Chapter 3 Estimating area variation in cancer survival

About this chapter

This chapter contains the manuscript titled "Estimating regional variation in cancer survival: a tool for improving cancer care" published in *Cancer Causes Control* 2004; 15:611-8.

The authors of this publication are Xue Qin Yu, Dianne O'Connell, Robert Gibberd, David Smith, Paul Dickman and Bruce Armstrong.

Changes have been made according to the guidelines for theses at the University of Sydney; therefore, this chapter differs from the published version.

A reprint version of this article is shown in an Appendix.

The tables and references have been renumbered to maintain consistency within the thesis.

Abstract

Objective: To improve estimation of regional variation in cancer survival and identify cancers to which priority might be given to increase survival.

Methods: Survival measures were calculated for 25 major cancer types diagnosed in each of 17 health service regions in New South Wales, Australia, from 1991 to 1998. Region-specific risks of excess death due to cancer were estimated adjusting for age, sex, and extent of disease at and years since diagnosis. Empirical Bayes methods were used to shrink the estimates. The additional numbers of patients who would survive beyond five years were estimated by shifting the State average risk to the 20^{th} centile.

Results: Statistically significant regional variation in the shrunken estimates of risk of excess death was found for nine of the 25 cancer types. It was estimated that the lives of 2,903 (6.4%) of the 45,047 people whose deaths within five years were attributable to cancer could have been extended beyond five years with reasonable survival improvement efforts. The highest number of these had died from lung cancer (791).

Conclusions: The empirical Bayes approach gives more precise estimates of region-specific risk of excess death and is preferable to standard methods for identifying cancer sites where gains in survival might be made. Estimates of the numbers of lives that could be extended can assist health authorities in prioritising investigation of and attention to causes of regional variation in survival.

Introduction

Survival is an indicator of the quality of cancer patient management. An analysis of cancer survival across regions can identify possible differences in the performance of regional health services with regard to cancer care. Identifying cancer types for which there is the greatest potential for increasing survival so that they can be targeted for action is a key element of such an analysis.

Place of residence is an important determinant of survival from cancer.[10;20;22;80] Regional variation in cancer survival may be due to a number of factors, including access to primary health care, the availability of diagnostic and treatment facilities and the treatment actually given. It may also be an artefact. While earlier diagnosis due to screening or improved diagnostic methods may truly increase survival, it may also just add lead time or extend average survival through diagnosis of cancers that would not otherwise have been diagnosed within the patients' lifetimes.[70;81] Sampling error may also produce spurious or spuriously large variation, particularly when the regions compared have small populations.

The standard approaches usually estimate regional variation by testing the hypothesis that all regional effects are identical, comparing extreme regions to the average, ranking the regions and focussing on the poor performers. The estimates from such approaches lack precision because of large sampling error. Consequently, use of these estimates may introduce errors in decision making for health service planning. Comparisons of survival among regions by producing a 'league table' is not very useful for decisions about where resources might best be targeted to improve survival because it focuses on the regional differences rather than the cancers for which the greatest gains might be made.[82]

There is, therefore, a need to develop more meaningful and useful measures of regional variation in survival. Empirical Bayes (EB) methods can be used to estimate a prior distribution for region-specific risks of excess death and to "shrink" the distribution of the observed estimates, bringing each estimate closer to the global mean roughly in inverse proportion to the sample size on which it is based. Shrinkage estimators have become popular and can be interpreted in many ways: they minimise the mean square error of the parameter estimates across all the regions;[83] take account of the regression to the mean for individual regions;[84] and take account of the variation in sample size.[85] The Bayesian approach also provides a posterior distribution for the parameters for each region, whose expectation is the shrunken estimator.[86]

This study aimed to explore the use of EB methods to produce more precise and robust estimators for regional variation in cancer survival. Estimates of the number of excess deaths due to cancer and lives that might be extended were also obtained to identify cancer types for which targeted action to increase survival by reducing regional variation in risk of excess death has the greatest potential to improve outcome.

Materials and Methods

Data

Data were obtained from the population-based New South Wales (NSW) Central Cancer Registry, Australia, for 25 major types of cancer diagnosed between 1991 and 1998. Notification of cancer is a statutory requirement in NSW. Data on the general population mortality rates needed to calculate relative survival ratios were obtained from the Australian Bureau of Statistics.

The first occurrence of a primary cancer for an individual was included in the survival analysis. Cases notified by death certificate only or identified at post-mortem, cases with place of residence information not available, or age at diagnosis greater than 89 years, were excluded from the analysis.

There are 17 Area Health Services in NSW; nine cover the major urban regions and contain populations ranging from 270,000 to 750,000 and eight cover the rural regions with populations ranging from 50,000 to 250,000. Assignment of cases to Health Service regions for the purpose of analysis was based on their place of residence at the time of diagnosis of their cancer.

All cases were followed up to December 2000 to determine survival status. People with cancer who were not known to be dead were matched against death records from the State Registrar of Births, Deaths and Marriages and the National Death Index. A modification of the period method described by Brenner et al[87] was used to compute five-year relative survival based on cancers diagnosed in the period 1991 to 1998 and deaths in the period 1994 to 2000. Patients diagnosed in 1994 and 1995 had been followed-up for the full five years, while the more recently diagnosed cases (1996 to 1998) had not. To supplement the experience of those diagnosed in 1994 to 1998, the survival experience in 1996 to 1998 of patients diagnosed in 1991 to 1993 was included in the analysis. Thus the fifth year of survival experience from patients diagnosed in 1991 was included in the analysis, together with the fourth and fifth years from patients diagnosed in 1992 and the third, fourth and fifth years from those diagnosed in 1993. The end of follow-up was the date of death for those who died within five years of diagnosis and before the end of 2000; those who had not died by the end of 2000 and had not been followed up for five years were censored.

Statistical methods

Relative survival

Relative survival is the ratio of the observed proportion surviving in a group of patients to the expected proportion that would have survived in a comparable group of people (with, for example, the same distribution by age, sex, and geographical area) from the general population.[3]

The survival time was measured from the month of diagnosis to the date of death or censoring and was grouped into annual intervals for this analysis. Observed survival was estimated by the life table method.[88] Expected survival was estimated using the Ederer and Heise method,[89] which is also a life table method. The region-specific population life tables for the period 1994-1998 were used for these analyses. All-cause mortality data and the NSW population by single year of age, sex and region of residence, were used to construct the region-specific life tables.

In our analyses, cumulative relative survival was calculated as the ratio of the cumulative observed survival proportion to the cumulative expected survival proportion as described in the SURV2 computer program manual.[90]

Relative excess risk of death

If cause of death was accurately known for all patients it would be possible to directly estimate the cancer-specific fatality rates in each region and compare these estimates to the estimates for NSW as a whole by calculating rate ratios. However, cause of death is not reliably reported for all cancer patients and even with access to medical records it is difficult

to classify each patient's death into one of the two categories "entirely due to cancer" or "entirely unrelated to cancer". A preferable approach is to estimate the cumulative death rate due to all causes in the cancer patients and subtract from it an estimate of the death rate in a similar population without a diagnosis of cancer and thus gain an estimate of the "excess cumulative death rate" or "excess risk of death". The major advantages of this measure (and its survival analogy, relative survival) are that information on cause of death is not required and it provides a measure of the excess death rate experienced by patients diagnosed with cancer, irrespective of whether the excess is directly or indirectly attributable to the cancer. Thus we estimated the excess risk of death for each cancer type in each region and then compared it with an estimate of the excess risk of death for the same cancer in the State as a whole to produce an estimate of the relative excess risk of death for that cancer in each region.[91]

Statistical modelling

To adjust for differences between the health service regions in variables other than treatment that might affect the survival of cancer patients, a Poisson regression model of excess risk of death during the first five years was constructed for each type of cancer and included age group, years since diagnosis, sex (where applicable), and spread of disease at diagnosis (where applicable) as main effects and the interaction between age group and years since diagnosis where possible. For most cancer sites, age was divided into four groups: 15-44 years, 45-59 years, 60-74 years and 75-89 years; these age groups were modified for cancer of the testis. Spread of disease at diagnosis was classified into four broad categories: localised, regional (including adjacent organs and regional lymph nodes), distant and unknown. The interaction term was included to allow for non-proportional hazards across the five years of follow-up; it was, however, removed from the model for testis cancer to achieve convergence.

For cancers of the lung, breast and prostate, an additional interaction term between spread of disease and years since diagnosis was added to the model to improve the goodness-of-fit. Nine models fitted the data well with very large p-values for the goodness-of-fit statistic, another six were reasonable fits with p-values ranging from 0.06 to 0.33, and three had p-values just less than 0.05. The remaining seven models did not fit the data well; the p-values for the goodness-of-fit statistic were very low. In order to separate the regional variation due to delay in diagnosis from the regional variation that may relate to differences in treatment, we fitted the same models omitting spread of disease and compared their results with those including this variable.

Empirical Bayes approach

To estimate the systematic regional variation in survival for each cancer type, we fitted a model for the relative excess risk using the SAS procedure NLIN. To stabilise the estimates of region-specific risk we applied an empirical Bayes method to get shrunken estimators for each region. We assumed that the region-specific excess risks followed a Gamma distribution, with mean μ, and variance σ^2. The shrunken estimators combined region-specific risk with the results from all other regions as in the following formula:

$$\text{Shrunken estimator } (\theta) = (\text{Obs} + \mu^2/\sigma^2)/(\text{Exp} + \mu/\sigma^2)$$

where Obs and Exp are the observed and expected numbers of excess deaths, μ is the average excess risk for all regions (global mean) and σ is its standard deviation for a given cancer site. The local estimates (Obs/Exp) are shrunken towards the global mean (set as 1.0). The amount of shrinkage varies according to the value of σ^2 and the value of Obs and Exp for each region. If the region has a large population then this approach will move the local estimates very little, whereas if the region is small then this approach will move the local estimate

considerably closer to the global mean. If the variance (σ^2) is large, the shrunken estimator will remain similar to the local estimate.

Hypothesis test

The hypothesis of no regional variation (i.e. $\sigma = 0$) was tested for each cancer type by comparing the statistic calculated as the ratio of σ and its standard error ($z = \sigma/se(\sigma)$) with the standard normal distribution. A p-value of 0.05 or less from the hypothesis test was taken to indicate statistically significant regional variation in the relative excess risk for the given cancer.

Lives that might be extended

To show the importance of regional variation in survival and identify the cancer sites in which improvement in care would result in large gains in survival, we estimated the number of lives that would be extended beyond five years after diagnosis in people with each type of cancer if the State average risk of excess death was shifted to the 20th centile of the distribution of region-specific risks of excess death. The number of lives that might be extended beyond five years was then estimated using the following formula:

$$\text{Number of lives that might be extended} = Obs*(1-\mu_{20th\%})*\sigma/SD(\mu_{shrunken})$$

where $\mu_{20th\%}$ is the 20th centile of the empirical distribution and $SD(\mu_{shrunken})$ is the standard deviation of the distribution of the shrunken estimators. In this way, we could provide an estimate of the importance of the regional variation in survival for each cancer.

Results

The commonest cancers during the study period were cancers of the prostate (25,713), female breast (24,316) and melanoma of the skin (18,574) (Table 4). Of the 25 chosen types of

cancer, mesothelioma was the least common (785). These 25 types accounted for 92.5% of all cancers in the study period.

Regional variation in the five-year relative survival ratios and crude and shrunken relative excess risks of death with and without adjustment for spread of disease for the 25 types of cancer are summarised in Table 4. The impact of the empirical Bayes method on the variation in relative excess risk of death is readily seen in this table, and the inverse association, generally, between the number of people with each cancer type and the amount of shrinkage. For example, for cancer of the testis, a relatively uncommon cancer (1,411 cases), the relative excess risks ranged from 0.00 to 3.9 while the shrunken estimates showed little variation. Statistically significant variation in relative excess risk was found for nine of the 25 cancer types analysed - cancers of the colon, liver, lung, female breast, ovary, prostate, and melanoma of the skin, multiple myeloma and leukaemia. As shown in Table 4, after adjustment for spread of disease, the regional variation in survival decreased for 11 sites out of the 20 sites that had disease stage, increased for four sites and changed little for the remaining five sites. There was statistically significant regional variation in survival for a 10th site (stomach) after omitting disease stage from the model.

Table 4. Regional variation in five-year relative survival (%), crude and shrunken relative excess risks (RER) of death and test for regional variation in 1994-2000 for 25 cancers in NSW Australia

Cancer type	Number of new cases	State-wide 5-year relative survival	Range of regional variation in relative survival	Range of variation in RER* of death				
				crude	Without stage adjustment		With stage adjustment	
					shrunken	p-value†	shrunken	p-value†
Head and neck	5,553	55.2	32.6 – 60.7	0.89 – 1.63	1.00 – 1.00¶	1.00	1.00 – 1.00¶	1.00
Oesophagus	1,652	16.3	9.2 – 27.4	0.66 – 1.99	0.92 – 1.10	0.18	0.94 – 1.07	0.31
Stomach	3,588	25.3	12 – 32.2	0.83 – 1.32	0.84 – 1.12	0.005	0.92 – 1.04	0.08
Colon	15,280	60.4	51.5 - 66.5	0.88 – 1.36	0.88 – 1.19	<0.001	0.89 – 1.19	<0.001
Rectum	8,768	60.2	49.7 – 64.4	0.87 – 1.50	0.98 – 1.01	0.65	0.98 – 1.01	0.69
Liver	1,051	12.6	4.0 – 36.3	0.62 – 1.75	0.81 – 1.34	0.006	0.79 – 1.33	0.009
Gallbladder	1,064	18.8	7.0 – 27.6	0.46 – 1.55	0.92 – 1.07	0.32	0.95 – 1.03	0.41
Pancreas	2,795	5.4	2.4 – 11.0	0.87 – 1.36	0.96 – 1.04	0.36	0.92 – 1.07	0.12
Lung	13,992	13.2	8.9 - 16.5	0.90 – 1.16	0.91 – 1.08	0.02	0.91 – 1.09	0.03
Melanoma	18,574	91.0	86.8 - 92.9	0.87 – 1.60	0.83 – 1.29	0.004	0.92 – 1.35	<0.001
Mesothelioma**	785	15.1	8.7 – 23.4	0.80 – 1.33	0.96 – 1.07	0.43	0.97 – 1.06	0.45
Breast (female)	24,316	84.9	79.6 - 88.3	0.79 – 1.45	0.81 – 1.13	0.001	0.83 – 1.12	<0.001
Cervix	2,419	72.6	40.9 – 78.8	0.62 – 1.89	0.95 – 1.03	0.64	0.90 – 1.08	0.25
Body of uterus	3,019	79.8	74.2 – 86.2	0.70 – 1.38	0.86 – 1.12	0.06	0.86 – 1.12	0.13
Ovary	2,278	39.5	20.9 – 57.6	0.63 – 1.76	0.79 – 1.15	0.002	0.82 – 1.22	0.006
Prostate	25,713	85.2	76.0 - 88.6	0.82 – 1.63	0.76 – 1.52	<0.001	0.85 – 1.43	<0.001
Testis	1,411	95.6	84.3 – 102.0	0.00 – 3.93	1.00 – 1.00¶	1.00	1.00 – 1.00¶	1.00
Bladder	4,753	62.0	52.1 – 69.5	0.82 – 1.38	0.86 – 1.13	0.05	0.91 – 1.07	0.12
Kidney	4,740	58.4	48.6 – 69.5	0.75 – 1.30	0.94 – 1.03	0.16	1.00 – 1.00¶	1.00
Brain	2,376	18.4	12.0 – 26.4	0.64 – 1.34	0.94 – 1.05	0.23	0.94 – 1.05	0.23
Thyroid	2,400	94.0	76.2 – 107.1	0.00 – 3.26	0.72 – 1.31	0.15	0.61 – 1.46	0.08
NHL‡	6,677	54.3	45.2 – 68.0	0.68 – 1.31	0.92 – 1.07	0.15	0.92 – 1.07	0.15
Hodgkin's disease	908	78.0	45.8 – 93.7	0.21 – 2.43	1.00 – 1.00¶	1.00	1.00 – 1.00¶	1.00
Multiple myeloma	2,035	34.8	18.6 – 51.5	0.40 – 1.57	0.87 – 1.20	0.02	0.87 – 1.20	0.02
Leukaemia	4,420	36.5	27.5 – 68.1	0.50 – 1.35	0.87 – 1.17	0.01	0.87 – 1.17	0.01

* The state average excess risk is the reference
† p-value of test for regional variation
¶ Very little regional variation was observed following shrinkage
** Only two-year relative survival was calculated due to small numbers of survivors.
‡ Non-Hodgkin lymphoma

A comparison of the un-shrunken and shrunken regional estimates of relative excess risk of death for liver cancer is given in Figure 1. The shrunken estimates have narrower confidence intervals than the crude estimates and regions with wide 95% confidence intervals and extreme values have shrunk more.

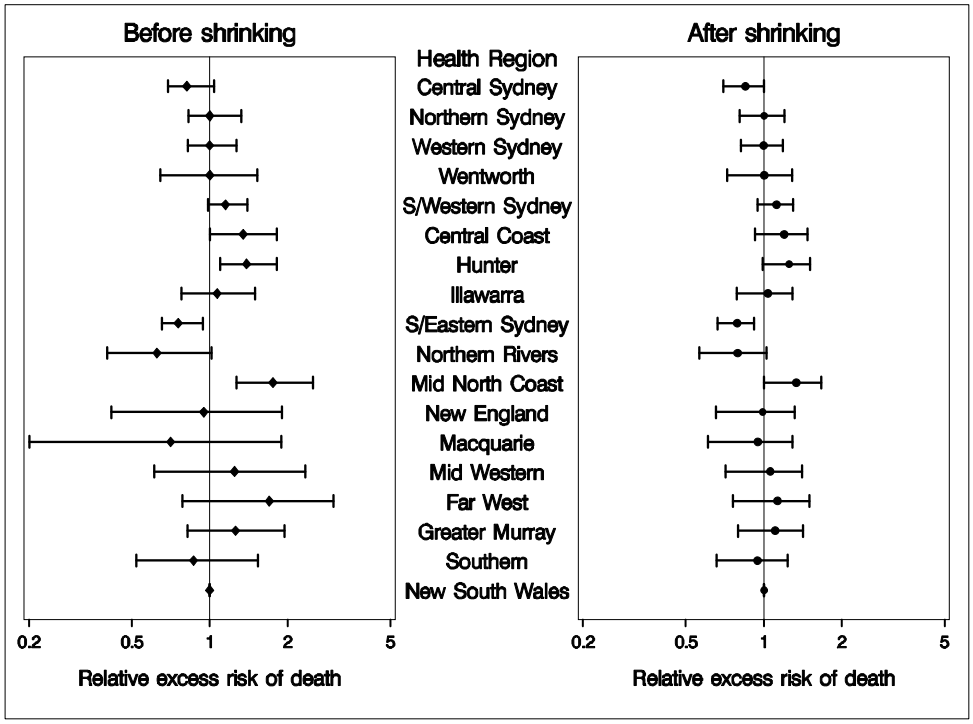

Figure 1. RER of death in 1994-2000 for patients with a diagnosis of liver cancer by health service region in NSW Australia before and after shrinkage

The estimated number and percent of lives that might be extended for the 25 cancers are shown in Table 5. The number of lives that might be extended depends on both the regional variation in survival (σ) and the number of excess deaths from the given cancer. The highest number of lives that might be extended (791) was in patients diagnosed with lung cancer although the regional variation was modest for this cancer. The estimated proportion of lives that might be extended beyond five years out of the total excess deaths for an individual cancer in the five years after diagnosis (lives lost within five years) was largest for thyroid cancer (39 lives that might be extended being 38.6% of the excess deaths).

Table 5. Number of lives that might be extended beyond 5 years of diagnosis and percentage of excess cancer deaths in 1994-2000 for 25 cancers in NSW, Australia

Cancer type	Number of excess deaths	Sigma (σ)	Lives that might be extended	
			Number	% of number of excess deaths
Lung	10732	0.07	791	7.4
Colon	4305	0.10	296	6.9
Leukaemia	1953	0.11	249	12.8
Prostate	2565	0.18	228	8.9
Non-Hodgkin lymphoma	2235	0.07	159	7.1
Pancreas	2440	0.07	152	6.2
Ovary	1074	0.15	119	11.1
Liver	808	0.20	119	14.7
Breast (female)	2467	0.10	110	4.4
Melanoma of the skin	1096	0.18	101	9.2
Multiple myeloma	1002	0.13	97	9.6
Oesophagus	1189	0.07	92	7.8
Stomach	2205	0.06	82	3.7
Rectum	2472	0.03	66	2.7
Bladder	1283	0.07	52	4.0
Brain	1514	0.06	44	2.9
Thyroid	100	0.42	39	38.6
Mesothelioma†	612	0.07	36	5.8
Cervix	444	0.10	34	7.6
Gallbladder	757	0.06	22	2.9
Body of uterus	406	0.13	14	3.5
Head and neck	1799	0.0005	1	0.1
Kidney	1412	0.0007	1	0.1
Hodgkin's disease	135	0.002	0	0.2
Testis	41	0.0002	0	0.0
All cancers	45047	0.07	2903	6.4

† Number of lives that might be extended beyond 2 years after diagnosis and % of excess deaths.

Discussion

We found statistically significant variation in the shrunken estimates of relative excess risk of death across 17 health service regions in NSW for nine of 25 cancer types - cancers of the colon, liver, lung, female breast, ovary, prostate, and melanoma of the skin, multiple myeloma and leukaemia. All of these cancer types, except melanoma and multiple myeloma, were also in the "top nine" for numbers of lives that might be extended; the two exceptions were in positions 10 and 11.

