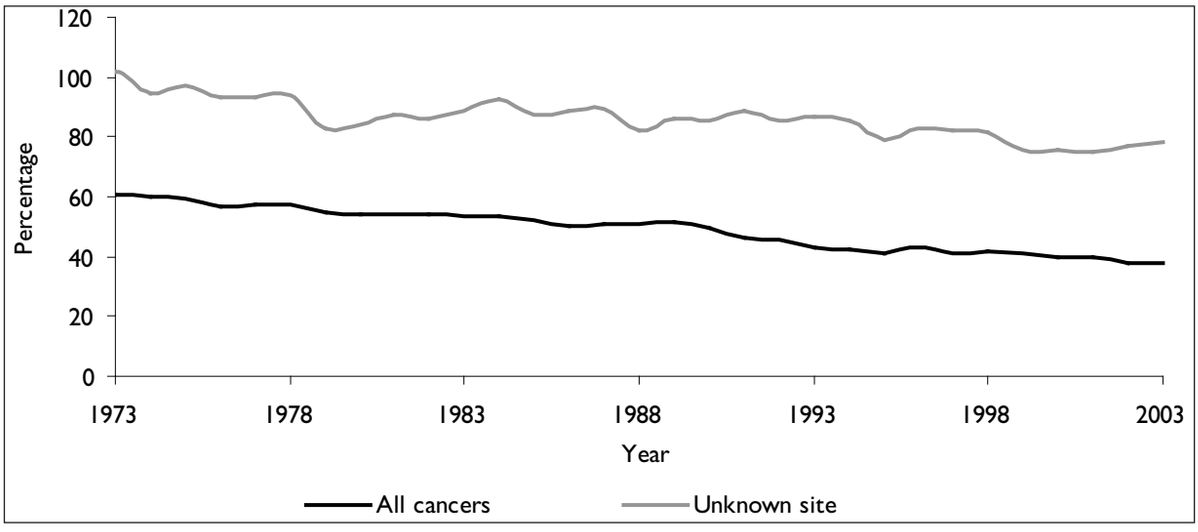
Comparison of this indicator in NSW with other registries for unknown primary site shows that the M:I ratio is 72, that is 72% died and 28% survived. This proportion is consistent with survival in the first year and is supportive of the view that all cases had been ascertained in NSW. The only international comparison of this indicator shows that in Nordic Europe the M:I ratio is similar to NSW males with M:I ratio of 76% while the UK has an M:I ratio of 87%. Canada and USA had M:I ratios of 116%, and 122% respectively.[28]

Ratios over 100% are considered to be due to less accurate diagnoses on the death certificate. Those countries that do not match and verify the cause of death, as registered on the death certificate against the original cause of cancer on the cancer registry, had been found to have poor accuracy in determining the true cause of death.[37]

Percy et al (1981) in a study of 48,826 resident cases of single primary cancers, found that the underlying cause of death as coded on the death certificate was accurate for about 65% of cancer deaths.[37] In this study, it was found that misclassification problems had occurred for colorectal cancer. Colon cancer was over reported and rectal cancer was under reported on death certificates. Other misclassification problems were found for cancers of the uterus, brain, and buccal cavity including most of its sub sites. Physicians tended to report a non-specific site of cancer on the death certificate rather than the specific site identified by the cancer registry.

The NSW Central Cancer Registry, like all Australian registries with the exception of Victoria, examines all principal and underlying causes of death provided on death certificates against the diagnosis of cancer found on the cancer registry and then determines the final cause of death. For this reason there is a high degree of confidence that the final cause of death is an unknown primary cancer.

Figure 31 Trends in the mortality to incidence ratios for known and unknown primary 1973–2003.



5. Discussion

Unknown primary cancer (CUP) has been considered a diagnosis of exclusion in the past. It is important to note that histological, cytological and imaging techniques have improved, which should increase the likelihood of finding the primary site and decrease the likelihood of a diagnosis of unknown primary.

There is some uncertainty whether unknown primary cancer forms a distinct biological entity with specific genetic and phenotypic characteristics, or whether it is merely a clinical presentation of metastases in patients in whom the primary tumour cannot be detected and does not result in any visible clinical signs.[9]

A review of the literature by Van de Wouw et al (2003) revealed only a limited number of publications describing the genetic and phenotypic features of CUP. Most focus has been directed towards potential of these markers to predict prognosis.[9] Further insight into the molecular mechanisms underlying the oncogenesis of unknown primary cancer by applying DNA and gene profiling microarray techniques, will be necessary to understand its specific biology and to develop more effective treatments.