We interpret these findings as indicating that the variation among regions in the excess risks of death from the nine cancers in which it was statistically significant is probably real and, therefore, that the outcomes of these cancers could be improved through attention to the causes of regional variation. In addition, because spread of disease at diagnosis was included in the statistical models from which excess risks of death were estimated, the variation in outcome we have described points to a need for improvement in cancer treatment services rather than in the earliness of diagnosis of these cancers. When spread of disease at diagnosis was omitted from the models there was significant regional variation for stomach cancer in addition to the same nine cancers. This suggests that variation in earliness of diagnosis may be an important contributor to variation in stomach cancer survival. We note also that our use of "statistical significance" ($p<0.05$) to identify potentially meaningful findings is to some extent arbitrary. It does, though, acknowledge the reality that "chance" contributes to variation in survival between regions and should be taken into account when deciding where action to improve survival might be targeted.

Further, among the nine types of cancer identified as having statistically significant variation, priority in improving cancer services should be given to those with the highest estimates of lives that might be extended, all other things being equal. In this respect, lung cancer stands out with 791 lives that might be extended, followed by cancer of the colon, leukaemia and cancer of the prostate with 296, 249 and 228 lives that might be extended respectively. In addition, however, knowledge of what interventions would be effective in improving cancer services, their feasibility and cost effectiveness and the equity of their effects would also have to be taken into account when determining priorities.[92]

It could be argued that having identified significant variation and a large number of lives that might be extended, the regions with the highest shrunken relative excess risks of death should be the focus of attention. For example, for cancer of the liver, for which relative excess risk of death showed statistically significant variation among regions and was ranked eighth in number of lives that might be extended, attention might be turned to the regions with the highest shrunken relative excess risks of death: Central Coast, Hunter and Mid North Coast regions, which are contiguous coastal regions immediately to the north of Sydney (Figure 1). However, if their relative excess risks of death from liver cancer had been 1.0 (ie, the same as in NSW as a whole) only 25 lives would have been extended beyond five years in the study period; whereas, if the State mean could have been shifted to 0.89, which is the 20th centile of the empirical distribution across regions, this number would have been 119. Thus a whole-of-State rather than an individual region approach to improving services would probably be more effective. Examining the variation in the shrunken estimates of relative excess risk between regions and the reasons underlying it though, may still assist in identifying which whole-of-State approaches might achieve the greatest gains.

While use of the 20th centile to determine the potential gains that would occur if this risk could be achieved as the State average is arbitrary, the 20th centile has been used since it is a value that is more likely to be achievable[85;93;94] than say the 5th centile.[22]

There are some limitations in our data and the analysis methods used. The data on spread of cancer at diagnosis were provided by hospital medical records departments and may not be accurate, although they are generally very highly predictive of survival.[95] In addition no data on stage were available for cancers like leukaemia, lymphomas and multiple myeloma for which the classification of spread of disease is of little relevance. Inaccuracy in the data on

spread of cancer at diagnosis would reduce the capacity to remove from the regional variation in relative excess risks of death that variation due to regional differences in screening for, and early diagnosis of, cancer. Thus the inference that any variation observed was due mainly to variation in cancer treatment may not be correct. More accurate data on stage at diagnosis of cancer would be highly desirable for analyses such as these but are rarely available at the whole population level. It is noteworthy that when spread of disease at diagnosis was omitted from the statistical models, the results regarding regional variation in survival were very similar.

The shrinkage of the region-specific excess risks to the State average risk, especially for remote regions with small populations may be excessive since the aggregation of widely different regions in the State average may make its distribution an implausible prior distribution for some regions. The models used in these analyses assume that the regions have relative excess risk ratios that are exchangeable: that is, *a priori*, the relative excess risk for a region could be high or low. It can be argued that the regions do differ and their ratios are not exchangeable. However, in the absence of any regional covariates that could be included in the model, there is no alternative but to assume they are exchangeable. Given this assumption, the results for all regions are used to improve the estimate for each individual region.

There is some independent evidence of remediable variation in quality of care in NSW for some of the cancers we have pinpointed above. Specifically, an Australian national survey of patterns of care for colorectal cancer in 2000, in which patients in NSW made up 30% of patients whose care was surveyed, found that the patients' care including the type of operation performed varied significantly according to the patients' place of residence and many patients were not treated in accord with the recommended guidelines.[96] Further in a study linking

cancer registry records of women diagnosed with ovarian cancer in NSW in 1993 to 1996 to hospital separation records, women experienced a higher risk of death if they were first admitted to a public hospital other than a public principal referral hospital rather than to a principal referral hospital or a private hospital, or if they were treated in that admission by a practitioner other than a gynaecologist, surgeon or oncologist rather than by one of these more appropriately specialised practitioners (Tracey and Armstrong, personal communication). These results suggest that the outcome of care for ovarian cancer in NSW could be improved by consistently ensuring early referral to a relevantly specialised practitioner or major referral centre, as recommended in published guidelines.[97]

While regional variation in cancer survival has been reported from many other countries, such as the USA,[10;13] Canada,[80] England,[29] Finland,[98] Scotland,[7;20] Italy[11] and Denmark,[31] and place of residence has been found to be an important determinant of survival for a number of different cancer types, including breast,[10;20;80] lung,[29;31] colon, rectum, uterus and prostate,[10] we know of no previous analysis that has been specifically oriented towards identifying the cancers incident within a particular region for which improvements in cancer care should be given priority because of the probable existence and size of the gains in survival that could be made. Dickman and colleagues[22] and Gibberd and colleagues[85] have elucidated the principles on which our analysis is based and we have taken their work further forward by extending the EB gamma-Poisson model to analysing variation in regional relative survival ratios and by including the stage of the cancer at diagnosis to control for that source of potential variation. We plan to use a more complete description of the results of this work as the basis for targeted improvement of cancer services in NSW.

Chapter 4 Area variation in colorectal cancer survival NSW, Australia 1996-2001

About this chapter

This chapter contains the manuscript titled "A population-based study from New South Wales, Australia 1996-2001: Area variation in survival from colorectal cancer" published in *Eur J Cancer* 2005; 41:2715-21.

The authors of this publication are Xue Qin Yu, Dianne O'Connell, Robert Gibberd, and Bruce Armstrong.

Changes have been made according to the guidelines for theses at the University of Sydney; therefore, this chapter differs from the published version.

A reprint version of this article is shown in an Appendix.

The tables and references have been renumbered to maintain consistency within the thesis.

Abstract

In this study, we investigated the impact of area of residence on survival for colon and rectal cancer. Relative survival and relative excess risk of death from cancer were calculated for each of 17 health areas in New South Wales, Australia. There were statistically significant differences in survival across areas for both cancers after adjusting for demographic factors. The variation remained for colon cancer but was reduced for rectal cancer after adjustment for spread of disease at diagnosis. This persistent variation in colon cancer survival suggests that variation in treatment contributes to it, and there is separate evidence for such variation. Of the 7,186 patients whose deaths within five years were attributable to colorectal cancer, 784 could have had their survival increased to more than five years if the excess risk of death in all areas was reduced to the 20th centile of its distribution. Estimates such as this can assist in prioritising improvements in cancer services.

Introduction

Over the last two decades, important improvements in survival for colorectal cancer have been observed. These improvements may be attributable to earlier diagnosis, improved treatment or both. New and improved surgical techniques and adjuvant therapy developed in the early 1990's have probably played an important role.[46;61] These developments may not have been applied universally in clinical practice however, and this may be reflected in geographical variation in colorectal cancer outcomes.

Geographical variation in survival from colorectal cancer has been reported in many countries.[10;25;26] Survival from colorectal cancer was found to vary markedly between European countries and between states of the USA.[10;25] Variation in survival from colorectal cancer across districts in southern England was found to persist after adjusting survival rates

for stage of disease, hospital size and surgery type.[26] A number of factors make it difficult to interpret this observed geographical variation. It is well established that the prognosis of colorectal cancer is strongly associated with spread of disease at diagnosis and treatment. But it is not easy to disentangle the effect of treatment from that of early diagnosis unless stage of disease at diagnosis can be controlled in the analysis. This has rarely been done in population-based studies of cancer outcome.[99]

This study aimed to investigate the influence of place of residence at diagnosis of colorectal cancer on survival, while adjusting for demographic and clinical factors such as age, sex, length of follow-up and spread of disease at diagnosis (a measure of stage) by using data from an Australian population-based cancer registry.

Patients and Methods

Study population

Data were provided by the New South Wales (NSW) Central Cancer Registry, a population-based cancer registry which covers the whole state of NSW with a population of approximately 6.6 million. Notification of cancer has been a statutory requirement for all NSW public and private hospitals, radiotherapy departments and nursing homes since 1972, and for pathology departments since 1985.[100] Only first occurrences of primary colorectal cancer in people between 15 and 89 years of age at diagnosis were included. Cases notified by death certificate only or first identified at post-mortem were excluded from analyses. All patients diagnosed during 1992 to 2000 were followed for survival up to 31 December 2001.

Spread of cancer at diagnosis is obtained by the Registry from statutory notification forms and from pathology reports and classified as localised (confined to tissue or organ of origin),

locally advanced (spread to adjacent organs or tissues), regional (spread to regional lymph nodes), distant (distant metastases) or unknown stage (no information available). Coding was done either by medical coders in the hospitals who notified the registry, or by medical coders in the registry who used pathology, inpatient and additional reports to determine stage. During the period of this study, the State of NSW was divided into 17 geographically defined Area Health Services; nine covered the major urban areas with larger populations ranging from 270,000 to 750,000 and eight were rural areas with populations ranging from 50,000 to 250,000. The assignment of cancer patients to an Area Health Service was based on their place of residence at the time of diagnosis.

An indicator of socio-economic status (SES) was also used in the analysis. It is a summary measure of educational and occupational levels of communities derived from the 1996 population Census.[101] An area with a high score on this index would have high concentrations of people with higher education and people employed in the higher skilled occupations and vice versa. The index values for each Local Government Area (LGA) in NSW were grouped into quintiles. The residential address recorded at the time of diagnosis was used to allocate each case to an LGA and to its corresponding SES quintile.

Data analysis

Variation in stage distribution between areas was assessed for colon and rectal cancers separately.

As information on cause of death may not be accurate in the Registry data, we computed relative survival to correct for mortality from competing causes of death. Five-year relative survival was estimated for each Area Health Service using a modified period analysis. The

period method has been described in detail elsewhere and is based on calendar year of survival rather than year of diagnosis (cohort method).[102;103] It focuses on a recent time interval (1996-2001) in which each patient's survival experience is observed and excludes short-term survival of patients diagnosed before the start of the interval (diagnosed 1992-1995 and dying before 1996) but includes their long-term survival within the period. Short-term survival of more recently diagnosed patients (those diagnosed between 1996 and 2000) was included. The survival time was measured from the month of diagnosis to the date of death or censoring and was grouped into annual intervals. Observed and expected survival was estimated using standard life table methods.[3;88] All-cause mortality data obtained from the Australian Bureau of Statistics and the NSW population by single year of age, sex and area of residence were used to construct the life tables for each Area Health Service.

A Poisson regression model[104] was used to examine variation in survival due to place of residence at diagnosis after adjustment for other potential determinants of survival. For this purpose, age at diagnosis was divided into four groups: 15-44 years, 45-59 years, 60-74 years and 75-89 years. Spread of disease at diagnosis was classified into five categories: localised, locally advanced, regional, distant and unknown stage. Other variables included in the model were patients' sex and length of follow-up.

Data from individual records were aggregated to yield one observation for each category of the variables included in the model and then a generalised linear model with a Poisson error structure based on grouped data using exact survival time was fitted for colon and rectal cancers separately. The relative excess risk (RER) of death derived from this model is the ratio of the excess risk of death in a given area (the excess minus the expected on the basis of the area-specific life table) to that in a reference category (in this case the State average risk of

excess death) after controlling for other factors included in the models. A RER of less than one for a given area indicated that the risk in that area was lower than that of the State average and vice versa. All analyses were done using SAS version 8.2, and the procedure GENMOD was used to fit the models and assess the prognostic effects of the variables on relative survival.

To estimate how much variation in survival between areas was due to variation in the extent of the disease and how much to variation in treatment, we fitted two models, one with and the other without spread of disease as a covariate, and then compared the estimates from the two models.[105] Variation in area-specific RERs of death from the model excluding spread of disease should reflect effects of variation in both diagnosis and treatment. That from the model including spread of disease should reduce the degree of variation in RER due to differences in spread of disease, subject to the accuracy of spread of disease as a measure of stage at diagnosis.

As many studies have identified SES as a moderate risk factor for colorectal cancer survival, we added it to the model without spread of disease to investigate its impact on the between area variation in RERs.

To stabilise the estimates of area-specific risk we applied an Empirical Bayes method to obtain shrunken estimators. The methods are described elsewhere.[106] Briefly, we assume that the area-specific excess risks follow a gamma distribution and variation of the gamma distribution (σ) was estimated using the SAS procedure NLIN. We specified the initial σ value as one (1) with bounds of 0.0001 to 3, and estimated its value. The standard errors of the shrunken RERs were calculated and used to estimate the 95% confidence intervals (CI)

using the normal approximation. The hypothesis of no area variation (i.e. $\sigma = 0$) was tested by comparing the statistic calculated as the ratio of σ and its standard error ($z = \sigma/se(\sigma)$) with the standard normal distribution. A P-value of less than 0.05 from the hypothesis test was taken to indicate statistically significant area variation in the RERs for the given cancer.

To show how important the factors underlying area variation in survival might be, we estimated the number of patients whose survival time could be extended to beyond five years after diagnosis if the overall excess risk of death in NSW following a diagnosis of colorectal cancer could be reduced to the 20th centile of the distribution of excess risks across the areas; 3 of the areas were below the 20th centile.[106;107] This was done in separate categories for spread of disease at diagnosis with the three advanced stage categories grouped together as non-localised.

Results

There were 17,678 patients with colon cancer and 10,283 with rectal cancer included in this analysis. The numbers in individual Area Health Services varied from 75 males and 59 females with colon cancer and 52 males and 21 females with rectal cancer in the least populous Health Service to 1,210 males and 1,211 females with colon cancer and 828 males and 588 females with rectal cancer in the most populous. The age and sex distribution of colon and rectal cancers reported to the NSW Central Cancer Registry in a recent year are available at **http://www.nswcc.org.au/editorial.asp?pageid=263**.

There was statistically significant variation between areas in the proportions of localised tumours and unknown stage tumours (P<0.0001 for both colon and rectal cancer) (Table 6). Four areas (South Western Sydney, Mid Western, New England and Far West) had lower

proportions of localised colon cancers (as a proportion of those of known stage) and two areas (Far West and Illawarra) had lower proportions of localised rectal cancer. Far West also had a higher proportion of unknown stage rectal cancer. It is the largest and most sparsely populated of the areas with the highest proportion of Indigenous Australians in its population, thus high proportions with late diagnosis of cancer would not be unexpected.[108]

Table 6. Stage distribution of colon and rectal cancer by NSW Areas Health Services 1996-2001

Area Health Service	Colon cancer			Rectal cancer		
	Localised stage	Unknown stage	Number of all stages	Localised stage	Unknown stage	Number of all stages
	% of known stages	% of all stages		% of known stages	% of all stages	
Central Sydney	34.9	9.2	1161	40.1	13.4	731
Northern Sydney	31.2	8.3	2421	43.9	10.5	1292
Western Sydney	35.6	9.3	1348	43.3	9.9	840
Wentworth	33.5	9.8	529	47.5	12.1	338
South Western Sydney	26.9	9.2	1475	38.4	12.7	850
Central Coast	34.2	17.7	1063	43.9	16.8	591
Hunter	30.5	11.4	1731	40.6	15.0	919
Illawarra	29.7	13.5	1097	35.1	16.6	669
South Eastern Sydney	30.5	8.1	2262	38.1	12.2	1416
Northern Rivers	32.3	11.0	942	42.3	16.2	463
Mid North Coast	33.1	12.8	1013	46.7	13.7	568
New England	27.6	16.1	479	43.9	17.7	277
Macquarie	36.6	11.5	278	47.2	16.3	129
Mid Western	27.5	12.6	508	40.5	16.7	264
Far West	28.1	14.9	134	33.9	23.3	73
Greater Murray	35.1	15.4	708	42.5	18.5	482
Southern	32.7	9.3	529	41.4	15.7	381
New South Wales	31.6	10.9	17678	41.4	13.8	10283

The relative excess risks for colon cancer varied significantly by age group (P<0.0001) and spread of disease at diagnosis (P<0.0001). RERs for rectal cancer varied significantly by age group (P<0.0001), sex (P=0.01) and spread of disease at diagnosis (P<0.0001). The goodness of fit for the Poisson models of both colon and rectal cancer without spread of disease at diagnosis as a covariate was poor (P<0.0001). After adding spread of disease, the goodness of fit was much better: P=0.36 for colon cancer and 0.56 for rectal cancer.

After adjustment for age at diagnosis, sex, and length of follow-up, there was statistically significant area variation in RER for colon (P=0.006) and rectal (P=0.049) cancers. The shrunken RERs ranged from 0.91 to 1.11 for colon cancer and from 0.90 to 1.07 for rectal cancer (Tables 7 and 8). There was also significant variation in RERs for colon cancer (P=0.015) and to a lesser extent for rectal cancer (P=0.08), across SES categories, after adjustment for age, sex and length of follow-up. For both, the RERs for the lower four categories of SES, relative to the highest, ranged from 1.03 to 1.15 with little trend across them. Adjustment for SES produced little change in the range of RERs for colon cancer across areas (from 0.91-1.11 to 0.93-1.09 with an increase in P-value from 0.006 to 0.02) but narrowed the range for rectal cancer appreciably (from 0.90-1.07 to 0.97-1.03 with an increase in P-value from 0.049 to 0.48). Adjustment for spread of disease at diagnosis similarly did not appreciably change the variation for colon cancer (RER 0.92 to 1.13, P=0.004) but reduced that for rectal cancer (RER 0.93 to 1.05, P=0.16) (Tables 7 and 8).

Table 7. Five-year relative survival, shrunken relative excess risk (RER) due to colon cancer with and without adjustment for disease stage at diagnosis and 95% confidence intervals (CI), by NSW Area Health Services 1996-2001

Area Health Service	Five-year relative survival (%)	RER* without adjustment for stage and its 95% CI		RER* with adjustment for stage and its 95% CI	
Central Sydney	60.0	1.01	(0.92-1.10)	1.04	(0.94-1.13)
Northern Sydney	63.4	0.91	(0.84-0.97)	0.92	(0.86-0.99)
Western Sydney	58.7	1.03	(0.95-1.12)	1.06	(0.97-1.15)
Wentworth	60.9	1.01	(0.90-1.13)	1.05	(0.93-1.17)
South Western Sydney	58.3	1.07	(0.99-1.16)	1.04	(0.96-1.13)
Central Coast	62.4	0.97	(0.88-1.06)	0.98	(0.89-1.08)
Hunter	61.0	1.02	(0.94-1.10)	1.03	(0.95-1.12)
Illawarra	64.0	0.93	(0.85-1.02)	0.93	(0.84-1.02)
South Eastern Sydney	61.4	0.96	(0.89-1.03)	0.95	(0.88-1.02)
Northern Rivers	62.6	0.95	(0.86-1.05)	0.95	(0.86-1.05)
Mid North Coast	62.8	0.95	(0.86-1.05)	0.98	(0.88-1.07)
New England	53.9	1.11	(0.99-1.23)	1.12	(1.00-1.25)
Macquarie	66.1	0.95	(0.83-1.07)	0.99	(0.86-1.13)
Mid Western	53.8	1.11	(0.99-1.23)	1.13	(1.00-1.25)
Far West	63.7	0.99	(0.86-1.13)	0.97	(0.83-1.11)
Greater Murray	59.5	1.04	(0.93-1.14)	1.09	(0.98-1.20)
Southern	59.3	1.02	(0.91-1.13)	1.02	(0.91-1.14)
New South Wales	61.3	1.00		1.00	

* Adjusted for age, sex, and length of follow-up with the state average risk as the reference.

Table 8. Five-year relative survival, shrunken relative excess risk (RER) due to rectal cancer with and without adjustment for disease stage at diagnosis and 95% confidence intervals (CI), by NSW Area Health Services 1996-2001

Area Health Service	Five-year relative survival (%)	RER* without adjustment for stage and its 95% CI		RER* with adjustment for stage and its 95% CI	
Central Sydney	60.2	1.00	(0.91-1.10)	1.00	(0.91-1.09)
Northern Sydney	64.8	0.90	(0.82-0.98)	0.93	(0.86-1.01)
Western Sydney	58.9	1.04	(0.94-1.14)	1.04	(0.95-1.13)
Wentworth	64.4	0.97	(0.86-1.08)	1.01	(0.90-1.11)
South Western Sydney	58.5	1.06	(0.96-1.16)	1.05	(0.96-1.14)
Central Coast	59.1	1.00	(0.90-1.11)	1.01	(0.91-1.10)
Hunter	57.1	1.07	(0.97-1.16)	1.04	(0.96-1.13)
Illawarra	62.0	0.99	(0.89-1.09)	0.99	(0.90-1.08)
South Eastern Sydney	61.1	0.98	(0.90-1.06)	0.95	(0.88-1.02)
Northern Rivers	62.4	0.95	(0.85-1.06)	0.97	(0.88-1.07)
Mid North Coast	64.7	0.95	(0.85-1.05)	0.99	(0.90-1.09)
New England	64.3	0.98	(0.87-1.10)	1.01	(0.91-1.12)
Macquarie	53.3	1.04	(0.92-1.17)	1.05	(0.93-1.16)
Mid Western	58.6	1.04	(0.92-1.16)	1.03	(0.92-1.13)
Far West	55.0	1.02	(0.89-1.15)	1.02	(0.91-1.13)
Greater Murray	62.9	0.97	(0.87-1.08)	0.99	(0.89-1.08)
Southern	60.0	1.02	(0.91-1.13)	1.00	(0.91-1.10)
New South Wales	61.6	1.00		1.00	

* Adjusted for age, sex, and length of follow-up with the state average risk as the reference.

Area variation in RERs, estimated from the model containing age group, sex, length of follow-up and stratified by spread of disease at diagnosis, was greatest for localised cancers, as indicated by the comparatively large values for σ, least for non-localised cancers and intermediate for cancers of unknown stage (Table 9). Variation was greater for colon than rectal cancer in each stage category.

Our estimate of the number of patients with colon cancer whose survival time might be increased to more than 5 years (559) was higher than that for patients with rectal cancer (225) due to the larger number of excess deaths and the greater area variation for colon cancer (Table 9). The most lives that might be extended were in patients with non-localised colon cancer (251) while the highest estimated proportion of lives that might be extended was for

localised colon cancer (64.5%), because of the larger variation between areas in this category (σ=0.55).

Table 9. Number of lives that might be extended beyond five years after diagnosis by degree of spread for colon and rectal cancer in NSW, 1996-2001

Cancer type	Number of excess deaths	Sigma (σ)*	SE(sigma)	P-value†	Number of lives might be extended‡	% of number of excess deaths
Localised tumours						
Colon	279	0.55	0.10	<0.0001	180	64.5
Rectum	321	0.27	0.10	0.005	82	25.4
Non-localised tumours						
Colon	3722	0.09	0.04	0.014	251	6.8
Rectum	1888	0.04	0.07	0.548	59	3.1
Unknown stage tumours						
Colon	564	0.27	0.09	0.002	128	22.7
Rectum	412	0.19	0.06	0.002	84	20.5

* σ is the standard deviation of the gamma distribution of area-specific risks and indicates the size of the area variation for a given cancer
† P-value for test of area variation equal to 0.
‡ Estimated from the model containing age, sex, length of follow-up and stratified by spread of disease at diagnosis.

Discussion

Relative excess risk of death following a diagnosis of colon cancer and rectal cancer in NSW varied between Area Health Services by 20% and 17% respectively. Controlling for spread of cancer at diagnosis had little impact on inter area variation in RERs for colon cancer (21% after adjustment) but reduced it to 12% for rectal cancer, thus suggesting that variation in extent of disease between areas contributed slightly to the variation in outcome for rectal cancer.

The significant variation in RERs for colon cancer between areas after adjustment for spread of disease suggests that differences in the application of treatments of known effectiveness contribute to variation in outcome. While SES of the patient's area of residence also contributed to variation in RERs between areas, we did not adjust for its effects when examining the effect of adjustment for stage of disease on variation in RERs because it is probably a contributor to variation in treatment quality rather than a confounder of it.[109] In this

regard, it is relevant to note the recent results of Lemmens and colleagues from the Netherlands, which showed that use of adjuvant chemotherapy for stage III colon cancer was less in people of lower SES, and in older people.[110]

A recent report on patterns of care for colorectal cancer in NSW throws some light on the possibility that treatment variation contributed to variation in outcome.[111] There is level I evidence that post-operative adjuvant chemotherapy improves outcome of node positive colon cancer.[112] In NSW in 2000, 31% of colon cancer patients received post-operative chemotherapy; 31% or more of patients received it in six of the eight Area Health Services in which the RER was less than or equal to 1.0 but in only three of nine areas in which the RER was greater than 1.0.[111]

Variation in surgical experience may also have contributed to variation in outcomes for colon cancer. A number of studies have found that outcomes for colorectal cancer patients is better when patients are treated by surgeons with higher case volumes and specialist expertise.[113-116]

The capacity to adjust for the effect of spread of cancer on survival depends on the accuracy of the data. Information on spread of cancer at diagnosis was obtained from hospital medical record departments and radiotherapy notifiers and its quality may vary between areas. This may reduce the capacity to adjust for its effect on area variation in survival. More accurate data on spread of cancer at diagnosis would be highly desirable but are rarely available at the population level. It is noteworthy, though, that when spread of disease at diagnosis was added to the statistical models, the fit of the models improved dramatically.

Our adjustment for cancer stage at diagnosis is by rather crude categorical measures and we cannot adjust for possible stage migration within each of these stage categories, as might be indicated, for example, by number of lymph nodes examined histopathologically if we had these data.[21] Thus, there may be residual effects due to differences in the extent of disease within stage. Information about patients is limited on population-based cancer registries and no treatment information is collected by the registry thus, the data themselves do not allow us to point a direct link between the poor outcomes and differences in treatments. However, we know from other data that some patients received suboptimal cancer therapy.[111]

The estimated number of lives that might be extended beyond 5 years after diagnosis offers a tool to health authorities to set priorities for treatment improvement. In this case non-localised colon cancer is the area of potentially greatest gain from improved treatment, with an estimated 251 lives over 5 years (50 a year) extendable by shifting the State average risk to the 20th centile. Some of this gain could almost certainly be achieved by ensuring that guidelines for adjuvant treatment of node positive colon cancer are fully implemented and consistently followed in all Area Health Services.[112] This could require improved access to medical oncology services in rural and remote areas of the State[105] as well as improved uptake of guidelines by treating practitioners. As radiotherapy centres are located in metropolitan areas in NSW,[105] patients living in rural and remote areas have relatively poorer access to the standard of cancer treatment services available to their metropolitan counterparts.[8] For localised colon cancer the estimated number of extendable lives over five years was also comparatively high at 180. Surgery is the critical treatment modality for these cancers and it may be here that low surgical caseloads in some areas may be contributing to poorer outcome.[113-116] This would, however, be a challenge to address. Surgical services are

undersupplied outside major centres in rural and remote Australia and population density is too low to be able to support any substantial degree of surgical sub-specialisation.[117]

Studying variation in RERs of death within 5 years of diagnosis of cancer, with use of Empirical Bayes methods to shrink RER estimates and adjustment for spread of cancer at diagnosis, can help identify cancers for which better application of treatment guidelines might improve outcome. Estimates of the numbers of lives that could be extended if the State average risk was reduced to the 20th centile of the distribution may assist in setting priorities for treatment improvement.

Chapter 5 Trends in survival from 1980 to 1996 in NSW Australia

About this chapter

This chapter contains the manuscript titled "Trends in survival and excess risk of death after a diagnosis of cancer in 1980 to 1996 in New South Wales Australia. *Int J Cancer* 2006; 119:894-900.

The authors of this publication are Xue Qin Yu, Dianne O'Connell, Robert Gibberd, Alan Coates and Bruce Armstrong.

Changes have been made according to the guidelines for theses at the University of Sydney; therefore, this chapter differs from the published version.

A reprint version of this article is shown in an Appendix.

The tables and references have been renumbered to maintain consistency within the thesis.

Abstract

Survival from almost all cancers has improved during the last 30 years. There is debate over the reasons for the improvement. We examined trends in survival for 28 cancers from 1980 to 1996 in New South Wales (NSW) Australia, with adjustment for disease spread at diagnosis. NSW Central Cancer Registry data were used to estimate 5-year relative survival and relative excess risk of death for patients diagnosed in 1980-84, 1985-88, 1989-92 and 1993-96. Statistical significance of variation in excess deaths between periods of diagnosis was assessed using Poisson regression with adjustment for age, sex, duration of follow-up, histology, and spread of disease at diagnosis. There were statistically significant falls in excess deaths for 20 of the cancers with a 25% fall for all cancers combined. Cancers of the prostate, liver, thyroid, breast, gallbladder, body of uterus, rectum, cervix and ovary had falls of >30%. The falls varied by spread of disease; the largest being in localised and regionally spread tumours. Overall survival, when unadjusted for spread of cancer, generally fell in parallel with that in the specific categories of spread, which implies that stage migration did not contribute importantly to survival trends. While acknowledging the limitations of incomplete data on stage of cancer at diagnosis, we conclude that falls in excess deaths in NSW from 1980 to 1996 are unlikely, for many cancers, to be due to earlier diagnosis or stage migration; thus advances in cancer treatment have almost certainly contributed to them.

Introduction

Survival from almost all cancers has improved, for some dramatically, during the last 30 years. Notable successes include childhood leukaemia, testicular cancer and Hodgkin's disease, in which survival improvement has been mainly due to the introduction of more effective treatments.[118-120] Between 1975-1979 and 1995-2000 in the USA, 5-year survival from female breast cancer increased from 75% to 88% and that for colorectal cancer from 50% to 64% (men) and 52% to 63% (women): these improvements were attributed to both earlier detection and more effective treatment of cancer.[49] There has been debate, however, over the extent to which improved treatment has contributed to the trend in survival.[53] By extrapolating trends in cancer mortality in the USA, Bailar and Gornick argued that newer cancer therapies have produced few real benefits and concluded that recent decreases in cancer mortality were due mainly to falling incidence or earlier detection.[51]

In this study we examined time trends in excess risk of death within 5 years of diagnosis in 1980 to 1996 in patients with one of 28 cancers in New South Wales (NSW) Australia using data from a population-based cancer registry. To try to exclude impacts of earlier detection, we examined the trends in excess risk of death with adjustment for a measure of disease spread at diagnosis, along with histological type of cancer, age and sex. In doing so, we also assessed possible effects of stage migration, a shift with time in the stage distribution of a cancer towards apparently higher stage disease due to more complete identification of disease spread. This shift produces an artificial increase in survival in each stage category because of the removal of more advanced disease from earlier stage categories and its transfer as relatively less advanced disease into later stage categories.[74] Taking confounding trends in stage and the possibility of stage migration into account allows an interpretation of trends in excess risk of death in terms of changes in disease management.

Material and Methods

Data

Data for patients diagnosed with any of the 28 major cancers during 1980-1996 were obtained from the population-based NSW Central Cancer Registry. Notification of cancer has been a statutory requirement for all NSW public and private hospitals, radiotherapy departments and nursing homes since 1972, and for pathology departments since 1985.[121] The Central Cancer Registry generally has high standards of data completeness, quality and follow-up; the data are accepted by the International Agency for Research on Cancer for publication in Cancer Incidence in Five Continents.[122] Individuals with the first occurrence of a primary cancer between 15 and 89 years of age were included. Cases notified by death certificate only or first identified at post-mortem were excluded from the analysis of survival, but included in the calculation of age-sex standardised incidence rates. These cases were 1.8% of the total and relatively constant over time, except for an increase to 3.3% in 1985-88 caused by lack of Registry resources to investigate them. Data on the population and population mortality used to calculate relative survival and age and sex standardised incidence rates were obtained from the Australian Bureau of Statistics, which conducts Australia's quinquennial population census and collates national death data.

All cases diagnosed from 1980 to 1996 were followed to December 2001 to determine survival status. Identifiers from each were compared with those of all records of deaths in the State Register of Deaths and the National Death Index from their date of diagnosis to 31st December 2001 to find a matching death record if present. This passive approach to follow-up may fail to ascertain all deaths and may incorrectly link some incidence and death records. A study investigating its completeness and accuracy found loss to follow-up to be uniform from

1980 to 1993 and estimated the resulting overestimation of relative survival to be a maximum of 2%.[95] The end of follow-up was the date of death for those who died within five years of diagnosis or five years after diagnosis for those who survived the first five years.

All information on primary cancer site and histology was coded according to the International Classification of Diseases for Oncology, second edition (ICDO-2).[123] Data on spread of disease at diagnosis were provided by hospital medical record departments and radiotherapy notifiers, and classified into four broad categories: localised, regional (including adjacent organs and regional lymph nodes), distant and unknown to the Registry. This summary classification of stage is used by a number of major cancer registries around the world including registries in the Surveillance, Epidemiology, and End Results (SEER) program in the USA. While not as detailed as the standard TNM staging system, it can be applied to most cancers occurring in whole populations.[124] Degree of spread was not applicable to staging for Hodgkin's disease, non-Hodgkin lymphoma, multiple myeloma, leukaemia and brain cancer and no other staging data were available for them. Because of the importance of spread of disease in our analysis and the possibility of stage migration, we tabulated changes in the distribution of spread in 1980-1996 for the sites for which it was available, with regional and distant spread combined as non-localised disease.

Statistical methods

Relative survival and relative excess risk of death

Cancer patients were followed for five years after diagnosis and relative survival was estimated using the cohort method. Relative survival is the ratio of the observed proportion surviving in a group of patients to the expected proportion that would have survived in a comparable group of people from the general population.[89] Observed survival was estimated

using the life table method.[88] The expected survival from the general population was calculated using all cause mortality for the NSW population by single year of age, sex and calendar year.[89]

The excess risk of death after diagnosis of a cancer is the risk of death above what would have been observed if the population death rates had applied to the cancer patients. To analyse trends in excess risk of death, four time periods were defined: 1980-1984, 1985-1988, 1989-1992 and 1993-1996. Grouping the dates of diagnosis in periods of a few years increases the likelihood that cancer patients diagnosed within a period followed similar treatment protocols and had similar access to screening. The period 1980-1984 preceded compulsory reporting of cancer to the Cancer Registry by pathology laboratories, which was introduced in 1985.

Statistical modelling of excess risk of death

To determine the change in survival over time after adjustment for possible confounders, we fitted a Poisson regression model for excess deaths from each type of cancer.[106] The model included time period of diagnosis, age group at diagnosis (15-44 years, 45-59 years, 60-74 years and 75-89 years), year of follow-up since diagnosis, sex (where applicable), histological type (based on ICDO-2 and with the less common histological types grouped together), and spread of disease at diagnosis (where applicable) as independent variables. We then fitted another model adding the interaction of spread of cancer by period of diagnosis to the main effects model for cancers to which spread of disease at diagnosis was applicable. Finally, we compared the difference between the deviance from this model with that from the main effects model to determine whether addition of the interaction produced a statistically significant difference in model deviance ($p<0.05$) using the chi-square test. If the difference was

statistically significant, we then carried out further analyses to examine the differences in trends across categories of spread of cancer.

The modelling methods we used are described in detail by Dickman et al.[104] Briefly, data from individual records were aggregated to yield a count of deaths for each combination of the variables included in the model and then a generalised linear model with a Poisson error structure based on aggregated data using exact survival time (person-years) was fitted for each cancer. This model quantifies the extent to which the excess risk of death in a given period differs from the excess risk of death in the reference period (1980-1984) after controlling for the factors included in the model. The relative excess risk of death (RER) in the period 1980-1984 was set to a value of one (1). A RER of less than one in another period indicates that the excess risk of death in that period was less than that in the reference period, and vice versa. Ninety-five per cent confidence intervals for the RERs were calculated using the estimated coefficients and standard errors from the Poisson models. The statistical significance of each variable in the model was determined by the log-likelihood ratio test with a p-value of <0.01 taken to indicate statistical significance. All analyses were done using SAS version 8.2 and the procedure GENMOD was used to fit the models and assess the effects of the variables on excess risk.

Trends in incidence rates

To estimate trends in incidence, which we report to give context to the survival trends, we calculated annual age-sex standardised incidence rates for the resident population in NSW for 1980 to 1996 for each of the 28 cancers. These rates were expressed per 100,000 of the population and age and sex adjusted by the direct method to the Australian estimated residential population of 2001. Trends in incidence were summarized by calculating the

annual percent change in age-standardised incidence rates over the 17 years for each cancer. The annual percent change was estimated by fitting a Poisson regression model to the natural logarithm of the rates with calendar year as a continuous independent variable. The assumption of a linear trend was reasonable for all cancers except for melanoma and prostate cancer in which there have been sizeable short-term perturbations in the long-term trend.[121]

Results

A total of 343,034 newly diagnosed cancers were included in this analysis with the commonest cancers being breast (41,476), lung (39,769) and prostate (37,374) (Table 10). Age-standardised incidence of most cancers increased during the period 1980-96. The largest annual percent increases were for cancers of the prostate, liver and thyroid, and mesothelioma, and the largest falls were for cancers of the stomach, cervix and bladder. The incidence of prostate cancer showed a dramatic rise between 1990 and 1994 followed by a fall after 1994.[121] The Registry's report on cancer incidence in 2003[121] is available at http://www.cancerinstitute.org.au/cancer_inst/statistics/pdfs/IncidenceMortalityReport2005.pdf.

Table 10. Age and sex standardised incidence rates (per 100,000) and average annual percent change, with the corresponding 95% confidence intervals (CI), for 28 cancers in NSW, Australia, 1980 - 1996

Cancer type	Number of new cases	Age-standardised incidence rates*	Average annual percent change 1980-1996	95% CI
Lip	3,562	4.5	2.52	0.86, 4.21
Head and neck	12,553	14.1	0.00	-0.58, 0.58
Oesophagus	4,167	5.2	1.20	0.53, 1.88
Stomach	10,354	11.2	-2.66	-3.11, -2.21
Colon	32,414	40.3	0.56	0.19, 0.92
Rectum	17,688	22.2	0.94	0.57, 1.31
Liver	1,891	3.4	7.89	6.47, 9.33
Gallbladder	2,709	3.3	0.30	-0.63, 1.24
Pancreas	8,091	9.9	0.05	-0.42, 0.52
Lung	39,769	45.2	-0.54	-0.77, -0.31
Melanoma	32,316	42.1	3.05	2.14, 3.96
Mesothelioma	1,634	2.6	5.11	4.14, 6.09
Connective tissue	2,088	2.3	-0.16	-1.25, 0.94
Breast	41,476	113.9	2.72	2.30, 3.13
Cervix	5,957	11.6	-1.63	-2.22, -1.04
Body of uterus	5,793	14.0	0.93	0.27, 1.59
Ovary	5,375	12.1	-0.30	-0.87, 0.27
Prostate	37,374	146.1	7.09	5.45, 8.75
Testis	2,314	5.4	2.68	1.79, 3.57
Bladder	12,139	12.5	-2.90	-3.63, -2.16
Kidney	9,053	12.1	2.79	2.25, 3.33
Thyroid	3,438	5.1	4.92	3.86, 5.99
Brain	5,404	6.4	1.08	0.62, 1.55
Hodgkin's disease	1,856	1.9	-0.76	-1.50, -0.02
Non-Hodgkin lymphoma	12,688	17.4	3.04	2.68, 3.41
Multiple myeloma	4,229	5.5	1.09	0.37, 1.81
Leukaemia	9,365	11.7	0.48	-0.04, 1.00
Unspecified	17,337	20.1	-0.49	-1.03, 0.06

*Age and sex adjusted to the Australian estimated residential population of 2001.

There were substantial changes in the distribution of the cancers by spread of disease at diagnosis over the period of study (Table 11). The proportion with localised disease fell for all but three cancer types – melanoma, breast cancer and testicular cancer – and the proportion with unknown stage increased for all except these same three cancer types. The proportions with regional and distant disease fell for 15 cancer types (including melanoma and breast cancer) and increased for 8 types, the most substantial being in cancers of the colon, rectum

and ovary (5 percentage points or more). The increase in the proportion of cancers of unknown stage occurred mainly in 1993-96 and, to a much less extent in 1989-92 for 13 of the 20 cancer types in which an increase occurred. These increases were probably largely due to a change from paper-based to electronic notification of cancer from some hospitals introduced from 1992, which meant that some information on stage provided through manual notification was no longer available to the Registry. In the remaining 7 cancer types, the increase was more gradual across the whole period of observation, indicating that additional factors, unknown to us, were influencing completeness of stage information reported to the Registry for these cancers.

Table 11. Proportion of spread of disease at diagnosis by period of diagnosis for 23 major cancers diagnosed in NSW, Australia 1980-1996*

Cancer type	Localised				Non-localised				Unknown			
	1980-84	1985-88	1989-92	1993-96	1980-84	1985-88	1989-92	1993-96	1980-84	1985-88	1989-92	1993-96
Lip	81.0	72.4	69.7	62.7	7.2	6.9	6.6	5.6	11.8	20.8	23.7	31.7
Head and neck	47.1	45.3	41.9	30.8	36.8	36.2	36.3	39.5	16.0	18.5	21.8	29.7
Oesophagus	34.8	42.0	38.5	27.4	42.3	36.0	35.7	37.9	22.9	22.0	25.8	34.7
Stomach	24.7	25.2	23.5	17.1	59.2	57.3	60.1	59.9	16.1	17.5	16.4	23.0
Colon	33.7	30.8	30.4	23.7	55.5	57.5	60.9	63.8	10.8	11.7	8.7	12.4
Rectum	42.3	39.4	38.2	30.9	47.9	49.5	51.9	52.8	9.8	11.2	9.9	16.2
Liver	49.6	39.1	37.7	23.6	32.7	23.5	22.5	18.7	17.7	37.3	39.7	57.8
Gallbladder	24.3	25.0	23.6	17.3	64.5	57.5	56.1	49.9	11.3	17.5	20.2	32.8
Pancreas	14.3	16.4	16.5	9.6	68.5	56.1	56.0	52.6	17.2	27.5	27.5	37.8
Lung	23.2	30.3	26.4	17.0	49.8	44.7	44.6	46.8	27.0	25.0	29.0	36.2
Melanoma	82.9	87.3	88.2	89.0	9.6	7.5	8.1	6.8	7.5	5.2	3.7	4.2
Mesothelioma	28.8	42.7	35.9	19.6	49.2	18.6	21.7	21.6	22.0	38.7	42.4	58.8
Connective tissue	53.8	55.6	48.2	34.3	27.0	21.8	18.9	16.0	19.2	22.5	32.9	49.7
Breast	47.3	47.9	49.3	51.0	37.6	37.8	37.8	33.5	15.1	14.3	12.9	15.4
Cervix	57.0	67.3	63.7	50.7	31.3	24.9	28.6	25.9	11.7	7.8	7.7	23.4
Body of uterus	67.9	69.4	65.7	61.5	17.2	17.8	20.8	21.3	14.9	12.8	13.5	17.2
Ovary	28.2	27.4	24.4	16.0	61.1	58.7	65.4	70.0	10.7	13.9	10.2	14.0
Prostate	59.0	52.5	51.1	40.6	21.8	21.4	16.6	10.0	19.3	26.1	32.3	49.4
Testis	59.1	65.5	66.6	60.5	20.4	23.5	23.1	21.2	20.4	11.0	10.4	18.3
Bladder	77.8	71.7	65.9	47.2	11.6	11.6	15.3	15.4	10.6	16.7	18.8	37.4
Kidney	51.2	49.8	50.1	44.3	38.5	38.8	36.0	35.1	10.3	11.4	13.9	20.6
Thyroid	64.9	59.0	62.7	51.7	25.4	28.6	24.3	24.9	9.7	12.4	13.1	23.4
Unspecified	0.7	1.4	1.2	0.8	95.6	88.6	89.4	87.4	3.7	10.0	9.4	11.8

* Brain cancers, non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma and leukaemia are not included in this table because classification of stage at diagnosis on the basis of spread of disease at diagnosis does not apply to them.