Rates of unknown primary cancer (C80.9) in NSW increased steadily from 13.4 per 100,000 in males and 8 per 100,000 in females in 1973 to 27 per 100,000 in males and 19 per 100,000 in females in 1982. Rates have stayed relatively consistent since then with rates in males at 24 per 100,000 and 18 per 100,000 in 2003.

The early increase in rates in NSW is similar to major studies reporting increases in the 1970s by Osteen, Didolkar and Stewart supporting the notion that cancer of unknown primary is a distinct clinical entity.

Unfortunately, Australian rates commence in 1982, so it is not possible to observe if there is a similar increase in rates in the 1970s in other Australian states besides NSW. Similar to NSW, rates have remained constant in Australia for unknown primary cancer similar since 1982; while mortality rates have declined slightly in Australia, but have remained constant in NSW.

In NSW, the proportion of unknown primary cancer is higher than the National Cancer Institute. Possible explanations may be that there really is more unknown primary cancer in NSW or there are differences in active and passive follow-up that would impact on the number of cancers finally diagnosed with unknown primary. In the US coding is considered active and is undertaken by medical coders who abstract information from medical records and would have access to clinical conferencing and other non-histological means of determining a cancer site. Passive follow-up of cancer in NSW involves receiving information from multiple sources including death certificates and then modifying the final cause of cancer.

In the USA, cause of death is determined on the basis of death certificates only. Ill-defined cancer mortality is the fourth leading cause of cancer mortality in the USA, and accounts for 7.4% of cancer deaths annually.[38] Because survival is poor in those with unknown primary cancer, the expectation is that both incidence and mortality should be very similar to one another.

However, in the USA there are differences in the proportion of unknown primary cancers in those who are diagnosed and those who die from unknown primary because, unlike NSW, death data is not linked.

Studies of survival that have used registry data are limited, largely because registries have considered unknown primary cancers as the result of insufficient follow-up or lack of information to diagnose the primary site rather than a true condition. There is, however, one major analysis undertaken on one million cases of histologically confirmed unknown primary cancers diagnosed in residents of Surveillance, Epidemiology, and End Results (SEER) areas for a 15-year time period: 1973–1987.[39] This study found that over the 15-year period, there had been a decrease in the number of cancers by race and by sex, but there had been very little change in histological type. The most frequent histological type was found to be adenocarcinoma which was responsible for 55% of all tumours, with approximately equal numbers of epidermoid carcinoma and carcinoma not otherwise specified at about 14%.

Similarly in this report, adenocarcinoma was also the most frequent histological type. However, of the adenocarcinoma reported here are less than that reported in the above study at 40% of all unknown primary cancer in males and 32% in females.

Due to limited number of population-based studies unknown primary cancers have routinely been excluded from trends in incidence, mortality and relative survival figures.

It is of note in this analysis that a decision has been made to use cause-specific survival. This is mainly because the method is more clinically relevant and in line with survival studies that have been largely conducted on small numbers of patients.

Most analyses of unknown primary cancer patients have been undertaken in hospitals or on patients less than 1,550 in number. In addition, most studies have included autopsy information in an effort to locate the primary site.

In this report 38,249 people were diagnosed with distant metastases in the NSW Central Cancer Registry, 8,624 had an unknown primary cancer and the remainder were known primary tumours that had been verified histological or cytologically. Controlling for sex, age, socioeconomic status, histological grouping at diagnosis and period of diagnosis, it is seen here that people diagnosed with metastatic disease have a 23% (95% CI 19–26%) higher risk of dying from unknown primary cancer.

This study supports the notion that unknown primary cancer is a true condition and not simply the result of inadequate follow-up and diagnosis. Characteristics of people who are both diagnosed with and die from unknown primary are different to those with distant metastases and a known tumour.

If unknown primary cancer is a metastatic disease where the primary cancer had not been found through investigation or post-mortem, it would have been expected that survival would be the same for all metastatic disease, regardless of whether the primary is known or not. However, this was not the case here. Also, if unknown primary cancers were simply undetected known primary cancers, then it would be expected that patterns in trends in all cancers in males and females would be reflected in the trends for unknown primary cancer. Again, this is not seen here.