The excess risk of death fell over time for most cancers except cancers of the connective tissue and unspecified site, for which it rose significantly ($p<0.0001$), and cancer of the bladder where the increase was not statistically significant (Table 12). For all cancers together, the excess risk of death fell by a relative 25%. The most dramatic falls were in cancers of the liver, prostate and thyroid, with the excess risk of death in the latest period being less than 60% of that in the earliest period. Other notable falls were for cancers of the oesophagus, rectum, gallbladder, breast, cervix, uterus, and ovary.

There were non-significant falls in excess risk of death from cancers of the lip and testis, mesothelioma, Hodgkin's disease and multiple myeloma. The confidence intervals about the RERs of less than unity for cancers of the lip and testis diagnosed in 1993-96 were wide and included the point estimate of 0.75 for RER of all cancers together. These were among the least frequent of the cancers studied and were in the three least fatal; thus real downtrends in excess risk of death for these cancers are possible but our data had limited statistical power to detect them with any certainty. Hodgkin's disease and multiple myeloma shared with non-Hodgkin lymphoma a 14-15% reduction of excess risk of death between 1980-84 and 1993-96, which was statistically significant for the latter.

Table 12. Relative excess risk (RER) during the first 5-years after diagnosis, with adjustment for age, sex, spread of cancer, years since diagnosis and histological type for 28 cancers diagnosed in 1980-1996 and followed to 2001, in NSW, Australia

Cancer type	5-year RSR * (%) 1993-96	RER† and 95% confidence interval				P-value
		1980-84	1985-88	1989-92	1993-96	
Lip	93.1	1.00	0.87 (0.52-1.47)	0.61 (0.36-1.04)	0.72 (0.43-1.19)	0.28‡
Head and neck	55.6	1.00	0.93 (0.86-1.01)	0.87 (0.81-0.95)	0.78 (0.72-0.85)	<0.0001‡
Oesophagus	15.4	1.00	0.85 (0.77-0.94)	0.75 (0.68-0.83)	0.70 (0.63-0.77)	<0.0001§
Stomach	23.8	1.00	0.93 (0.87-1.00)	0.88 (0.82-0.94)	0.82 (0.77-0.88)	<0.0001§
Colon	60.0	1.00	0.84 (0.80-0.89)	0.80 (0.76-0.85)	0.71 (0.68-0.75)	<0.0001§
Rectum	59.4	1.00	0.86 (0.80-0.92)	0.75 (0.70-0.81)	0.67 (0.62-0.71)	<0.0001§
Liver	11.4	1.00	0.71 (0.60-0.85)	0.73 (0.62-0.87)	0.55 (0.47-0.65)	<0.0001‡
Gallbladder	19.5	1.00	0.83 (0.73-0.93)	0.78 (0.69-0.88)	0.61 (0.54-0.69)	<0.0001§
Pancreas	5.3	1.00	0.85 (0.79-0.91)	0.94 (0.88-1.01)	0.86 (0.80-0.92)	<0.0001§
Lung	12.5	1.00	0.94 (0.91-0.97)	0.90 (0.87-0.93)	0.82 (0.79-0.84)	<0.0001§
Melanoma	90.9	1.00	0.82 (0.73-0.93)	0.72 (0.64-0.81)	0.72 (0.64-0.81)	<0.0001‡
Mesothelioma	4.9	1.00	0.88 (0.74-1.04)	0.87 (0.74-1.02)	0.92 (0.79-1.07)	0.35‡
Connective tissue	63.0	1.00	1.08 (0.86-1.35)	1.11 (0.89-1.39)	1.05 (0.84-1.30)	<0.0001§
Breast	85.0	1.00	0.88 (0.82-0.94)	0.76 (0.71-0.81)	0.61 (0.57-0.65)	<0.0001§
Cervix	73.1	1.00	1.03 (0.91-1.18)	0.78 (0.68-0.89)	0.68 (0.59-0.78)	<0.0001‡
Body of uterus	79.2	1.00	0.79 (0.66-0.94)	0.66 (0.55-0.79)	0.61 (0.51-0.72)	<0.0001‡
Ovary	37.3	1.00	1.03 (0.93-1.14)	0.84 (0.76-0.92)	0.68 (0.62-0.75)	<0.0001§
Prostate	86.9	1.00	1.09 (1.01-1.19)	0.95 (0.87-1.03)	0.54 (0.49-0.59)	<0.0001§
Testis	95.5	1.00	0.72 (0.42-1.23)	0.51 (0.31-0.84)	0.63 (0.38-1.04)	0.05‡
Bladder	62.5	1.00	1.06 (0.96-1.18)	1.08 (0.97-1.21)	1.13 (1.02-1.26)	0.14‡
Kidney	57.4	1.00	0.86 (0.78-0.94)	0.85 (0.77-0.93)	0.73 (0.67-0.80)	<0.0001§
Thyroid	93.5	1.00	0.81 (0.57-1.14)	0.63 (0.44-0.89)	0.58 (0.42-0.81)	<0.0001‡
Brain¶	17.9	1.00	0.88 (0.80-0.96)	0.94 (0.86-1.02)	0.86 (0.79-0.94)	0.003‡
Hodgkin's disease¶	77.3	1.00	1.13 (0.86-1.48)	0.99 (0.74-1.33)	0.85 (0.63-1.15)	0.26‡
NHL**¶	53.6	1.00	0.94 (0.86-1.02)	0.92 (0.85-0.99)	0.86 (0.80-0.93)	0.002‡
Multiple myeloma¶	31.9	1.00	0.95 (0.85-1.07)	0.91 (0.82-1.02)	0.86 (0.77-0.97)	0.07‡
Leukaemia¶	38.2	1.00	0.84 (0.78-0.92)	0.74 (0.68-0.80)	0.82 (0.76-0.88)	<0.0001‡
Unspecified	11.0	1.00	1.06 (1.01-1.11)	1.04 (0.99-1.09)	1.10 (1.05-1.15)	<0.0001§
All cancer	59.6	1.00	0.92 (0.91-0.94)	0.86 (0.85-0.88)	0.75 (0.74-0.76)	<0.0001§

* Five-year relative survival for the period 1993-1996.
† RER for the period of 1980-1984 as reference (set to 1.0). Each model included age group at diagnosis, sex, year since diagnosis, period of diagnosis, histological type and spread of cancer.
‡ P-value for the main effect of period for cancer types with non-significant interaction term for period by stage
§ P-value for the interaction of period by stage for cancer types with significant interaction term for period by stage.
¶ Classification of stage by spread of cancer not applicable for these cancers.
** NHL stands for non-Hodgkin lymphoma.

The trend in excess risk of death was significantly heterogeneous among categories of spread of disease for 13 of the 23 cancers for which disease stage was available. Some patterns are shown in terms of trends in 5-year relative survival in Figure 2. For all cancers combined and cancers of the colon, breast and prostate, the main trends in 5-year relative survival were

increases in the localised, regional and unknown categories, with no improvement for distant cancers. For cancer of the rectum, the 5-year relative survival increased in all categories though much less so for cancers with distant spread. For ovarian cancer, the increase in survival was evident in cancers that were localised, regional or distant but hardly at all in unknown spread or all degrees of spread together (unadjusted for degree of spread); this strongly suggests that stage migration caused the apparently increased survival in the individual degree of spread categories (Figure 2).

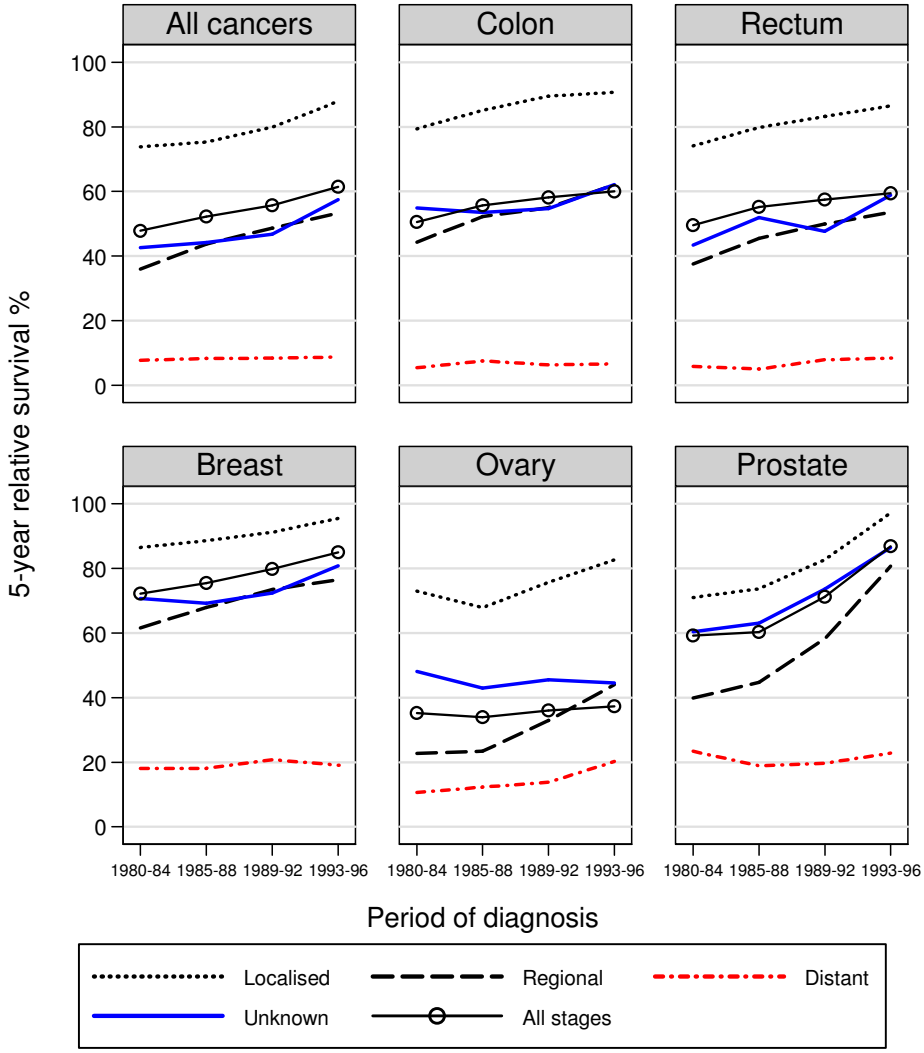

Figure 2. Trends in 5-year relative survival by spread of cancer for all cancers combined, and cancers of the colon, rectum, breast, ovary and prostate, New South Wales Australia 1980-96

There was also evidence of stage migration in the pattern of change in the degree of spread with time for cancer of the ovary: the proportion of localised cancers fell, that of regionally and distant spread cancers increased correspondingly and that of unknown spread cancers changed little. Cancers of the colon, rectum, head and neck and body of uterus showed similar patterns of change in degree of spread. For colon and rectal cancers, however, overall survival, unadjusted for spread of disease, paralleled the trends in survival in the individual spread of cancer categories, thus ruling out substantial stage migration (Figure 2). For cancers of the head and neck and body of uterus, the uptrend in overall survival was modest relative to that in individual categories of degree of spread (data not shown), thus suggesting some stage migration.

Discussion

We found that excess risk of death after diagnosis for 20 of 28 categories of cancer type, adjusted where possible for degree of spread of cancer (cancer stage) at diagnosis, fell significantly between 1980 and 1996 in New South Wales. These results are consistent with beneficial effects of newer cancer therapies on cancer survival but incomplete data on degree of spread and its increase with time may limit the confidence with which this conclusion can be drawn.

Our data are population-based and thus represent the experience of a general population of people with cancer, not one that has been selected by referral to a particular hospital or expert centre. We were able to take some account of trends in stage, which many population-based studies cannot because stage data are not collected by the relevant cancer registry. Our observations are also based on large numbers of patients and deaths and thus can give quite precise estimates of trends for many different cancers.

That our data on stage of cancer are incomplete and have become more incomplete with time mean that we cannot rule out entirely the possibility that increased cancer screening or better methods of diagnosis, leading to earlier diagnosis, have contributed to the favourable trends we have observed.[125] In addition to the impacts on cancer mortality that screening and improved diagnosis might have had, both lead-time bias (advancing the date of diagnosis without postponing the time of death) and length bias (detection of slower growing tumours that would not otherwise have been diagnosed or have caused death) could have produced apparent falls in excess risk of death.[70;81] The measure we used to adjust for stage, spread of disease at diagnosis, is a very powerful predictor of survival in our data[95] but it was missing for more than 10% of most cancer types; this high prevalence of missing data would reduce our ability to control statistically for effects of trends in earlier diagnosis on trends in survival. These issues notwithstanding, the lack, for most cancers, of an increase in the proportion of cases with localised stage (Table 11) suggests that these factors were not generally important contributors to apparently improved survival.

Stage migration could also have produced artefactual falls in observed excess risk of death. As suggested above, this might explain the whole of the apparent improvement in stage-adjusted survival for ovarian cancer and might have contributed to the falls in stage-adjusted survival for cancers of the head and neck and body of uterus. It was probably not important for other cancers.

There would, perhaps, be greatest concern with inadequate adjustment for stage at diagnosis for cancers for which the proportion of early stage disease increased with time: melanoma, breast cancer and testicular cancer. Introduction of mammographic screening for breast cancer

in the 1980s should have reduced the excess risk of death from breast cancers diagnosed in 1980 to 1996.[126] Its effects are probably evidenced in the increasing proportion of localised disease and the somewhat greater downtrend in excess risk for breast cancers than for most other cancers (Table 12). However, if screening was the main reason for the reduced excess risk of death, survival improvement should have been most evident in the target age group for screening, 50-69 years; whereas it was seen in all age groups (Figure 3). There is no formal screening program for melanoma in Australia, self and professional skin examination is strongly encouraged and there is evidence of its impact.[127] Here the problem of adequate stage adjustment is even greater: as most melanomas are diagnosed when localised to the skin, a measure of local stage, namely thickness of the melanoma, is a much better indicator of early diagnosis than is clinical stage. We did not use it in this study. Thus we cannot infer benefits from trends in melanoma treatment from our results. While testicular self-examination has been promoted in Australia, the trend towards an increase in localised cancer was paralleled by an increase in non-localised cancer (Table 11) and a fall in cancer of unknown stage. Thus there is no certain trend to earlier diagnosis of testicular cancer and the reduction in excess risk of death for this cancer probably reflects the known improvements in treatment in the 1970s and 80s,[119] with the lowest RER in 1989-92 (Table 12) consistent with achievement of a minimum in testicular cancer mortality in NSW in this period.[121]

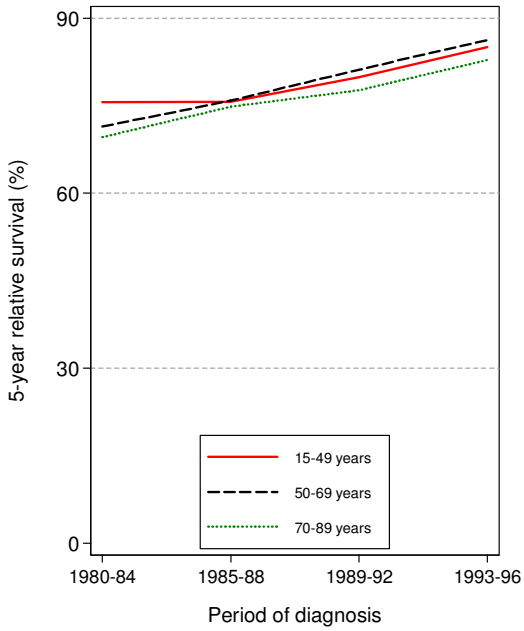

Figure 3. Trends in 5-year relative survival by age at diagnosis for breast cancer, New South Wales Australia 1980-96

Although there is no formal screening program for prostate cancer in Australia and any trend towards earlier diagnosis of it has probably been masked by the great increase in proportion of cancers of unknown stage, the near 50% apparent fall in excess risk of death from it has probably been caused by the large increase in screening with prostate specific antigen (PSA) testing in Australia in the 1990s, with the associated large increase in prostate cancer incidence.[128] The 5-year relative survival for localised prostate cancers increased from 82.7% in 1989-1992 to 97.2% in 1993-1996 (Figure 2). Compared with the model without adjustment for spread of cancer, adjustment increased the RER in 1993-96 from 0.38 to 0.54 (data not shown). Thus, while adjustment for spread of cancer removed more than 40% of the reduction in excess risk for prostate cancer, the recently increased proportion of prostate cancers (49.4%; Table 11) with missing spread of disease would probably have prevented full control of the effects of the stage shift. The increasing proportion with unknown stage for cancers of the liver and thyroid would similarly reduce our ability to control for stage; these also showed substantial falls in excess risk over the period. The fall in excess risk for liver

cancer may be due to its rapidly rising incidence due to chronic viral hepatitis in Australia[121;129] and associated greater detection due to surveillance of infected patients. Thyroid cancer is similarly increasing in incidence[121] and at least some of this is due to greater detection, possibly of lesions with limited potential to advance.[130]

Our results are consistent with those of population-based studies of trends in cancer survival from other countries in which the effects of trends in stage at diagnosis have been considered. The most comprehensive analysis of this type was presented by Dickman et al using 560,000 cases in 37 categories of cancer type registered by the Finnish cancer registry, diagnosed in 1955 to 1994 and followed up to 1995.[54] Stage data were available in the same categories as we have used and 22% of all cancers were of unknown stage. Time trends in relative survival were presented only graphically and without adjustment for possible confounding variables. Five-year relative survival from all cancers increased by about 20 percentage points from 1955-64 to 1985-94. Similar uptrends were observed in each category of stage, with the absolute increase being greater in localised and, to a lesser extent, disease with regional spread than disease with distant spread. This is similar to the pattern we observed (Figure 2). A few population-based studies of cancer survival in other countries, limited to colorectal or breast cancers, have taken account of trends in stage at diagnosis. All except one, of colorectal cancer in Singapore, were done in European countries, and all found reductions in fatality or increases in survival that were apparently independent of trends in stage.[57;59-62]

How plausible is it that downtrends in excess risk of death that we have observed are due to improvements in cancer management? There are good grounds for believing that such improvements have occurred. Surgical techniques developed during the 1980s and the introduction of adjuvant chemotherapy in the 1990s for colorectal cancer patients may have

contributed to their apparently improved outcome.[131] These modalities are now in common use in NSW.[111] The increased use of tamoxifen and adjuvant chemotherapies since the later 1980s should have contributed to the improved survival for breast cancer patients.[125;132;133] These therapies too are in common use in Australia.[134;135] For prostate cancer, increased survival could also be due to changes in treatment practice in the late 1980s and early 1990s when hormonal therapy was introduced for patients with advanced disease and older patients.[136;137] More recently, increasing use of radical prostatectomy in early stage prostate cancer may also have improved outcome.[138]

The approximate 15% fall in excess risk of death from each of Hodgkin's disease, non-Hodgkin lymphoma and multiple myeloma is compatible with 9 to 16% relative increases in 5-year survival from these cancers between 1980-84 and 1995-97 in data from the US SEER registries.[139] The relatively modest changes for these three related cancers are probably due to the most important therapies that changed outcomes for these diseases having been already well established in 1980.[140-142]

The small but significant uptrends in excess risk of death from cancers of the connective tissue and unspecified sites might be explained by their falls in incidence over the period of study (Table 10) due, perhaps, to increasing classification of better differentiated or less widely spread cancers to more specific sites with more specific histopathological diagnosis or more effective location of the probable site. The statistically non-significant uptrend in excess risk for bladder cancer is probably mainly due to a fall in registration of non-invasive tumours of the bladder after 1985 with availability of pathology reports and reduced reporting of bladder papillomata as cancer.[143]

These considerations notwithstanding, there remains justifiable concern about the impact of the increase in the proportion of unknown stage cancers on our adjustment for stage of cancer and especially the possibility that the distribution of stages within this unknown stage group may also have changed with time, a possibility we cannot rule out. There was, however, little correlation (Pearson's correlation coefficient of 0.10) between the size of the change in the proportion of unknown stage between 1989-92 and 1993-96 and the effect of stage adjustment on the RER in 1993-96, which suggests little such bias. Moreover, a comparison of Tables 11 and 12 shows that for all cancers for which there was little change in the proportion of unknown stage cancer between 1980-84 and 1989-92 there was still an important reduction in excess risk with an upper confidence limit for the RER of less than 1.0 in this interval. This was so for cancers of the oesophagus, stomach, colon, rectum, lung, cervix, body of uterus and kidney, for which we suspect no other sources of bias, as well as for melanoma, breast cancer and thyroid cancer, for which we do. Thus for the former set of these, at least, the best explanation for reduced fatality in the period of study is improvement in treatment.

Chapter 6 Misclassification of colorectal cancer stage and area variation in survival

About this chapter

This chapter contains the manuscript titled "Misclassification of colorectal cancer stage and area variation in survival" accepted by *Int J Cancer* subject to minor revision.

The authors of this publication are Xue Qin Yu, Dianne O'Connell, Robert Gibberd, Michal Abrahamowicz and Bruce Armstrong.

Changes have been made according to the guidelines for theses at the University of Sydney; therefore, this chapter differs from the accepted version.

The tables and references have been renumbered to maintain consistency within the thesis.

Abstract

We previously investigated the impact of health area of residence on colon and rectal cancer survival by estimating area-specific relative excess risk of death (RER), stratified by stage at diagnosis. The aims of this study were to quantify errors in colorectal cancer stage obtained from an Australian population-based cancer registry and assess the potential impact of errors in stage on these estimates. For a subset of cases, we compared the cancer registry stage with that from a survey of treating surgeons. We then randomly reallocated all cases to a simulated "corrected" stage according to the estimated misclassification probabilities and repeated the analysis of area variation stratified by simulated stage 1,000 times. We found 70% agreement between the Registry and Survey stage. This reallocation of the Registry cases by stage resulted in substantial variation in area-specific RERs across the simulated samples. Area variation in survival for localised colon and localised rectal cancer, which were previously statistically significant when classified using Registry stage, appeared no longer to be so. Misclassification of cancer registry stage can have an important impact on estimates of spatial variation in stage-specific colon and rectal cancer survival. If population-based cancer registry data are to be effectively used in evaluating and improving cancer care, the quality of stage data may need to be improved.

Introduction

Stage at diagnosis is the most important predictor of survival for patients with colorectal cancer. Accurate staging is critical for appropriate treatment and meaningful evaluation of treatment outcome. While the TNM system is the most commonly used system of tumour staging for clinicians, population-based cancer registries, including the registries in the Surveillance, Epidemiology, and End Results (SEER) program in the USA, use a summary classification of stage, which categorises how far a cancer has spread from its site of origin. This classification usually identifies four stages: in situ, localised, regional (including direct extension and to regional lymph nodes), or distant spread.[144] It uses all information available in the medical record.

There are few reports that assess the amount of error in the summary staging of cancer. Summary staging of SEER data was said to be 98% accurate in cancers of known stage on the basis of a personal communication.[145] However, stage was missing for 14% of cases.[145] Studies of the stage recorded by population-based cancer registries for specific cancer types have usually compared the registry stage with more accurate staging information from other sources such as medical records. Such studies report error rates of 12% to 35% for individual stage categories in cancers of the prostate, lung and breast in the USA and Europe.[2;146-148]

Data on spread of cancer from population-based cancer registries are widely used to adjust survival rates when the objective is, for example, to assess the impact of cancer treatment on outcome.[21;25;106;149] Errors in stage, however, may reduce the ability to control for effects of earlier detection on survival rates and thus lead to incorrect inferences about the impacts of treatment. While inaccurately measured or recorded stage may affect stage-specific survival

estimates and leave residual confounding by stage in stage-adjusted estimates, the magnitude and impact of staging error in this context has been rarely quantified.

In this study, we quantified errors in baseline staging of incident cases of colorectal cancer by comparing data on spread of cancer from an Australian population-based cancer registry with that collected directly from treating doctors. Next, we assessed the potential impact of such misclassification on stage-specific estimates of area variation in colon and rectal cancer survival. To this end, we reallocated a fraction of all cases to different stages, based on the distribution of the Registry stage across categories of Survey stage. We then investigated to what extent the area-specific and overall area variation estimates might be affected by such stage reallocation.

Patients and Methods

Study population

The study population included all patients diagnosed with colon and rectal cancer (ICD-O-2 site codes C18-C21) in 1992-2000 in the State of New South Wales (NSW), Australia, and reported to the NSW Central Cancer Registry, the only population-based cancer registry in Australia that collects cancer stage at diagnosis. Eligible subjects were cases with a single primary invasive tumour and aged 15-89 years. Cases known to the Registry through death certificate only or first identified at post-mortem were excluded. There were 27,961 cases included in the main study with 150 (0.5%) death certificate only cases excluded from the analysis. To focus on more recent survival, those who were diagnosed in 1992-95 and died before 1996 were also excluded.[102;103] All eligible cases were followed up to 31 December 2001 to determine survival status.

Registry stage

Cancer stage at diagnosis is obtained by the Registry from statutory notification forms and pathology reports. It is classified using a modified summary classification, similar to that used by SEER, of localised (confined to tissue or organ of origin), locally advanced (spread to adjacent organs or tissues), regional (spread to regional lymph nodes), distant (distant metastases) or unknown stage (no information available).[144] Coding was done either by medical coders in the hospitals that notified the Registry, or by medical coders in the Registry, who generally assigned stage based on pathology reports in addition to the hospital notifications.

Survey stage

For a subset of the study population, we were able to compare stage data from the NSW Colorectal Cancer Care Survey.[111] The Survey covered all colorectal cancer cases reported to the Registry between 1 February 2000 and 31 January 2001 in NSW. Stage for the Survey was obtained from the surgeons, who completed a questionnaire that sought information on the local extent of the cancer, the involvement of lymph nodes and the presence of distant spread. The vast majority of the patients (97%) had surgery with the rest (3%) having chemotherapy or radiotherapy.

Because the Registry stage and ID number had not been recorded in the Survey database, cases in the Survey dataset were matched probabilistically to the Registry records of colorectal cancer by use of the Integrity software package[150] with names, sex and date of birth as the matching variables. Such techniques usually provide a 95-99% accuracy rate for true matches.[151] A de-identified linked dataset, which included the Registry stage for each case,

was provided to the authors for analysis. The Cancer Council NSW Ethics Committee approved the project.

Statistical methods

Assessing agreement between the Registry and survey-based stages

The stage information obtained from the Survey was mapped to the stage categories used by the Registry. The Registry stage data were then compared with those obtained from the Survey, which were considered to be more accurate. Among cases with known stages, agreement between the Registry and Survey stage was measured by calculating the Kappa coefficient, which quantifies the extent of agreement, beyond that expected purely by chance, between alternative classifications.[152] Kappa values of 0.4-0.6 are generally considered to show moderate to good agreement and those of 0.6-0.8 show very good agreement.[152] To identify subgroups for which the Registry data might be less accurate, multiple logistic regression was used to estimate the odds ratios for stage misclassification as the binary outcome. The variables included in the model were age group at diagnosis, sex, area of residence, and cancer type (colon or rectum).

Estimation of area variation

The main analyses focused on the impact of stage misclassification on the area variation in survival between the then 17 health areas in NSW, which we have previously published without consideration of stage misclassification.[149] Because we expected that the frequency of misclassification would be different for different stages and the treatments of colon and rectal cancer depend heavily on disease stage at diagnosis, we performed all analyses separately for each of the three stages: localised, non-localised, and unknown stage. To assess area variation, we used the same approach as our original study,[149] with detailed methods described

elsewhere.[106] Briefly, the analyses involved four major steps. First, we calculated relative survival for each area stratified by age group at diagnosis, sex, years since diagnosis, and cancer stage at diagnosis in three categories: localised, non-localised and unknown. Relative survival was estimated as the ratio of the observed proportion surviving in a given stratum to the expected proportion that would have survived in a group of people of the same age and sex, who experienced the overall mortality rates in the general population of the corresponding area.[3] Second, we estimated the relative excess risk due to cancer (RER) in each area using a Poisson regression model for excess risk of death and adjusted for age group, sex, and years of follow-up.[104] In the Poisson model, the dependent variable was the number of excess deaths (calculated as the observed number of deaths minus the expected number of deaths based on the population death rates) among cancer patients in a given stratum corresponding to a particular combination of the variables included in the model. Then, we estimated the stage-specific coefficient of area variation (σ) in area-specific RERs, assuming they follow a Gamma distribution.[153] The null hypothesis of no area variation ($\sigma=0$) was tested by the z-statistic calculated as the ratio of σ to its standard error.[106;149] Finally, in order to avoid numerically unstable estimates, especially in areas with small populations, we used the empirical Bayes approach to shrink the area-specific RERs toward the State average risk. This amount of shrinkage is approximately inversely proportional to the number of cases in a given area[106;153;154] and the variance of the estimates is based on the estimated σ coefficient.

To show how important area variation in survival may be, we estimated the number of lives that might be extended if the NSW average excess risk of death due to each of the three stage categories (localised, non-localised and unknown) was shifted to the 20th centile of the empirical Gamma distribution.[85;94;149]

Assessing the impact of stage misclassification

To assess the potential impact of error in the Registry stage on our previous estimates of area variation in stage-specific RERs, we attempted to quantify the uncertainty due to inaccurate staging. To this end, we repeated the original analyses of area variation[149] but used "corrected" stages based on the Survey results. Because we could not determine a "corrected" stage for individual subjects, we simulated a plausible stage for each person. The "simulated" stage was randomly generated from the multinomial conditional distribution of the "corrected" stages corresponding to the "observed" Registry stage. These simulated stages were categorised into 5 groups as originally in the Registry, separately for colon cancer and rectal cancer. Next, to avoid unstable estimates for some areas due to a very low number of cases for a given stage, all subjects allocated to one of the three advanced stage categories were grouped together as "non-localised" cancer.

While we could expect what proportion of cases assigned a given Registry stage was incorrectly classified, we did not know which individual cases should be reallocated. Therefore, we repeated a random reallocation of the Registry-based stages 1,000 times based on the estimated stage-specific misclassification probabilities for NSW as a whole. Each of the resulting 1,000 samples of the original data was then analysed using the methods described in the previous section. This yielded the distributions of 1,000 estimates of the RER for each area, the coefficients of area variation (σ), the corresponding p-values, and the numbers of lives extended. These distributions were then analysed to assess the uncertainty due to stage misclassification in the estimates of area variation and lives that might be extended.

To assess to what extent the variation across 17,000 RERs (17 areas × 1,000 simulations) was attributable to systematic differences between areas rather than to random variation across simulations within area, we estimated the intraclass correlation coefficient (ICC) from a two-way ANOVA model using a method described by Morton and Dobson.[155] In this context, the ICC is a measure of the proportion of variance in RERs accounted for by area and its complement, 1 − ICC, is an estimate of the proportion of variance accounted for by random reclassifications of cancer stages within area.[156] The SAS procedure GLM was used with RERs as the dependent variable and simulation number and area as independent fixed-effects. All analyses were done using SAS version 8.2.

Results

Of 3,094 patients aged 15-94 years diagnosed between 1 February 2000 and 31 January 2001 in NSW, with a surgical questionnaire in the Survey, 2,855 (92%) were matched with single primary colorectal cancer patients in the Registry dataset. The remaining 8% were multiple primary cases (181), cases with a postcode outside of NSW (24), cases with non-invasive tumour (20), and unmatched cases (14).

For 2,650 cases with known Registry and Survey stage, the Registry stage agreed with the Survey stage in 1,842 patients (69.5%) (Table 13). Kappa was 0.57 with 95% confidence interval (CI) 0.55-0.60, showing "good" overall agreement. However, agreement varied considerably by stage. In those classified as localised by the Registry, 26% were locally advanced according to the Survey. For those classified as locally advanced by the Registry, the extent of upstaging and downstaging was similar (12.3% vs. 13.4%). Among those classified as regional stage by the Registry, as many as 73% were distant stage according to the Survey. The highest agreement (90.4%) between the Registry and Survey stage was for

distant disease. In the Registry 10.9% of colon cancers and 13.9% of rectal cancers were of unknown stage. The majority (77%) of these with unknown stage were of localised or regional stage in the Survey, leaving only 2.5% of colon cancers and 4.5% of rectal cancers with unknown stage in the Survey (data not shown).

Table 13. Agreement of disease stage at diagnosis (%) between the Registry database and Survey database in 2,650 patients with known stage in both, colorectal cancer NSW 2000

Stage according to Cancer Registry	Stage according to Survey				Total
	Localised	Locally advanced	Regional	Distant	n (%)†
Localised	65.3	26.0	1.1	7.6	973 (36.7)
Locally advanced	13.4	74.3	0.5	11.8	627 (23.7)
Regional	1.9	2.8	22.5	72.8	325 (12.3)
Distant	1.4	3.1	5.1	90.4	775 (29.2)
Total	716 (27.0%)	737 (27.8%)	124 (4.7%)	1073 (40.5%)	2650 (100.0)

*The Cancer Registry stage was unknown for 155 patients and the Survey stage for 73; 32% of the latter were also among the former.
† Percentages in the body of the table are row percentages

Multiple logistic regression analysis showed that age at diagnosis was the only important predictor for misclassification of stage. The highest agreement (80%, Kappa = 0.66) was in the youngest patients (15-59 years) and the lowest (75%, Kappa = 0.56) in the oldest (75-94 years) (p=0.04). Colon cancer stage was marginally more likely to be misclassified than rectal cancer stage (p=0.05). There was little variation in misclassification by area of residence at diagnosis or sex (data not shown).

The expected stage distributions based on the simulations showed a substantial reduction in the proportion of cases with unknown stage. Moreover, the re-assignment of both unknown and many "localised" stage cases to "regional" together resulted in a sizeable increase in the proportion with non-localised stage, while for localised colon cancer there was a small reduction. (Table 14)

Table 14. Comparison of the registry stage distribution and the expected stage distribution from simulations for colon and rectal cancers

		Registry stage distributions (%)	Expected stage distributions (%) from simulations*		
			Localised	Non-localised	Unknown
Colon cancer					
Registry stage classification	Localised	28.2	58.2	38.8	3.0
	Non-localised	60.9	5.2	94.1	0.7
	Unknown	10.9	41.9	46.5	11.6
	All	100	24.1	73.3	2.5
Rectal cancer					
Registry stage classification	Localised	35.7	70.6	26.4	2.9
	Non-localised	50.5	7.5	90.7	1.8
	Unknown	13.8	46.5	34.9	18.6
	All	100	35.4	60.1	4.5

* Average proportion of each simulated stage based on 1000 samples

The distributions of area variation and proportion of lives that might be extended obtained from simulations of individual stage (based on the observed association between Registry and Survey stage) are shown separately for colon and rectal cancers and for each of the three main stage groups (including unknown) in Table 15. Only for non-localised colon cancers were the values at the lower end of the distribution of the 1,000 area variation coefficients (σ) appreciably above zero; the same was correspondingly true for the simulated estimates of lives that might be extended. For this category too, 90% of the p-values for the test of the null hypothesis of no area variation ($\sigma = 0$) were <0.05, which is consistent with the p-value of 0.014 that we obtained based on the original Registry stage.[149] Further the ICC of 0.89 for non-localised cancers suggests that 89% of the variance in the simulated coefficients could be attributed to systematic differences between areas (Table 15).

Table 15. Comparison of area variation in survival and number of lives that might be extended beyond 5 years after diagnosis by the Registry and simulated stage and distributions of estimated coefficients across 1,000 samples with simulated cancer stages

Cancer type and stage	Previous results[149] based on the Registry stage			Area variation (σ) quantiles					% of p-values <0.05 for H_0	Quantiles of number of lives that might be extended					ICC for 17 RERs
	σ	p-value	No. of lives extended	2.5%	25%	50%	75%	97.5%		2.5%	25%	50%	75%	97.5%	
Colon															
Localised	0.55	<0.0001	180	0.0005	0.11	0.16	0.20	0.27	46%	0	53	78	101	149	0.39
Non-localised	0.09	0.014	251	0.06	0.07	0.08	0.09	0.10	90%	180	232	260	294	356	0.89
Unknown	0.27	0.002	128	0.0002	0.08	0.25	0.38	0.59	34%	0	7	23	33	56	0.10
Rectum															
Localised	0.27	0.005	82	0.02	0.13	0.16	0.20	0.27	53%	10	60	80	100	137	0.55
Non-localised	0.04	0.55	59	0.0006	0.03	0.05	0.06	0.08	2%	1	53	83	108	161	0.61
Unknown	0.19	0.002	84	0.0002	0.09	0.24	0.33	0.52	30%	0	9	23	33	50	0.14

For localised colon cancer and for non-localised rectal cancer, the distributions of the simulated values of the coefficient of area variation ranged down to near zero and were statistically significant in fewer than 50% of simulated samples, and the estimates of extended lives were substantially less than previously.[149] (Table 15) Similarly for localised rectal cancer, while the 2.5% quantile, at 0.02, was further from zero, only 53% of the p-values were <0.05, suggesting there is less likely to be significant area variation in RER after correction for error in staging. We previously reported highly statistically significant variation between-areas in RER for localised colon and rectal cancers using original Registry stage.[149] For both, the median coefficient of area variation from the simulations is substantially lower than the coefficient estimated using Registry stage: 0.16 vs 0.55 for colon and 0.16 vs 0.27 for rectum (Table 15 compared with Yu et al[149]). The difference between the median of the simulated values and original coefficients for non-localised cancers were much less: 0.08 vs 0.09 for colon and 0.05 vs 0.04 for rectum.

The comparative robustness of our estimate of variation between areas for non-localised colon cancer is further illustrated in Figure 4, which shows the distribution of the 1,000 simulated area-specific RER estimates for each of the 17 areas in NSW. The boxes, corresponding to the interquartile range (IQR), are tight, reflecting the fact that in each simulated sample most (94%) of these cancers were not reclassified (Table 14). Moreover, many IQRs and some of the full ranges of the area-specific estimates do not overlap one or more of the others, suggesting that there is meaningful variation between areas in the RERs.

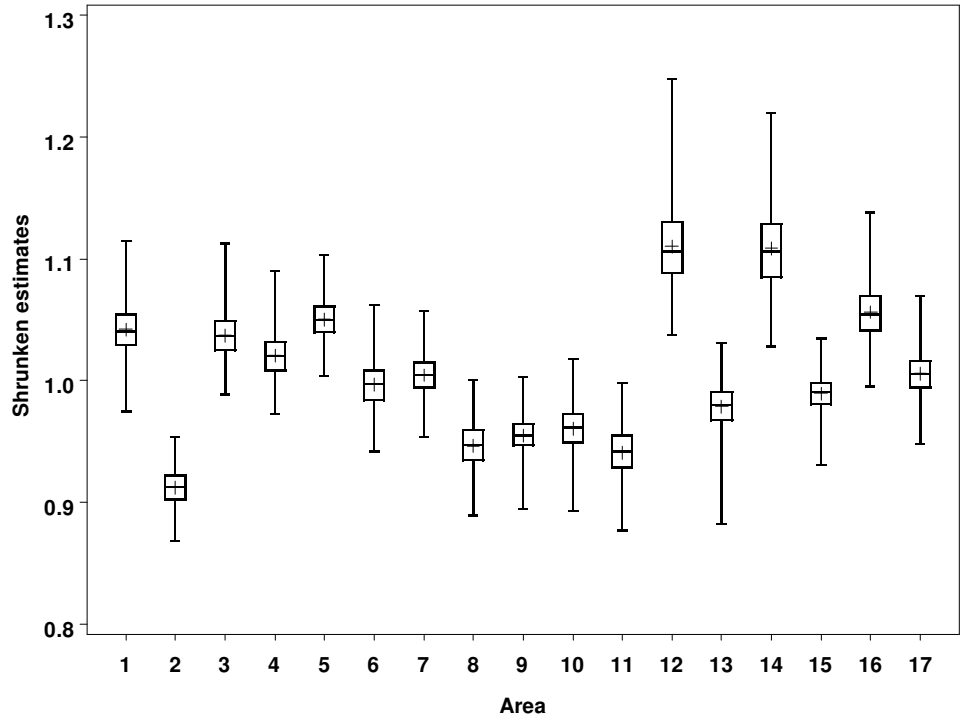

Figure 4. Distribution of relative excess risks by area for non-localised colon cancers from 1,000 simulated samples: The mean is indicated by the sign (+); bars (from bottom to top) indicate the minimum, 1st quartile, median, 3rd quartile and maximum values.

Discussion

We found 70% overall agreement between stage of colorectal cancer at diagnosis recorded by the Registry and that recorded in a survey of treating practitioners. The Registry stage was biased towards over-reporting of localised disease and spread to regional lymph nodes and under-reporting of spread to adjacent tissues (locally advanced) and distant metastases. This suggests that errors in the Registry stage may have had an important impact on our stage-specific estimates of area variation and therefore the validity of their interpretation in terms of treatment-related differences in outcome.

Ideally, our assessment of the impact of error in Registry stage on estimates of area variation in stage specific RER for colon and rectal cancer would have used stage data from treating surgeons for the whole study population. Rather, using limited data comparing Registry stage

with the stage assigned by surgeons, we had to rely on simulation to estimate a "corrected" stage for each individual case. Because we had no way of knowing which cases were truly misclassified by the Registry stage, none of these simulated stages can be considered really "correct". Accordingly, we could not determine the 'correct' amount of area variation; but the simulations allowed us to assess the impact of the uncertainty regarding true staging of individual cases on the robustness of our estimates and conclusions. With 6% misclassification for non-localised colon cancers (Table 14), the simulation process for the correction of this error induced relatively little uncertainty (ICC=0.89) (Table 15). As the misclassification increased, the simulation process added more uncertainty to the estimates of area variation, with an ICC of 0.61 for non-localised rectal cancers to one of only 0.10 for unknown colon cancers (Table 15). Only 12% of unknown stage colon cancers in the Registry were truly unknown according to the surgeon's records (Table 14).

Area variation in RER for non-localised colon cancer remained significant after we assessed the possible impact of misclassification of stage on it. This supports our previous conclusion, based on results obtained by using Registry stage,[149] that variation in the application of known effective treatments may be the cause. On the other hand, area variation in RER for localised colon cancer and for localised rectal cancer, which appeared statistically significant when Registry stage was used,[149] now appears less likely to be significant when the impact of misclassification of stage is considered. Thus we are less certain in concluding that variation in treatment between areas caused area variation in survival for these localised cancers.