In this report, trends are very consistent for unknown primary cancer, with the shape of most incidence and mortality curves in both males and females very similar to one another. However, the rates for males are always consistently higher than females.

Compared to those with a known primary cancer the relative risk of dying with unknown primary cancer is higher:

- in females compared to males
- aged 75 years and older compared to younger age groups
- more likely to be diagnosed with squamous cell, unspecified cancer and carcinoma than adenocarcinoma
- clinically verified rather than histological or cytological verification
- in earlier time periods (years) compared to the latest time period (years).

The risk of dying of unknown primary cancers is, however, lower if:

- living in a high SES area at diagnosis compared to a the lowest SES area
- diagnosed with adenocarcinoma, squamous cell carcinoma and specified cancer compared to unspecified cancer.

The logistic regression analysis and the proportional hazards regression analysis show that the characteristics of unknown primary cancer patients are the same at diagnosis and death, which is not surprising given there is only three months median survival.

Most studies, including Nissneblatt in a review of unknown primary cancers, highlight the characteristics of unknown primary cancer patients. This review shows that they often originate in organs other than the expected pattern of known primaries and are most likely below the diaphragm (75%). The most common source is pancreas followed by liver and stomach. A further 25% originate above the diaphragm with lung the usual site.

Population-based data from two European registries report a median survival for unknown primary cancer of three months. Markman et al (1982) in a study of 249 patients at John Hopkins (between 1965 and 1974) with unknown primary cancers found that median survival was 3.1 months and that there was no effect of age, sex, race and year of diagnosis on survival from unknown primary. There was no clinically significant change in survival.[8]

Survival results by histological category in this study are similar to those seen previously. In this study, the median survival time for those diagnosed with metastatic disease at diagnosis was five months for a known primary site and three months for an unknown primary site. Survival for each of the explanatory variables was considered by stratifying the outcome variable and determining whether the primary was known or unknown with each of the explanatory variables. No difference in the median survival was found for those with unknown primary cancer by sex, age, socioeconomic status, index of remoteness and period of diagnosis. In all cases survival remained at three months.

Other factors that support the view that we are looking at separate clinical entity is that the trend pattern of unknown primary cancer is similar over time for males and females. Patterns for age-specific rates and histological groupings are also similar for males and female; and different to those of a known primary.

Altman et al (1986), in a study of 1539 cases of unknown primary cancer diagnosed between 1922 and 1981, had a slightly higher median survival of five months.[7] However, it was but also found that age, sex and year of diagnosis did not significantly influence survival. The best survival outcome for patients diagnosed with unknown primary cancer in this study was in patients diagnosed with squamous cell carcinoma with a median survival of nine months.[7]

In this report, similar to Altman et al, the median survival for squamous cell carcinoma in someone with unknown primary cancer was nine months. This is because, according to Hainsworth et al, these tumours are likely to be head and neck tumours and generally have the best outcomes. Similarly, adenocarcinoma of unknown primary cancer had a median survival time of four months, compared to Altman's study with three months median survival.[40]

Most of the studies of unknown primary cancer have a median age ranging from 57 to 60 years. In our study the median age was much older and increased over successive diagnostic periods. In 1980–1984 the median age at diagnosis was at 67 this had increased to 70 years of age in 1990–1995. Females were slightly older again with the median age of 70 and 74 years in 1980–1984 and 1990–1995 respectively.

Limitations of this analysis are that we do not know what treatments or investigations have taken place or location of the metastasis. However, with a survival time as low as three months, valuable time could be wasted looking for the primary site unnecessarily.

Prognosis and treatment

Identification of treatable patients within this group is the biggest challenge, according to Hainsworth et al 1993.[40] All patients should have careful history documented, pelvic and rectal examinations, as well as routine laboratory evaluation (blood counts and chemistry profile) and chest x-ray and CT of the abdomen. Open biopsy of the specimen and pathological evaluation including standard light microscopy and immunoperoxidase staining should also be considered. In some cases electron microscopy can assist in determining neuroendocrine tumours, melanomas and adenocarcinomas. Some studies however, advise against investigation for primaries since identification does not seem to alter final prognosis in some metastases.[18]

Depending on the histological group identified, the treatment regime varies. One of the most difficult sites to determine is histologically undifferentiated carcinomas, as their site of origin usually remains undiscovered. According to Ringenberg 1985, tumours of this type may often originate in the lung.[41]