That both the Survey and Registry datasets were population-based is a strength of our analysis. Thus the results have the potential to reflect the experience of the whole of colorectal cancer in everyday practice in NSW. Our analysis is limited, though, by the

assumption that stage was perfectly measured in the Survey, which we cannot validate. We believe, however, that the Survey stage information should be reasonably accurate, as data on stage from clinical records are generally considered to be the best available.[2;157] Moreover, stage of colorectal cancer is heavily dependent on the surgical and pathological findings and 97% of the patients in the Survey had surgery. We also assumed that the stage-specific error rates in the Registry stage were similar in the Survey period (2000) and the eight years before (1992-1999). While this seems a plausible assumption, we have no data by which it could be validated.

Our findings on the accuracy of cancer registry stage data are generally similar to those obtained in several other studies of population-based cancer registries.[2;146-148;158] Liu et al found that 23% of the patients with prostate cancer were staged incorrectly in a US cancer registry when compared with clinical records,[147] Jensen et al reported 87% agreement for local and regional stage but only 65% for distant stage in a Danish study of breast cancer.[146] All these studies recommended that the quality of staging from cancer registries should be improved.[2;146-148;158]

Poor recording of stage information in pathology reports and clinical records and coding errors in hospital medical records departments or by Registry personnel are some of the causes for error in cancer stage as recorded by cancer registries.[2;146-148;158] Additionally, in this study, the Registry procedure of determining stage within the first four months after diagnosis, when information may still be incomplete, might have contributed to the systematic under-estimation of the extent of the cancer. The time frame for SEER summary staging is either completion of surgery as the first course of treatment or four months after diagnosis,

whichever is longer.[144] The NSW Registry uses the "four months" criterion because it does not collect treatment information.

A number of steps could be taken to improve the quality of staging information collected by cancer registries. Routine collection of additional information on diagnostic procedures performed to define stage, such as lymph nodes examined pathologically or imaging for distant metastasis, might be considered because such information is usually very important for determining stage.[21;25;159] More rigorous quality assurance might also be introduced to ensure complete recording of stage, and the information contributing to its assignment, in hospital medical records. Coding errors could be reduced with more rigorous quality assurance in medical records departments and Registry staging.

The practical relevance of this study stems from the fact that an increasing number of studies use stage information from population-based cancer registries, including EUROCARE,[17;18;21;25] SEER,[2;160;161] and other Australian studies.[105;106;108;149;162] The possible impact of error in stage on conclusions regarding cancer outcome, however, has rarely been considered. One small, cancer registry based study of inoperable lung cancers treated with radiotherapy compared the cancer registry stage with stage extracted from clinical records and observed little difference in stage-specific median survival between the two stage classifications.[148] Our study appears to be unique, though, in having both quantified the errors in cancer registry stage data and examined their potential impact on the results of a more complex outcome analysis. Additional studies will be required before we can fully understand the impact of errors in cancer stage on inferences about variation in stage specific and, more particularly, stage-adjusted cancer survival.

Chapter 7 Discussion and conclusions

About this chapter

This chapter provides a summary of the main findings from this thesis and a discussion of the strengths and limitations. I broadly discuss the usefulness of survival analysis of cancer registry data and raise some potential directions for future research. This chapter is intended to bring all the findings from the previous chapters together and to discuss what the thesis as a whole contributes to new knowledge about the usefulness of survival analysis based on cancer registry data.

Summary of findings

The cancer registry data in Australia are currently underutilised in measuring the performance of cancer care, compared to EUROCARE registries and SEER registries in the USA. This thesis highlighted their usefulness in evaluating and potentially monitoring the improvement in the quality of cancer care. Despite the limitations of the data and the difficulties in the interpretation of comparative survival, I have demonstrated in the four papers that creative, informed use of such data, with appropriate statistical methods and awareness of its limitations, can be a valuable tool for evaluating and improving cancer care.

As described in Chapter 3, my analysis of geographical variation in survival had three steps. First, I applied an overall test to estimate the probability that there is real variation across geographical areas. Secondly, I extended the standard methods by using an empirical Bayes approach to shrink the area-specific estimates towards the global mean to reduce numerically unstable individual estimates. Thirdly, I proposed a measure of the importance of area

variation in contrast to statistical significance by estimating how many additional cancer patients could have survived beyond 5 years after diagnosis, if mean survival was moved to the 20th centile. We can use this method to identify cancer sites for which targeted interventions have the greatest potential to improve outcome and help decision makers in determining causes of geographical variation in survival.

In Chapter 4, I applied these methods to colon and rectal cancers, with an in-depth analysis of area variation in survival. In this study, significant variation was found for both colon ($p=0.006$) and rectal cancer ($p=0.049$) after adjusting for demographic factors. The statistical significance of the variation remained for colon cancer ($p=0.004$) but was reduced for rectal cancer ($p=0.16$) after adjusting for stage at diagnosis, suggesting that variation in stage between areas contributed importantly to the variation in outcome for rectal cancer. I interpreted significant residual variation in colon cancer as indicative of differences in the application of effective treatments between areas. This significant area variation in survival also had important public health implications; with reasonable efforts to reduce it, an additional 784 patients could have survived beyond 5 years after diagnosis.

In Chapter 5, I examined time trends in survival from 1980 to 1996 by taking confounding trends in stage and possible stage migration into account. The results showed that excess mortality from many cancers dropped significantly ($p<0.01$) over this period with a 25% reduction for all cancers combined. The falls varied by stage at diagnosis and the largest were in localised and regionally spread tumours. With the exception of cancers of the prostate, liver and thyroid, for which a substantial proportion of staging information was missing in the most recent periods, the observed improvements in survival for many cancers were probably

attributable to newer cancer therapies introduced in NSW since 1980. This has been reported elsewhere in the literature.

In Chapter 6, I found that there was 70% agreement between the Registry stage and staging information collected from treating surgeons for colorectal cancer patients diagnosed from February 2000 to January 2001 in NSW. After accounting for this error in the Registry stage by using simulation, I found that area variation in survival for localised colon and localised rectal cancer, which were previously statistically significant when classified using Registry stage, appeared no longer to be so. This result indicates that inaccurate stage recorded in the Registry could bias estimates of stage-specific area variation. Hence, if cancer registry data are to be used effectively in evaluating cancer care, the quality of the stage data should be improved. This finding sounds a cautionary note to researchers who use such data. However, it is not certain to what extent the impact of staging error that I observed will be applicable in other similar circumstances.

Strengths and limitations

My data were population-based, having large numbers of cases with a long period of follow-up; they represent a wide range of individual cancer types from cancers with excellent prognosis (lip, testis and thyroid) and moderate prognosis (colon and rectum, bladder and NHL) to cancers with extremely poor survival (pancreas and mesothelioma). The results provide a complete picture of how cancer patients are managed in our day-to-day practice, and reflect the practical effectiveness of treatments in a well-defined population.

My methods of analyses have several strengths. First, my measure of geographical variation in survival took into account several biases. I applied an empirical Bayes approach to adjust

for sampling errors and used adjustment for stage to account for lead-time bias. More importantly, I had a measure of the importance of geographical variation, which could be used to identify cancer sites for which targeted interventions have the greatest potential to improve outcome and help decision makers determine the causes of area variation in survival. Secondly, my measure of temporal trends in survival take into account lead-time bias and length bias by use of adjustment for stage over time, which many cancer registries cannot do because stage data are not routinely collected. To deal with the impact of stage migration on trends in survival, I interpreted survival trends carefully in relation to incidence trends and changes in distribution of stage over time. Thirdly, the study in Chapter 6 is unique having both quantified the errors in cancer registry stage and examined the potential impact on stage-specific estimates of area variation in survival.

However, there are some limitations in both the data and the methods used in this thesis. Population-based cancer registries collect data primarily to estimate cancer incidence rates. They often do not collect treatment information and lack detailed information on comorbidity. Thus the data do not allow us to confidently conclude that the differences in outcome were due to differences in treatment, although we had evidence for such variation from elsewhere. Information on cancer stage is often not collected and when collected may be incomplete and inaccurate. Misclassification in stage could lead to incorrect inferences about the impacts of treatment, as we found in Chapter 6. More accurate data on stage would be highly desirable but are rarely available at the population level.

My approach to shrink individual area estimates towards the global mean may over-shrink the estimates from remote areas with small populations, especially when studying rare cancers. This might mask significant geographical variation in survival but would only have minimal

impact on the measure of the importance of this variation. The survival measure may not be sensitive enough to determine improvements for cancers with extremely poor survival such as liver and pancreas from one period to another, thus quality of life and quality of palliative care may be better indicators of improvements of outcome for them.

Future research directions

To maximize the usefulness of cancer registry data in measuring quality of cancer control, a number of steps should be taken, including: improving the quality of key clinical information collected, such as stage at diagnosis, tumour size and histology, together with the possible collection of additional information for determining stage; application of geographic information systems to accurately locate patient's residential address to a smaller unit, such as census collection district; linkage with hospital records and medical services data to track information on treatment including surgery, chemotherapy and radiotherapy. With such enhancements, population-based cancer registries could become a valuable component of data systems for assessing the quality of cancer care.

More accurate data on stage at diagnosis with additional information on the thoroughness of diagnostic procedures and tumour size would improve the interpretation of both temporal and geographical variation in survival by analysing the impact of stage at diagnosis, tumour size and lymph nodes examined on survival.

Geographic information systems can be used to identify geographical clusters where patients have very poor outcomes, or an excess proportion of them are diagnosed at a later stage. For breast cancer, for example, this could be mapped along with the location of mammography

sites and other diagnostic and therapy centres. It also helps in understanding the relationships between cancer survival and other sociodemographic factors.

Linked data would help overcome many of the limitations associated with studies relying on registry data alone by combining information on clinical characteristics of the cancer at diagnosis and patient's sociodemographic factors. Registry data are a good tool for ascertaining all incident cases in a defined geographical area with detailed information about the timing of diagnosis, histology and whether the cancer is the first cancer. Hospital records provide more detailed information on disease stage at diagnosis, comorbidity and treatment, such as surgery, chemotherapy or radiotherapy. Health insurance claims data may complement the hospital records by identifying which key services, such as surgery, chemotherapy or radiotherapy were used in the outpatient department or out of hospital settings, as well as to identify additional incident cases. Linking the registry data with hospital records and claims data would allow us to quantify the proportion of patients that are managed according to best practice guidelines by geographical areas or socioeconomic status; to identify inappropriate or poor-quality care, which needs to be improved; to evaluate various patient outcomes including survival following diagnosis and treatment of cancer, which would enable us to investigate how variation in treatment is correlated with differences in outcomes.

However, data quality is highly dependent on the co-operation between hospitals and cancer registries, and cancer registries can only obtain data that are recorded on the medical record or on the notification form and pathology reports. Therefore, more stringent quality control must be implemented to reduce incomplete recording of key clinical information in hospital medical records. While improving the data, which may take years, more rigorous analysis of

existing registry data using appropriate statistical methods and evaluating its limitations, can contribute greatly to the quality of health-related research on cancer care and to the appropriateness of the conclusions drawn from such studies.

Conclusions

This thesis shows that population-based cancer registry data are useful in evaluating and potentially monitoring improvements in cancer control efforts. I found significant geographical variation in survival from several cancers in NSW. Although the reasons for the variation are not entirely clear, an important contributing factor could be the differences in the quality of care. The results from Chapters 3 and 4 indicate that there may be opportunities to improve the outcome of cancer care for some cancers, especially the common cancers with large geographical variation and large numbers of lives that may be extended if this variation was reduced. If these findings can be used to stimulate evaluation and improvement of the quality of cancer care, the value of the investment in cancer registries should be greatly enhanced.

As shown in Chapter 5, data from population-based cancer registries can be a useful tool for monitoring and evaluating the effectiveness of cancer treatments over time. Although some uncertainties remain because more staging information was missing for the most recent period for certain cancers, the best explanation for the improved survival over time is advances in cancer treatments for many of the cancers studied. The quality of data on stage also has a significant impact on estimates of spatial variation in stage-specific colorectal cancer survival, as shown in Chapter 6. Results from Chapters 5 and 6 suggest that, if cancer registry data are to be used effectively in monitoring and evaluating cancer care, the quality of data on stage should be improved. On the basis of these results and evidence from elsewhere, I recommend

that the quality of data on stage from population-based cancer registries should be improved (increasing the accuracy of known stages and reducing the proportion of unknown stage). Furthermore, consideration should be given to collecting further information on the diagnostic procedures performed to define stage, such as number of lymph nodes examined pathologically and/or imaging used to detect distant metastasis, as these are the most important determinants of many cancer stages.

References

1. Krzyzanowska MK, Weeks JC, Earle CC. Treatment of locally advanced pancreatic cancer in the real world: population-based practices and effectiveness. *J Clin Oncol* (2003); **21:** 3409-3414.

2. Malin JL, Kahn KL, Adams J et al. Validity of cancer registry data for measuring the quality of breast cancer care. *J Natl Cancer Inst* (2002); **94:** 835-844.

3. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: A statistical methodology. *National Cancer Institute Monograph*. 1961: 101-121.

4. Coleman MP, Aylin P (eds). *Death certification and mortality statistics: an international perspective*. London: TSO, 2000.

5. Percy C, Stanek E, III, Gloeckler L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am J Public Health* (1981); **71:** 242-250.

6. BERKSON J, GAGE RP. Calculation of survival rates for cancer. *Mayo Clin Proc* (1950); **25:** 270-286.

7. Campbell NC, Elliott AM, Sharp L et al. Rural factors and survival from cancer: analysis of Scottish cancer registrations. *Br J Cancer* (2000); **82:** 1863-1866.

8. Australian Institute of Health and Welfare and Australasian Association of Cancer Registries. *Cancer survival in Australia 1992-1997: geographic categories and socioeconomic status.* Canberra: Australian Institute of Health and Welfare, 2003.

9. Ellison LF, Gibbons L. Five-year relative survival from prostate, breast, colorectal and lung cancer. *Health Rep* (2001); **13:** 23-34.

10. Farrow DC, Samet JM, Hunt WC. Regional variation in survival following the diagnosis of cancer. *J Clin Epidemiol* (1996); **49:** 843-847.

11. Gatta G, Buiatti E, Conti E et al. Variations in the survival of adult cancer patients in Italy. *Tumori* (1997); **83:** 497-504.

12. Gatta G, Capocaccia R, Coleman MP et al. Toward a comparison of survival in American and European cancer patients. *Cancer* (2000); **89:** 893-900.

13. Goodwin JS, Freeman JL, Mahnken JD et al. Geographic variations in breast cancer survival among older women: implications for quality of breast cancer care. *J Gerontol A Biol Sci Med Sci* (2002); **57:** M401-M406.

14. Quinn MJ, Martinez-Garcia C, Berrino F. Variations in survival from breast cancer in Europe by age and country, 1978-1989. *Eur J Cancer* (1998); **34:** 2204-2211.

15. Sant M, Capocaccia R, Verdecchia A et al. Survival of women with breast cancer in Europe: variation with age, year of diagnosis and country. The EUROCARE Working Group. *Int J Cancer* (1998); **77:** 679-683.

16. Sant M, Capocaccia R, Coleman MP et al. Cancer survival increases in Europe, but international differences remain wide. *Eur J Cancer* (2001); **37:** 1659-1667.

17. Sant M, Allemani C, Capocaccia R et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. *Int J Cancer* (2003); **106:** 416-422.

18. Sant M, Allemani C, Berrino F et al. Breast carcinoma survival in Europe and the United States. *Cancer* (2004); **100:** 715-722.

19. Spilsbury K, Semmens JB, Saunders CM et al. Long-term survival outcomes following breast cancer surgery in Western Australia. *ANZ J Surg* (2005); **75:** 625-630.

20. Twelves CJ, Thomson CS, Dewar JA et al. Variation in survival of women with breast cancer: Health Board remains a factor at 10 years. *Br J Cancer* (2001); **85:** 637-640.

21. Ciccolallo L, Capocaccia R, Coleman MP et al. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. *Gut* (2005); **54:** 268-273.

22. Dickman PW, Gibberd RW, Hakulinen T. Estimating potential savings in cancer deaths by eliminating regional and social class variation in cancer survival in the Nordic countries. *J Epidemiol Community Health* (1997); **51:** 289-298.

23. Engeland A, Haldorsen T, Dickman PW et al. Relative survival of cancer patients--a comparison between Denmark and the other Nordic countries. *Acta Oncol* (1998); **37:** 49-59.

24. Gatta G, Faivre J, Capocaccia R et al. Survival of colorectal cancer patients in Europe during the period 1978-1989. *Eur J Cancer* (1998); **34:** 2176-2183.

25. Gatta G, Capocaccia R, Sant M et al. Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study. *Gut* (2000); **47:** 533-538.

26. Kim YE, Gatrell AC, Francis BJ. The geography of survival after surgery for colorectal cancer in southern England. *Soc Sci Med* (2000); **50:** 1099-1107.

27. Prior P, Woodman CB, Collins S. International differences in survival from colon cancer: more effective care versus less complete cancer registration. *Br J Surg* (1998); **85:** 101-104.

28. Sant M, Aareleid T, Berrino F et al. EUROCARE-3: survival of cancer patients diagnosed 1990-94--results and commentary. *Ann Oncol* (2003); **14 Suppl 5:** v61-118.

29. Cartman ML, Hatfield AC, Muers MF et al. Lung cancer: district active treatment rates affect survival. *J Epidemiol Community Health* (2002); **56:** 424-429.

30. Janssen-Heijnen ML, Gatta G, Forman D et al. Variation in survival of patients with lung cancer in Europe, 1985-1989. EUROCARE Working Group. *Eur J Cancer* (1998); **34:** 2191-2196.

31. Madsen FF, Norskov B, Frolund L et al. [Lung cancer: survival rate differences in Danish counties. Survival analysis of 33,838 patients during the period 1984-1998]. *Ugeskr Laeger* (2002); **164:** 483-487.

32. Post PN, Damhuis RA, van der Meyden AP. Variation in survival of patients with prostate cancer in Europe since 1978. *Eur J Cancer* (1998); **34:** 2226-2231.

33. Verdecchia A, Corazziari I, Gatta G et al. Explaining gastric cancer survival differences among European countries. *Int J Cancer* (2004); **109:** 737-741.

34. Berrino F, Gatta G, Sant M et al. The EUROCARE study of survival of cancer patients in Europe: aims, current status, strengths and weaknesses. *Eur J Cancer* (2001); **37:** 673-677.

35. Berrino F. The EUROCARE Study: strengths, limitations and perspectives of population-based, comparative survival studies. *Ann Oncol* (2003); **14 Suppl 5:** v9-13.

36. Sant M, Gatta G. The EUROCARE database. *IARC Sci Publ* (1995); 15-31.

37. Berrino F, Sant M, Verdecchia A et al. *Survival of Cancer Patients in Europe: The EUROCARE Study.* Lyon: IARC Scientific Publications, 1995.

38. Coebergh JW, Sant M, Berrino F et al. Survival of adult cancer patients in Europe diagnosed from 1978-89: the EUROCARE II study. *Eur J Cancer* (1998); **34:** 2137-2278.

39. Mullee MA, De Stavola B, Romanengo M et al. Geographical variation in breast cancer survival rates for women diagnosed in England between 1992 and 1994. *Br J Cancer* (2004); **90:** 2153-2156.

40. Woodman CB, Gibbs A, Scott N et al. Are differences in stage at presentation a credible explanation for reported differences in the survival of patients with colorectal cancer in Europe? *Br J Cancer* (2001); **85:** 787-790.

41. Berrino F, Gatta G. Variation in survival of patients with head and neck cancer in Europe by the site of origin of the tumours. *Eur J Cancer* (1998); **34:** 2154-2161.

42. Campbell NC, Elliott AM, Sharp L et al. Rural and urban differences in stage at diagnosis of colorectal and lung cancers. *Br J Cancer* (2001); **84:** 910-914.

43. Blomqvist P, Ekbom A, Nyren O et al. Survival after colon cancer 1973-1990 in Sweden. Convergence between catchment areas. *Ann Surg* (1997); **225:** 208-216.

44. Eaker S, Dickman PW, Hellstrom V et al. Regional differences in breast cancer survival despite common guidelines. *Cancer Epidemiol Biomarkers Prev* (2005); **14:** 2914-2918.

45. Ellison LF, Gibbons L. Leading cancers--changes in five-year relative survival. *Health Rep* (2004); **15:** 19-32.

46. Coleman MP, Rachet B, Woods LM et al. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *Br J Cancer* (2004); **90:** 1367-1373.

47. Chia KS, Du WB, Sankaranarayanan R et al. Population-based cancer survival in Singapore, 1968 to 1992: an overview. *Int J Cancer* (2001); **93:** 142-147.

48. Talback M, Stenbeck M, Rosen M et al. Cancer survival in Sweden 1960-1998--developments across four decades. *Acta Oncol* (2003); **42:** 637-659.

49. Jemal A, Clegg LX, Ward E et al. Annual report to the nation on the status of cancer, 1975-2001, with a special feature regarding survival. *Cancer* (2004); **101:** 3-27.

50. Levi F, Randimbison L, Te VC et al. Trends in survival for patients diagnosed with cancer in Vaud, Switzerland, between 1974 and 1993. *Ann Oncol* (2000); **11:** 957-963.

51. Bailar JC, III, Gornik HL. Cancer undefeated. *N Engl J Med* (1997); **336:** 1569-1574.

52. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? *JAMA: The Journal of the American Medical Association* (2000); **283:** 2975-2978.

53. Kramer BS, Klausner RD. Grappling with cancer--defeatism versus the reality of progress. *N Engl J Med* (1997); **337:** 931-934.