Positive results have been reported with various treatment modalities.[1,10,42–44] This seems to be affected by the age, sex, histological analysis, performance status, response to initial treatment and number of metastasis sites.[19,21,23,26,45–47]

Recent studies looking at the biological profile of unknown primaries may increase the likelihood of specific and targeted pharmaceutical agents.[24]

Other studies have found that Positron Emission Tomography (PET) is superior to conventional patient investigations. In 11 out of 43 cases (27%) of unknown primary cancer, the primary lesion was detected in 10 cases. These would have remained unknown with the standard conventional investigations.[13]

More recent studies have suggested that fluorodeoxyglucose (FDG) combined with PET can improve the detection of the primary site in patients with unknown primary cancer. Unfortunately, these studies had small numbers of patients with unknown primaries detected in 29 of 52 and six out of 24 patients respectively.[14,48]

Of note, in a study done by Alberini et al (2003),10 out of 41 had their treatment modified after detection of the primary cancer. Six lung cancer patients received chemotherapy, two breast cancer patients received chemotherapy and radiotherapy, one head and neck cancer was treated by chemotherapy and one patient with pancreatic cancer received chemotherapy. Only one breast cancer patient was still alive at six months and eight of the 41 patients never had a primary site found died within 11 weeks of their diagnosis.[13] In a study by Kolesnikov, only 25% (six) out of 24 patients whose primary was identified, had their treatment modified.[15]

Given the small number of patients in these studies, larger studies would need to be done to determine whether modification to treatment and long-term survival in those whose primary is detected is worthwhile.

To assist clinicians in determining those patients who can best benefit from treatment, a statistical algorithm has been developed classifying 1000 patients with unknown primary cancer.[47] This analysis initially split unknown primary patients into two categories those with and without liver involvement. Ten terminal subgroups were formed. Median survival of the subgroups ranged from 40 months with one or two metastatic organ sites, with non-adenocarcinoma histology and without liver, bone adrenal or pleural metastases to five months in patients with liver metastases. The main application of using this method is once patients had been worked up and a description applied to their clinical features then survival probabilities could be applied to individual patients.

Briasoulis et al (1997) suggested that cancer of unknown primary patients have a unique biological profile, which is different to cancers with a known primary site.[49] This study found an over expression of tumour markers and oncoproteins tumours of unknown primary site. Similarly, in an immunohistochemical study of 81 unknown primary patients in 2005 (who were reviewed by two pathologists blinded to written pathology report) found that angiogenesis was very active and expression

of Vascular Endothelial Growth Factor (VEGF) was universal in cancers of unknown primary.[24] These findings support clinical investigation of VEGF targeted therapy in a clinical setting.

In a recent Australian study, Tothill et al (2005) found that using gene expression profiling could be applied to determine the origin of cancer of unknown primary (CUP). In this study a single cDNA microarray platform was used to profile 229 primary and metastatic tumours. Thirteen patients were selected who had disseminated metastases and no clinically detectable sign of a primary tumour using histopathology and computed tomography imaging. Gene expression profiling detected the primary cancer in 11 of 13 unknown primary cancers. It remains to be investigated whether there is a common gene expression profile for unknown primary cancer as a specific clinical type.[50]

There are currently 20 registered clinical trials, recruiting unknown primary patients. Two clinical trials recruiting unknown primary cancer patients are considering the use of chemotherapeutic agents Paclitaxel, Carboplatin and Etoposide or Irinotecan and Gemcitabine. In addition, 'A Phase II Trial of Oxaliplatin and Capecitabine in the Treatment of Patients with Relapsed/Refractory Carcinoma of Unknown Primary Site' is also taking place.

As far as treatment of unknown primary patients is concerned, those who were not evaluated at a cancer centre tended to be older and had a worse functional status than those who were treated. Moderate and severe comorbidities were found to impact on survival in 389 patients in Northern Alberta who were diagnosed with CUP from 2000 to 2003 and who had a performance status > or =2. The median overall survival of the 121 patients who had a good performance status was 317 days, and overall survival was not associated significantly with chemotherapy. An age-related decline was observed in the percentage of adults with good performance status who received chemotherapy.[51]

6. Conclusion

A greater understanding is required of the gene profile for unknown primary cancers.

Findings in this study support the premise that unknown primary cancers are a specific cancer rather than the absence of a primary site. Patterns of rates broken down by histological subtype were similar for both males and females with unknown primary, unlike trends with known primary cancers where trends differed by sex. The pattern of rates for adenocarcinoma and squamous cell carcinoma was different in males and females where the primary site was known. By contrast, the pattern of rates for adenocarcinoma and squamous cell carcinoma was similar in both males and females where the primary site was unknown. The characteristics of people who are both diagnosed with and die from unknown primary cancer are also different.

The majority of unknown primary cancers in all persons are late stage (distant metastases). In 1973 in NSW, 90% of unknown primary cases had distant metastases; this proportion declined to 70% in 2003. Rates have been steadily increasing for the proportion of unknown stage and regional stage to 20% and 10% respectively of total unknown primary cancers in 2003.

Those diagnosed with late stage cancer (distant metastases) have 80% (95% CI 70% to 92%) greater chance of dying in the first year after diagnosis, compared to the same stage in those with a known primary tumour.

The following statements hold true regardless of whether the period of diagnosis is recent (1999–2003 or 1980–2003), or whether metastatic stage is selected or only cases that are histologically verified. Cases diagnosed with unknown primary cancer compared to those with known primary cancer are: less likely to be male; more likely to be aged over 75 years; more likely to be diagnosed with squamous cell carcinoma (in 1999–2003 but less likely from 1980–1995), unspecified neoplasm and unspecified carcinoma than adenocarcinoma, less likely to be diagnosed with specific cancer; more likely to be cytologically verified than clinically verified and less likely to be histologically verified; less likely if the period of diagnosis is more recent.

Compared to people with a known primary cancer, people with an unknown primary cancer are less likely to be male, more likely to be older at diagnosis, more likely to be diagnosed with squamous cell, unspecified cancer and carcinoma, than adenocarcinoma and more likely to be diagnosed clinically or cytologically than through histological verification. This relationship holds true regardless of whether only metastatic cases are considered. If unknown primary cancer is a metastatic disease where the primary cancer had not been found through investigation, it would be expected that survival would be the same for metastatic cancer where the primary site was known.

However, among metastatic cases the median survival was three months where the primary site was unknown compared to five months where the primary was known. Modelling also showed that the risk of death for cancers of unknown primary site is 23% higher than for cases where the primary site is known while controlling for age, sex, socioeconomic status and histological subtype. In the future, specific and targeted pharmaceutical agents for unknown primary cancer could be developed as more is understood about the biology of unknown primary cancer. More specific immunohistological stains, development of tumour markers and gene expression profiling will most likely provide a greater understanding of the biology of this disease.

7. Recommendations

Clinical

1. Consider the role of Vascular Endothelial Growth Factor (VEGF) in a large number of unknown primary cases.
2. Consider the role of multi-disciplinary teams in unknown primary patients.
3. Participate in gene expression profiling for CUP.

Coding and definition issues

4. Raise the issue of coding with Australian Association of Cancer Registries and the International Association of Cancer Registers.
    i. Differentiate between unknown primary cancers where an investigation has taken place.
    ii. Unknown primary at diagnosis but the diagnosis is declared at death.
    iii. A death certificate only case that is the first diagnosis is at death, there may be characteristics of this group.
    iv. Need to ensure that squamous cell carcinomas that may be skin in origin are systematically excluded.
    v. Continue to review deaths certificates as validation of cause of death.
    vi. Breakdown the reporting of ill defined and unknown in future reports.
5. Consider further studies on specific subgroups of unknown primary cancer.

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9. Appendix

Presented is a typical example from the NSW Central Cancer Registry

Male, 54 years of age

Clinical notes

2/52 history of low back pain

X–ray sacral lesion

CT sacral lesion, right lung lesion, possible bulky prostate?

Bronchoscopy and washings? NAD

Macroscopic description

FNA/ sacral lesion

Microscopic description

The smear shows clusters of pleomorphic epithelioid cells. Focally there is a suggestion of acinar differentiation. No multivacuolated cytoplasm or myxoid stroma is seen.

Immunohistochemical stains shows that atypical cells have the following characteristics

Positive: AE1, AE3, CEA

Negative: CK20, PSA, Pacp

Suboptimal: TTF–1

" Dr Jo Bloggs and I agree that the features are of a metastatic adenocarcinoma. It is not possible to determine the primary site of origin of the tumour from this specimen. The main possibilities include, lung, upper gastrointestinal tract, hepatobiliary tract and pancreas. Clinicopathological correlation is suggested."