54. Dickman PW, Hakulinen T, Luostarinen T et al. Survival of cancer patients in Finland 1955-1994. *Acta Oncol* (1999); **38 Suppl 12:** 1-103.

55. Jensena AR, Ewertz M, Cold S et al. Time trends and regional differences in registration, stage distribution, surgical management and survival of breast cancer in Denmark. *Eur J Cancer* (2003); **39:** 1783-1793.

56. Taylor R, Davis P, Boyages J. Long-term survival of women with breast cancer in New South Wales. *Eur J Cancer* (2003); **39:** 215-222.

57. Thomson CS, Brewster DH, Dewar JA et al. Improvements in survival for women with breast cancer in Scotland between 1987 and 1993: impact of earlier diagnosis and changes in treatment. *Eur J Cancer* (2004); **40:** 743-753.

58. Webb PM, Cummings MC, Bain CJ et al. Changes in survival after breast cancer: improvements in diagnosis or treatment? *Breast* (2004); **13:** 7-14.

59. Angell-Andersen E, Tretli S, Coleman MP et al. Colorectal cancer survival trends in Norway 1958-1997. *Eur J Cancer* (2004); **40:** 734-742.

60. Du WB, Chia KS, Sankaranarayanan R et al. Population-based survival analysis of colorectal cancer patients in Singapore, 1968-1992. *Int J Cancer* (2002); **99:** 460-465.

61. Faivre-Finn C, Bouvier-Benhamiche AM, Phelip JM et al. Colon cancer in France: evidence for improvement in management and survival. *Gut* (2002); **51:** 60-64.

62. Martijn H, Voogd AC, van de Poll-Franse LV et al. Improved survival of patients with rectal cancer since 1980: a population-based study. *Eur J Cancer* (2003); **39:** 2073-2079.

63. Dahlberg M, Pahlman L, Bergstrom R et al. Improved survival in patients with rectal cancer: a population-based register study. *Br J Surg* (1998); **85:** 515-520.

64. Birgisson H, Talback M, Gunnarsson U et al. Improved survival in cancer of the colon and rectum in Sweden. *Eur J Surg Oncol* (2005); **31:** 845-853.

65. Laurvick CL, Semmens JB, Leung YC et al. Ovarian cancer in Western Australia (1982-1998): trends in surgical intervention and relative survival. *Gynecol Oncol* (2003); **88:** 141-148.

66. Reeves GK, Beral V, Bull D et al. Estimating relative survival among people registered with cancer in England and Wales. *Br J Cancer* (1999); **79:** 18-22.

67. Ponz dL, Benatti P, Di Gregorio C et al. Staging and survival of colorectal cancer: are we making progress? The 14-year experience of a Specialized cancer Registry. *Dig Liver Dis* (2000); **32:** 312-317.

68. McMullen EA, Kee F, Patterson CC et al. Improved survival for melanoma in Northern Ireland: a comparison of two 5-year periods (1984-88 and 1994-98). *Br J Dermatol* (2004); **151:** 587-593.

69. Engel J, Eckel R, Schubert-Fritschle G et al. Moderate progress for ovarian cancer in the last 20 years: prolongation of survival, but no improvement in the cure rate. *Eur J Cancer* (2002); **38:** 2435-2445.

70. Black WC, Welch HG. Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. *N Engl J Med* (1993); **328:** 1237-1243.

71. Etzioni R, Penson DF, Legler JM et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. *J Natl Cancer Inst* (2002); **94:** 981-990.

72. Helgesen F, Holmberg L, Johansson JE et al. Trends in prostate cancer survival in Sweden, 1960 through 1988: evidence of increasing diagnosis of nonlethal tumors. *J Natl Cancer Inst* (1996); **88:** 1216-1221.

73. Shen Y, Yang Y, Inoue LY et al. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. *J Natl Cancer Inst* (2005); **97:** 1195-1203.

74. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* (1985); **312:** 1604-1608.

75. Devine OJ, Louis TA, Halloran ME. Empirical Bayes methods for stabilizing incidence rates before mapping. *Epidemiology* (1994); **5:** 622-630.

76. Schaapveld M, Otter R, de Vries EG et al. Variability in axillary lymph node dissection for breast cancer. *J Surg Oncol* (2004); **87:** 4-12.

77. Jatoi I, Hilsenbeck SG, Clark GM et al. Significance of axillary lymph node metastasis in primary breast cancer. *J Clin Oncol* (1999); **17:** 2334-2340.

78. Moran T, Collins S, Gibbbs A et al. Survival of patients with colon cancer in Europe: a cautionary tale. *Colorectal Disease* (2000); **2:** 190-192.

79. Robinson D, Sankila R, Hakulinen T et al. Interpreting international comparisons of cancer survival: the effects of incomplete registration and the presence of death certificate only cases on survival estimates. *Eur J Cancer* (2007); **43:** 909-913.

80. The Canadian Institute for Health Information. Location plays role in cancer survival: study. http://www.cbc.ca/stories/2002/05/30/cancer_report020530 . 30-5-2002.

81. Cole P, Morrison AS. Basic issues in population screening for cancer. *J Natl Cancer Inst* (1980); **64:** 1263-1272.

82. Jacobson B, Mindell J, McKee M. Hospital mortality league tables. *BMJ* (2003); **326:** 777-778.

83. Efron B, Morris C. Data analysis using Stein's estimator and its generalizations. *Journal of American Statistical Association* (1975); **70:** 311-319.

84. Christiansen CL, Morris CN. Improving the statistical approach to health care provider profiling. *Ann Intern Med* (1997); **127:** 764-768.

85. Gibberd R, Pathmeswaran A, Burtenshaw K. Using clinical indicators to identify areas for quality improvement. *J Qual Clin Pract* (2000); **20:** 136-144.

86. Spiegelhalter DJ, Myles JP, Jones DR et al. Methods in health service research. An introduction to Bayesian methods in health technology assessment. *BMJ* (1999); **319:** 508-512.

87. Brenner H, Soderman B, Hakulinen T. Use of period analysis for providing more up-to-date estimates of long-term survival rates: empirical evaluation among 370 000 cancer patients in Finland. *Int J Epidemiol* (2002); **31:** 456-462.

88. Chiang CL. *Introduction to stochastic processes in biostatistics*. New York: John Wiley, 1968.

89. Ederer F, Heise H. *Instructions to IMB 650 programers in processing survival computations. Methodological note No. 10, End Results Evaluation Section*. Bethesda MD: National Cancer Institute, 1959.

90. Voutilainen ET, Dickman PW, and Hakulinen T. SURV2: Relative Survival Analysis Program. [Version 2.02ß]. 2000. Helsinki: Finnish Cancer Registry.

91. Suissa S. Relative excess risk: an alternative measure of comparative risk. *Am J Epidemiol* (1999); **150:** 279-282.

92. Cancer Strategies Group. Priorities for action in cancer control 2001-2003. 2001. Canberra, Australia, Commonwealth Department of Health and Aged Care.

93. Australian Council on Healthcare Standards. Determining the Potential to Improve the Quality of Care - ACHS Clinical Indicator Results for Australia and New Zealand 1998-2001. 2003. Sydney, Australian Council on Healthcare Standards.

94. Howley PP, Gibberd R. Using hierarchical models to analyse clinical indicators: a comparison of the gamma-Poisson and beta-binomial models. *Int J Qual Health Care* (2003); **15:** 319-329.

95. Supramaniam R, Smith DP, Coates MS et al. Survival from cancer in New South Wales in 1980 to 1995. 1999. Sydney, Australia, NSW Cancer Council.

96. Clinical Governance Unit. The National Colorectal Cancer Care Survey Australian clinical practice in 2000. 2002. Melbourne, Australia, National Cancer Control Initiative.

97. Accounts Commission for Scotland. Fighting the silent killer: optimising ovarian cancer management in Scotland. 1998. Edinburgh, Scotland, Accounts Commission for Scotland.

98. Karjalainen S. Geographical variation in cancer patient survival in Finland: chance, confounding, or effect of treatment? *J Epidemiol Community Health* (1990); **44:** 210-214.

99. Osnes K, Aalen OO. Spatial smoothing of cancer survival: a Bayesian approach. *Stat Med* (1999); **18:** 2087-2099.

100. Tracey E, Supramaniam R, and Chen W. Cancer in New South Wales: Incidence and Mortality 2001. 2003. Sydney, The Cancer Council New South Wales.

101. Australian Bureau of Statistics. *Information paper: 1996 Census Socio-Economic Indexes For Areas (SEIFA).* Canberra: ABS, 1998.

102. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer* (1996); **78:** 2004-2010.

103. Brenner H, Gefeller O. Deriving more up-to-date estimates of long-term patient survival. *J Clin Epidemiol* (1997); **50:** 211-216.

104. Dickman PW, Sloggett A, Hills M et al. Regression models for relative survival. *Stat Med* (2004); **23:** 51-64.

105. Jong KE, Smith DP, Yu XQ et al. Remoteness of residence and survival from cancer in New South Wales. *Med J Aust* (2004); **180:** 618-622.

106. Yu XQ, O'Connell DL, Gibberd RW et al. Estimating regional variation in cancer survival: a tool for improving cancer care. *Cancer Causes Control* (2004); **15:** 611-618.

107. Gibberd R, Hancock S, Howley P et al. Using indicators to quantify the potential to improve the quality of health care. *Int J Qual Health Care* (2004); **16 Suppl 1:** i37-i43.

108. Condon JR, Barnes T, Armstrong BK et al. Stage at diagnosis and cancer survival for Indigenous Australians in the Northern Territory. *Med J Aust* (2005); **182:** 277-280.

109. Kelley E, Moy E, Stryer D et al. The national healthcare quality and disparities reports: an overview. *Med Care* (2005); **43:** I3-I8.

110. Lemmens VE, van Halteren AH, Janssen-Heijnen ML et al. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* (2005); **16:** 767-772.

111. Armstrong K, O'Connell DL, Leong D et al. The New South Wales colorectal cancer care survey - Part 1 surgical management. 2004. Sydney, The Cancer Council New South Wales.

112. National Health and Medical Research Council. *Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer*. Canberra, Australia: AGPS, 1999.

113. Hodgson DC, Fuchs CS, Ayanian JZ. Impact of patient and provider characteristics on the treatment and outcomes of colorectal cancer. *J Natl Cancer Inst* (2001); **93:** 501-515.

114. Meagher AP. Colorectal cancer: is the surgeon a prognostic factor? A systematic review. *Med J Aust* (1999); **171:** 308-310.

115. Smith JA, King PM, Lane RH et al. Evidence of the effect of 'specialization' on the management, surgical outcome and survival from colorectal cancer in Wessex. *Br J Surg* (2003); **90:** 583-592.

116. McArdle CS, Hole DJ. Influence of volume and specialization on survival following surgery for colorectal cancer. *Br J Surg* (2004); **91:** 610-617.

117. Australian Institute of Health and Welfare. Health in rural and remote Australia. [AIHW]. 1998. Canberra, Australia, AIHW.

118. Pui CH. Childhood leukemias. *N Engl J Med* (1995); **332:** 1618-1630.

119. Horwich A, Mason M, Hendry W. Testicular tumours. In: Souhami RL, Tannock I, Hohenberger P, Horiot J-C, eds. *Oxford textbook of oncology*. New York: Oxford University Press, 2001: 2007-2035.

120. Diehl V, Mauch PM, Harris NL. Hodgkin's Disease. In: Devita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia, USA: Lippincott Williams and Wilkins, 2001: 2339-2387.

121. Tracey E, Roder D, Bishop J et al. Cancer in New South Wales: Incidence and Mortality 2003. 2005. Sydney, Cancer Institute NSW.

122. Parkin DM, Muir CS. Cancer Incidence in Five Continents. Comparability and quality of data. *IARC Sci Publ* (1992); 45-173.

123. Percy C, Van Holten V, Muir CS et al. *International classification of diseases for oncology*. Geneva, Switzerland: World Health Organisation, 1990.

124. Muir CS, Percy C. Cancer registration: principles and methods. Classification and coding of neoplasms. *IARC Sci Publ* (1991); 64-81.

125. Berry DA, Cronin KA, Plevritis SK et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* (2005); **353:** 1784-1792.

126. Kricker A, Farac K, Smith D et al. Breast cancer in New South Wales in 1972-1995: tumor size and the impact of mammographic screening. *Int J Cancer* (1999); **81:** 877-880.

127. Burton RC, Coates MS, Hersey P et al. An analysis of a melanoma epidemic. *Int J Cancer* (1993); **55:** 765-770.

128. Smith DP, Armstrong BK. Prostate-specific antigen testing in Australia and association with prostate cancer incidence in New South Wales. *Med J Aust* (1998); **169:** 17-20.

129. Law MG, Roberts SK, Dore GJ et al. Primary hepatocellular carcinoma in Australia, 1978-1997: increasing incidence and mortality. *Med J Aust* (2000); **173:** 403-405.

130. Burgess JR, Dwyer T, McArdle K et al. The changing incidence and spectrum of thyroid carcinoma in Tasmania (1978-1998) during a transition from iodine sufficiency to iodine deficiency. *J Clin Endocrinol Metab* (2000); **85:** 1513-1517.

131. Moertel CG, Fleming TR, Macdonald JS et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* (1990); **322:** 352-358.

132. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* (1998); **351:** 1451-1467.

133. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* (1998); **352:** 930-942.

134. National Breast Cancer Centre. National survey of women with early breast cancer: their perceptions of care (1997). 2004. Sydney, National Breast Cancer Centre.

135. McEvoy SP, Ingram DM, Byrne MJ et al. Breast cancer in Western Australia: clinical practice and clinical guidelines. *Med J Aust* (2004); **181:** 305-309.

136. Akaza H. Adjuvant goserelin improves clinical disease-free survival and reduces disease-related mortality in patients with locally advanced or localized prostate cancer. *BJU Int* (2004); **93:** 42-46.

137. D'Amico AV, Manola J, Loffredo M et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA: The Journal of the American Medical Association* (2004); **292:** 821-827.

138. Bill-Axelson A, Holmberg L, Ruutu M et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* (2005); **352:** 1977-1984.

139. Ries LA, Eisner MP, Kosary CL et al. *SEER Cancer Statistics Review, 1975-2002*. Bethesda, MD: National Cancer Institute. 2005.

140. DeVita VT, Jr., Simon RM, Hubbard SM et al. Curability of advanced Hodgkin's disease with chemotherapy. Long-term follow-up of MOPP-treated patients at the National Cancer Institute. *Ann Intern Med* (1980); **92:** 587-595.

141. McKelvey EM, Gottlieb JA, Wilson HE et al. Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. *Cancer* (1976); **38:** 1484-1493.

142. Alexanian R, Haut A, Khan AU et al. Treatment for multiple myeloma. Combination chemotherapy with different melphalan dose regimens. *JAMA: The Journal of the American Medical Association* (1969); **208:** 1680-1685.

143. McCredie M, Stewart J, Smith D et al. Observations on the effect of abolishing analgesic abuse and reducing smoking on cancers of the kidney and bladder in New South Wales, Australia, 1972-1995. *Cancer Causes Control* (1999); **10:** 303-311.

144. Young JL Jr, Roffers SD, Ries LAG et al. SEER Summary Staging Manual - 2000: Codes and Coding Instructions. NIH Pub. No. 01-4969. 2001. Bethesda, MD, National Cancer Institute.

145. Cooper GS, Yuan Z, Stange KC et al. The utility of Medicare claims data for measuring cancer stage. *Med Care* (1999); **37:** 706-711.

146. Jensen AR, Overgaard J, Storm HH. Validity of breast cancer in the Danish Cancer Registry. A study based on clinical records from one county in Denmark. *Eur J Cancer Prev* (2002); **11:** 359-364.

147. Liu WL, Kasl S, Flannery JT et al. The accuracy of prostate cancer staging in a population-based tumor registry and its impact on the black-white stage difference (Connecticut, United States). *Cancer Causes Control* (1995); **6:** 425-430.

148. Schouten LJ, Langendijk JA, Jager JJ et al. Validity of the stage of lung cancer in records of the Maastricht cancer registry, The Netherlands. *Lung Cancer* (1997); **17:** 115-122.

149. Yu XQ, O'Connell DL, Gibberd RW et al. A population-based study from New South Wales, Australia 1996-2001: area variation in survival from colorectal cancer. *Eur J Cancer* (2005); **41:** 2715-2721.

150. Vality Technology Incorporated. The INTEGRITY Data Re-engineering Environment User Guide (Version 3.6). 2000. Boston, USA, Vality Technology Incorporated.

151. Brameld KJ, Thomas MA, Holman CD et al. Validation of linked administrative data on end-stage renal failure: application of record linkage to a 'clinical base population'. *Aust N Z J Public Health* (1999); **23:** 464-467.

152. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* (1977); **33:** 159-174.

153. Coory M, Gibberd R. New measures for reporting the magnitude of small-area variation in rates. *Stat Med* (1998); **17:** 2625-2634.

154. Greenland S, Robins JM. Empirical-Bayes adjustments for multiple comparisons are sometimes useful. *Epidemiology* (1991); **2:** 244-251.

155. Morton AP, Dobson AJ. Assessing agreement. *Med J Aust* (1989); **150:** 384-387.

156. Shrout PE, Fleiss JL. Intraclass Correlations: Uses in Assessing Rater Reliability. *Psychol Bull* (1979); **86:** 420-428.

157. Phillips KA, Milne RL, Buys S et al. Agreement between self-reported breast cancer treatment and medical records in a population-based Breast Cancer Family Registry. *J Clin Oncol* (2005); **23:** 4679-4686.

158. Gulliford MC, Bell J, Bourne HM et al. The reliability of Cancer Registry records. *Br J Cancer* (1993); **67:** 819-821.

159. Jestin P, Pahlman L, Glimelius B et al. Cancer staging and survival in colon cancer is dependent on the quality of the pathologists' specimen examination. *Eur J Cancer* (2005); **41:** 2071-2078.

160. Johnson PM, Porter GA, Ricciardi R et al. Increasing negative lymph node count is independently associated with improved long-term survival in stage IIIB and IIIC colon cancer. *J Clin Oncol* (2006); **24:** 3570-3575.

161. Riley GF, Potosky AL, Klabunde CN et al. Stage at Diagnosis and Treatment Patterns Among Older Women With Breast Cancer: An HMO and Fee-for-Service Comparison. *JAMA: The Journal of the American Medical Association* (1999); **281:** 720-726.

162. Yu XQ, O'Connell DL, Gibberd RW et al. Trends in survival and excess risk of death after diagnosis of cancer in 1980-1996 in New South Wales, Australia. *Int J Cancer* (2006); **119:** 894-900.

Appendix

Publications relating to the thesis

Reprinted from *Cancer Causes and Control*, Volume 15, 2004, 611-618. Estimating regional variation in cancer survival: a tool for improving cancer care. Yu XQ, O'Connell DL, Gibberd RW, Smith DP, Dickman PW, Armstrong BK. Copyright (2004), with kind permission from Springer Science and Business Media.

Reprinted from *European Journal of Cancer*, Volume 41, 2005, 2715-2721. A population-based study from New South Wales, Australia 1996-2001: area variation in survival from colorectal cancer. Yu XQ, O'Connell DL, Gibberd RW, Armstrong BK. Copyright (2005), with kind permission from Elsevier Ltd.

Reprinted from *International Journal of Cancer*, Volume 119, 2006, 894-900. Trends in survival and excess risk of death after a diagnosis of cancer in 1980 to 1996 in New South Wales Australia. Yu XQ, O'Connell DL, Gibberd RW, Coates AS, Armstrong BK. Copyright (2006), with kind permission from Wiley-Liss Inc. a subsidiary of John Wiley & Sons, Inc.

Cancer Causes and Control **15**: 611–618, 2004.

Estimating regional variation in cancer survival: a tool for improving cancer care

Xue Q. Yu[1,*], Dianne L. O'Connell[1], Robert W. Gibberd[2], David P. Smith[1], Paul W. Dickman[3] & Bruce K. Armstrong[4]

[1]*Cancer Epidemiology Research Unit, The Cancer Council New South Wales, Australia;* [2]*Health Services Research Group, Faculty of Medicine and Health Sciences, University of Newcastle, Australia;* [3]*Department of Medical Epidemiology, Karolinskat Institutet, Sweden;* [4]*School of Public Health, The University of Sydney, Australia*

Received 25 June 2003; accepted in revised form 9 March 2004

Key words: cancer, empirical Bayes methods, regional variation, relative survival.

Abstract

Objective: To improve estimation of regional variation in cancer survival and identify cancers to which priority might be given to increase survival.
Methods: Survival measures were calculated for 25 major cancer types diagnosed in each of 17 health service regions in New South Wales, Australia, from 1991 to 1998. Region-specific risks of excess death due to cancer were estimated adjusting for age, sex, and extent of disease at, and years since, diagnosis. Empirical Bayes (EB) methods were used to shrink the estimates. The additional numbers of patients who would survive beyond five years were estimated by shifting the State average risk to the 20th centile.
Results: Statistically significant regional variation in the shrunken estimates of risk of excess death was found for nine of the 25 cancer types. The lives of 2903 people (6.4%) out of the 45,047 whose deaths within 5 years were attributable to cancer could be extended with the highest number being for lung cancer (791).
Conclusions: The EB approach gives more precise estimates of region-specific risk of excess death and is preferable to standard methods for identifying cancer sites where gains in survival might be made. The estimated number of lives that could be extended can assist health authorities in prioritising investigation of and attention to causes of regional variation in survival.

Introduction

Survival is an indicator of the quality of cancer patient management. An analysis of cancer survival across regions can identify possible differences in the performance of regional health services with regard to cancer care. Identifying cancer types for which there is the greatest potential for increasing survival so that they can be targeted for action is a key element of such an analysis.