Summary

FNA of sacrum – Metastatic adenocarcinoma

Inpatient notification – clinically it is still considered as an unknown primary otherwise the medical record would have nominated a more specific site.

Coding in the NSW Central Cancer Registry

C80 unknown primary

M8140/3 Adenocarcinoma, NOS

Coding rules in the NSW Central Cancer Registry for coding unknown primary or ill defined site.

In cases falling into this category, staging is sometimes difficult because of the ambiguous nature of the tumour's origin. Coders should consider using:

Involvement of regional lymph nodes.

Distant metastases

Coders are asked to use the topography C80.9 only where absolutely necessary. It is often helpful to investigate the possibility of using one of the topographies in categories C26, C39, C76 which can allow for a more accurate localisation than C80.9. A comment can be made regarding the pathologist's preference for the site of origin in the "comments" field.

Where a pathologist gives a report that indicates that the lesion may represent either a primary or a metastasis, it is appropriate to use one of the ill defined or unknown primary site topographies, most often the latter.

Where a pathologist reports that the origin of the tumour is not apparent from the information available, it is appropriate to use one of the ill–defined or unknown primary site topographies. These cases may present difficult morphological challenges as well as having topographic ambiguity. Coders may wish to add a comment in the "comments field" to indicate the morphological considerations, such as "the differential diagnosis includes…" or "the morphology favours…" etc.

Coders are asked to take particular care in the case of malignancy, notably adenocarcinoma, involving pleura or pleural fluid. Before assigning lung topography as the primary site, the coder must be very sure that the case does not represent metastatic disease. In the specific instance of squamous cell carcinoma involving the parotid region, coders are reminded that these cases usually represent metastatic disease of the intra-parotid lymph nodes from tumours of the oral cavity, the upper aero-digestive tract or skin.

In summary, an unknown primary cancer diagnosis in the NSW Central Cancer Registry is a complex mixture of insufficient information to determine a primary cancer and considerable investigation where the primary site cannot be determined.

Appendix Table 1 Unknown primary cancer by Area Health Service of Residence at diagnosis.

AHS at diagnosis	Sex	1974–1978	1979–1983	1984–1988	1989–1993	1994–1998	1999–2003
Greater Southern	Male	79	152	152	177	213	302
	Male	3.2	3.6	3.2	3.4	3.9	4.7
	Female	57	115	129	152	171	240
	Female	2.3	2.7	2.8	2.9	3.2	3.7
Greater Western	Male	77	111	111	126	174	210
	Male	3.1	2.6	2.4	2.4	3.2	3.2
	Female	57	97	105	118	136	174
	Female	2.3	2.3	2.2	2.2	2.5	2.7
Hunter & New England	Male	180	290	335	434	430	528
	Male	7.2	6.9	7.2	8.3	8.0	8.2
	Female	137	249	272	349	334	444
	Female	5.5	5.9	5.8	6.6	6.2	6.9
North Coast	Male	63	114	161	223	241	307
	Male	2.5	2.7	3.4	4.2	4.5	4.7
	Female	54	96	116	144	184	253
	Female	2.2	2.3	2.5	2.7	3.4	3.9
Northern Sydney & Central Coast	Male	243	399	414	435	445	489
	Male	9.7	9.5	8.8	8.3	8.2	7.6
	Female	220	388	424	462	458	583
	Female	8.8	9.3	9.1	8.8	8.5	9.0
South East Sydney & Illawarra	Male	299	450	559	554	522	599
	Male	12.0	10.7	11.9	10.5	9.7	9.3
	Female	215	401	482	504	536	509
	Female	8.6	9.6	10.3	9.6	9.9	7.9
Sydney South West	Male	294	467	433	513	458	529
	Male	11.8	11.1	9.3	9.8	8.5	8.2
	Female	262	368	366	435	430	500
	Female	10.5	8.8	7.8	8.3	8.0	7.7
Sydney West	Male	143	251	327	326	374	396
	Male	5.7	6.0	7.0	6.2	6.9	6.1
	Female	117	245	288	301	294	402
	Female	4.7	5.8	6.2	5.7	5.4	6.2
		100.0	100.0	99.9	100.0	99.9	99.9
Subtotal	Male	1378	2234	2492	2788	2857	3360
Subtotal	Female	1119	1959	2182	2465	2543	3105
Grand Total	persons	2498	4193	4678	5253	5404	6469

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