Place of residence is an important determinant of survival from cancer [1–4]. Regional variation in cancer survival may be due to a number of factors, including access to primary health care, the availability of diagnostic and treatment facilities and the treatment actually given. It may also be an artefact. While earlier diagnosis due to screening or improved diagnostic methods may truly increase survival, it may also just add lead time or extend average survival through diagnosis of cancers that would not otherwise have been diagnosed within the patients lifetimes [5, 6]. Sampling error may also produce spurious or spuriously large variation, particularly when the regions compared have small populations.

The standard approaches usually estimate regional variation by testing the hypothesis that all regional effects are identical, comparing extreme regions to the average, ranking the regions and focussing on the poor performers. The estimates from such approaches lack precision because of large sampling error. Consequently, use of these estimates may introduce errors in decision making for health service planning. Comparisons of survival among regions by producing a 'league table' is not very useful for decisions about where resources

* Address correspondence to: Xue Q. Yu, Cancer Epidemiology Research Unit, The Cancer Council New South Wales, P. O. Box 572, Kings Cross, NSW 1340, Australia; Ph.: +61-2-93341851; Fax: +61-2-93341778; E-mail: xueqiny@nswcc.org.au

might best be targeted to improve survival because it focuses on the regional differences rather than the cancers for which the greatest gains might be made [7].

There is, therefore, a need to develop more meaningful and useful measures of regional variation in survival. Empirical Bayes (EB) methods can be used to estimate a prior distribution for region-specific risks of excess death and to 'shrink' the distribution of the observed estimates, bringing each estimate closer to the global mean, roughly in inverse proportion to the sample size on which it is based. Shrinkage estimators have become popular and can be interpreted in many ways: they minimise the mean square error of the parameter estimates across all the regions [8]; take account of the regression to the mean for individual regions [9]; and take account of the variation in sample size [10]. The Bayesian approach also provides a posterior distribution for the parameters for each region, whose expectation is the shrunken estimator [11].

This study aimed to explore the use of EB methods to produce more precise and robust estimators for regional variation in cancer survival. Estimates of the number of excess deaths due to cancer and lives that might be extended were also obtained to identify cancer types for which targeted action to increase survival has the greatest potential to improve outcome.

Materials and methods

Data

Data were obtained from the population-based New South Wales (NSW) Central Cancer Registry, Australia, for 25 major types of cancer diagnosed between 1991 and 1998. Notification of cancer is a statutory requirement in NSW. Data on the general population mortality rates needed to calculate relative survival ratios were obtained from the Australian Bureau of Statistics.

The first occurrence of a primary cancer for an individual was included in the survival analysis. Cases notified by death certificate only or identified at post-mortem, cases with place of residence information not available, or age at diagnosis greater than 89 years, were excluded from the analysis.

There are 17 Area Health Services in NSW; nine cover the major urban regions and contain populations ranging from 270,000 to 750,000 and eight cover the rural regions with populations ranging from 50,000 to 250,000. Assignment of cases to Health Service regions for the purpose of analysis was based on their place of residence at the time of diagnosis of their cancer.

All cases were followed up to December 2000 to determine survival status. People with cancer who were not known to be dead were matched against death records from the State Registrar of Births, Deaths and Marriages and the National Death Index. A modification of the period method described by Brenner *et al.* [12] was used to compute five-year relative survival based on cancers diagnosed in the period 1991–1998 and deaths in the period 1994–2000. Patients diagnosed in 1994 and 1995 had been followed-up for the full five years, while the more recently diagnosed cases (1996–1998) had not. To supplement the experience of those diagnosed in 1994–1998, the survival experience in 1996–1998 of patients diagnosed in 1991–1993 was included in the analysis. Thus the fifth year of survival experience from patients diagnosed in 1991 was included in the analysis, together with the fourth and fifth years from patients diagnosed in 1992 and the third, fourth and fifth years from those diagnosed in 1993. The end of follow-up was the date of death for those who died within five years of diagnosis and before the end of 2000; those who had not died by the end of 2000 and had not been followed up for 5 years were censored.

Statistical methods

Relative survival

Relative survival is the ratio of the observed proportion surviving in a group of patients to the expected proportion that would have survived in a comparable group of people (with, for example, the same distribution by age, sex, and geographical area) from the general population [13].

The survival time was measured from the month of diagnosis to the date of death or censoring and was grouped into annual intervals for this analysis. Observed survival was estimated by the life table method [14]. Expected survival was estimated using the Ederer and Heise method [15], which is also a life table method. The region-specific population life tables for the period 1994–1998 were used for these analyses. All-cause mortality data and the NSW population by single year of age, sex and region of residence, were used to construct the region-specific life tables.

In our analyses, cumulative relative survival was calculated as the ratio of the cumulative observed survival proportion to the cumulative expected survival proportion as described in the SURV2 computer program manual [16].

Relative excess risk (RER) of death

If cause of death was accurately known for all patients it would be possible to directly estimate the cancer-specific

fatality rates in each region and compare these estimates to the estimates for NSW as a whole by calculating rate ratios. However, cause of death is not reliably reported for all cancer patients and even with access to medical records it is difficult to classify each patient's death into one of the two categories 'entirely due to cancer' or 'entirely unrelated to cancer'. A preferable approach is to estimate the cumulative death rate due to all causes in the cancer patients and subtract from it an estimate of the death rate in a similar population without a diagnosis of cancer and thus gain an estimate of the 'excess cumulative death rate' or 'excess risk of death'. The major advantages of this measure (and its survival analogy, relative survival) are that information on cause of death is not required and it provides a measure of the excess death rate experienced by patients diagnosed with cancer, irrespective of whether the excess is directly or indirectly attributable to the cancer. Thus we estimated the excess risk of death for each cancer type in each region and then compared it with an estimate of the excess risk of death for the same cancer in the State as a whole to produce an estimate of the RER of death for that cancer in each region [17].

Statistical modelling

To adjust for differences between the health service regions in variables other than treatment that might affect the survival of cancer patients, a Poisson regression model of excess risk of death during the first five years was constructed for each type of cancer and included age group, years since diagnosis, sex (where applicable), and spread of disease at diagnosis (where applicable) as main effects and the interaction between age group and years since diagnosis where possible. For most cancer sites, age was divided into four groups: 15–44, 45–59, 60–74 and 75–89 years; these age groups were modified for cancer of the testis. Spread of disease at diagnosis was classified into four broad categories: localised, regional (including adjacent organs and regional lymph nodes), distant and unknown. The interaction term was included to allow for non-proportional hazards across the five years of follow-up; it was, however, removed from the model for testis cancer to achieve convergence. For cancers of the lung, breast and prostate, an additional interaction term between spread of disease and years since diagnosis was added to the model to improve the goodness-of-fit. Nine models fitted the data well with very large p-values for the goodness-of-fit statistic, another six were reasonable fits with p-values ranging from 0.06 to 0.33, and three had p-values just less than 0.05. The remaining seven models did not fit the data well; the p-values for the goodness-of-fit statistic were very low.

EB approach

To estimate the systematic regional variation in survival for each cancer type, we fitted a model for the RER using the SAS procedure *NLIN*. To stabilise the estimates of region-specific risk we applied an EB method to get shrunken estimators for each region. We assumed that the region-specific excess risks followed a Gamma distribution, with mean μ, and variance σ^2. The shrunken estimators combined region-specific risk with the results from all other regions as in the following formula:

$$\text{Shrunken estimator}(\theta) = (\text{Obs} + \mu^2/\sigma^2)/(\text{Exp} + \mu/\sigma^2)$$

where Obs and Exp are the observed and expected numbers of excess deaths, μ is the average excess risk for all regions (global mean) and σ is its standard deviation for a given cancer site. The local estimates (Obs/Exp) are shrunken towards the global mean (set as 1.0). The amount of shrinkage varies according to the value of σ^2 and the value of Obs and Exp for each region. If the region has a large population then this approach will move the local estimates very little, whereas if the region is small then this approach will move the local estimate considerably closer to the global mean. If the variance (σ^2) is large, the shrunken estimator will remain similar to the local estimate.

Hypothesis test

The hypothesis test of no regional variation (*i.e.*, $\sigma = 0$) was tested for each cancer type by comparing the statistic calculated as the ratio of σ and its standard error ($z = \sigma/\text{se}(\sigma)$) with the standard normal distribution. A p-value of 0.05 or less from the hypothesis test was taken to indicate statistically significant regional variation in the RER for the given cancer.

Lives that would be extended

To show the importance of regional variation in survival and identify the cancer sites in which improvement in care would result in large gains in survival, we estimated the number of lives that would be extended beyond 5 years after diagnosis in people with each cancer type if the State average risk of excess death was shifted to the 20th centile of the distribution of region-specific risks of excess death. The number of lives that might be extended beyond 5 years was then estimated using the following formula:

$$\text{Number of lives that might be extended} = \text{Obs} \times (1 - \mu_{20\text{th}\%}) \times \sigma/SD(\mu_{\text{shrunken}})$$

where $\mu_{20\text{th}\%}$ is the 20th centile of the empirical distribution and $\text{SD}(\mu_{\text{shrunken}})$ is the standard deviation

Table 1. Regional variation in 5-year relative survival (%), crude and shrunken RER of death and test for regional variation in 1994–2000 for 25 cancers in NSW Australia

Cancer type	Number of new cases	State-wide 5-year relative survival	Range of regional variation in relative survival	Range of variation in RER[a] of death		*p*-Value[b]
				Crude	Shrunken	
Head and neck	5553	55.2	32.6–60.7	0.89–1.63	1.00–1.00[c]	1.00
Oesophagus	1652	16.3	9.2–27.4	0.66–1.99	0.94–1.07	0.31
Stomach	3588	25.3	12–32.2	0.83–1.32	0.92–1.04	0.08
Colon	15280	60.4	51.5–66.5	0.88–1.36	0.89–1.19	<0.001
Rectum	8768	60.2	49.7–64.4	0.87–1.50	0.98–1.01	0.69
Liver	1051	12.6	4.0–36.3	0.62–1.75	0.79–1.33	0.009
Gallbladder	1064	18.8	7.0–27.6	0.46–1.55	0.95–1.03	0.41
Pancreas	2795	5.4	2.4–11.0	0.87–1.36	0.92–1.07	0.12
Lung	13992	13.2	8.9–16.5	0.90–1.16	0.91–1.09	0.03
Melanoma of the skin	18574	91.0	86.8–92.9	0.87–1.60	0.92–1.35	<0.001
Mesothelioma[d]	785	15.1	8.7–23.4	0.80–1.33	0.97–1.06	0.45
Breast (female)	24316	84.9	79.6–88.3	0.79–1.45	0.83–1.12	<0.001
Cervix	2419	72.6	40.9–78.8	0.62–1.89	0.90–1.08	0.25
Body of uterus	3019	79.8	74.2–86.2	0.70–1.38	0.86–1.12	0.13
Ovary	2278	39.5	20.9–57.6	0.63–1.76	0.82–1.22	0.006
Prostate	25713	85.2	76.0–88.6	0.82–1.63	0.85–1.43	<0.001
Testis	1411	95.6	84.3–102.0	0.00–3.93	1.00–1.00[c]	1.00
Bladder	4753	62.0	52.1–69.5	0.82–1.38	0.91–1.07	0.12
Kidney	4740	58.4	48.6–69.5	0.75–1.30	1.00–1.00[c]	1.00
Brain	2376	18.4	12.0–26.4	0.64–1.34	0.94–1.05	0.23
Thyroid	2400	94.0	76.2–107.1	0.00–3.26	0.61–1.46	0.08
Non-Hodgkin lymphoma	6677	54.3	45.2–68.0	0.68–1.31	0.92–1.07	0.15
Hodgkin's disease	908	78.0	45.8–93.7	0.21–2.43	1.00–1.00[c]	1.00
Multiple myeloma	2035	34.8	18.6–51.5	0.40–1.57	0.87–1.20	0.02
Leukaemia	4420	36.5	27.5–68.1	0.50–1.35	0.87–1.17	0.01

[a] The state average excess risk is the reference.
[b] *p*-Value for test for regional variation.
[c] Very little regional variation was observed following shrinkage.
[d] Only 2-year relative survival was calculated due to small numbers.

of the distribution of the shrunken estimators. In this way, we could provide an estimate of the importance of the regional variation in survival for each cancer.

Results

The commonest cancers during the study period were cancers of the prostate (25,713), female breast (24,316) and melanoma of the skin (18,574) (Table 1). Of the 25 chosen types of cancer, mesothelioma was the least common (785). These 25 types accounted for 92.5% of all cancers in the study period.

Regional variation in the five-year relative survival ratios and crude and shrunken RERs of death after a diagnosis of cancer for the 25 types of cancer are summarised in Table 1. The impact of the EB method on the variation in RER of death is readily seen in this table, and the inverse association, generally, between the number of people with each cancer type and the amount of shrinkage. For example, for cancer of the testis, a relatively uncommon cancer (1411 cases), the RERs ranged from 0.00 to 3.9 while the shrunken estimates showed little variation. Statistically significant variation in RER was found for nine of the 25 cancer types analysed – cancers of the colon, liver, lung, female breast, ovary, prostate, and melanoma of the skin, multiple myeloma and leukaemia.

A comparison of the un-shrunken and shrunken regional estimates of RER of death for liver cancer is shown in Figure 1. The shrunken estimates have narrower confidence intervals than the crude estimates and regions with wide 95% confidence intervals and extreme values have been shrunk more.

The estimated number and percent of lives that might be extended for the 25 cancers are shown in Table 2. The number of lives that might be extended depends on both the regional variation in survival (σ) and the number of excess deaths from the given cancer. The highest number of lives that might be extended (791) was in patients diagnosed with lung cancer although the regional variation was modest for this cancer. The estimated pro-

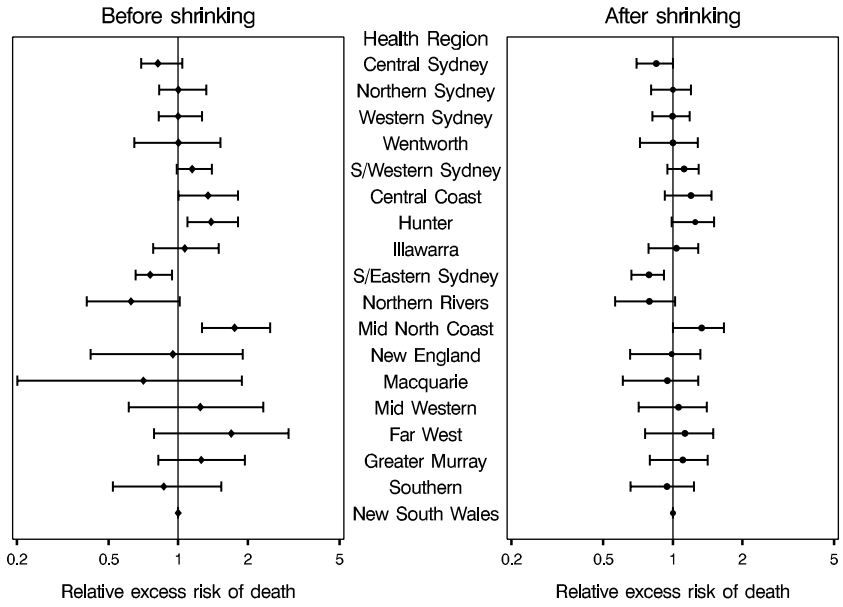

Fig. 1. RER of death in 1994–2000 for patients with a diagnosis of liver cancer by health service region in NSW Australia before and after shrinkage.

Table 2. Number of lives that might be extended beyond 5 years of diagnosis and percent of excess cancer deaths in 1994–2000 for 25 cancers in NSW, Australia

Cancer type	Number of excess deaths	Sigma (σ)	Number of lives that might be extended	% of total excess deaths from this cancer
Lung	10732	0.07	791	7.4
Colon	4305	0.10	296	6.9
Leukaemia	1953	0.11	249	12.8
Prostate	2565	0.18	228	8.9
Non-Hodgkin lymphoma	2235	0.07	159	7.1
Pancreas	2440	0.07	152	6.2
Ovary	1074	0.15	119	11.1
Liver	808	0.20	119	14.7
Breast (female)	2467	0.10	110	4.4
Melanoma of the skin	1096	0.18	101	9.2
Multiple myeloma	1002	0.13	97	9.6
Oesophagus	1189	0.07	92	7.8
Stomach	2205	0.06	82	3.7
Rectum	2472	0.03	66	2.7
Bladder	1283	0.07	52	4.0
Brain	1514	0.06	44	2.9
Thyroid	100	0.42	39	38.6
Mesothelioma*	612	0.07	36	5.8
Cervix	444	0.10	34	7.6
Gallbladder	757	0.06	22	2.9
Body of uterus	406	0.13	14	3.5
Head and neck	1799	0.0005	1	0.1
Kidney	1412	0.0007	1	0.1
Hodgkin's disease	135	0.002	0	0.2
Testis	41	0.0002	0	0.0
All cancers	45,047	0.07	2903	6.4

[a] Number of lives that might be extended beyond 2 years of diagnosis and % of excess deaths.

portion of lives that might be extended beyond five years out of the total excess deaths for an individual cancer in the five years after diagnosis (lives lost within five years) was largest for thyroid cancer (39 lives that might be extended being 38.6% of the excess deaths).

Discussion

We found statistically significant variation in the shrunken estimates of RER of death across 17 health service regions in NSW for nine of 25 cancer types – cancers of the colon, liver, lung, female breast, ovary, prostate, and melanoma of the skin, multiple myeloma and leukaemia. All of these cancer types, except melanoma and multiple myeloma, were also in the 'top nine' for numbers of lives that might be extended; the two exceptions were in positions 10 and 11.

We interpret these findings as indicating that the variation among regions in the excess risks of death from the nine cancers in which it was statistically significant is probably real and, therefore, that the outcomes of these cancers could be improved through attention to the causes of regional variation. In addition, because spread of disease at diagnosis was included in the statistical models from which excess risks of death were estimated, the variation in outcome we have described points to a need for improvement in cancer treatment services rather than in the earliness of diagnosis of these cancers. When spread of disease was omitted from the models (results not shown) there was significant regional variation for stomach cancer in addition to the same nine cancers. This suggests that variation in earliness of diagnosis may be an important contributor to variation in stomach cancer survival. We note also that our use of 'statistical significance' ($p < 0.05$) to identify potentially meaningful findings to some extent arbitrary. It does, though, acknowledge the reality that 'chance' contributes to variation in survival between regions and should be taken into account when deciding where action to improve survival might be targeted.

Further, priority in improving cancer services should be given to those of the nine types of cancer identified as having statistically significant variation with the highest estimates of lives that might be extended, all other things being equal. In this respect, lung cancer stands out with 791 lives that might be extended, followed by cancer of the colon, leukaemia and cancer of the prostate with 296, 249 and 228 lives that might be extended respectively. In addition, however, knowledge of what interventions would be effective in improving cancer services, their feasibility and cost effectiveness and the equity of their effects would also have to be taken into account when determining priorities [18].

It could be argued that having identified significant variation and a large number of lives that might be extended, the regions with the highest shrunken RERs of death should be the focus of attention. For example, for cancer of the liver, for which RER of death showed statistically significant variation among regions and was ranked eighth in number of lives that might be extended attention might be turned to the regions with the highest shrunken RERs of death: Central Coast, Hunter and Mid North Coast regions, which are contiguous coastal regions immediately to the north of Sydney (Figure 1). However, if their RERs of death from liver cancer had been 1.0 (i.e., the same as in NSW as a whole) only 25 lives would have been extended beyond five years in the study period; whereas, if the State mean could be shifted to 0.89, which is the 20th centile of the empirical distribution across regions, this number would have been 119. Thus a whole-of-State rather than an individual region approach to improving services would probably be more effective. Examining the variation in the shrunken estimates of RER between regions and the reasons underlying it though, may still assist in identifying which whole-of-State approaches might achieve the greatest gains.

While use of the 20th centile to determine the potential gains that would occur if this risk could be achieved as the State average is arbitrary, the 20th centile has been used since it is a value that is more likely to be achievable [10, 19, 20] than say the 5th centile [1].

There are some limitations in our data and the analysis methods used. The data on spread of cancer at diagnosis were provided by hospital medical records departments and may not be accurate, although they are generally very highly predictive of survival [21]. In addition no data on stage were available for cancers like leukaemia, lymphomas and multiple myeloma for which the classification of spread of disease is of little relevance. Inaccuracy in the data on spread of cancer at diagnosis would reduce the capacity to remove from the regional variation in RERs of death that variation due to regional differences in screening for, and early diagnosis of, cancer. Thus the inference that any variation observed was due mainly to variation in cancer treatment may not be correct. More accurate data on stage at diagnosis of cancer would be highly desirable for analyses such as these but are rarely available at the whole population level. It is noteworthy that when spread of disease at diagnosis was omitted from the statistical models, the results regarding regional variation in survival were very similar.

The shrinkage of the region-specific excess risks to the State average risk, especially for remote regions with small populations may be excessive since the aggregation of widely different regions in the State average may make its distribution an implausible prior distribution for some regions. The models used in these analyses assume that the regions have RER ratios that are exchangeable: that is, *a priori*, the RER for a region could be high or low. It can be argued that the regions do differ and their ratios are not exchangeable. However, in the absence of any regional covariates that could be included in the model, there is no alternative but to assume they are exchangeable. Given this assumption, the results for all regions are used to improve the estimate for each individual region.

There is some independent evidence of remediable variation in quality of care in NSW for some of the cancers we have pinpointed above. Specifically, an Australian national survey of patterns of care for colorectal cancer in 2000, in which patients in NSW made up 30% of patients whose care was surveyed, found that the patients' care including the type of operation performed varied significantly according to the patients' place of residence and many patients were not treated in accord with the recommended guidelines [22]. Further in a study linking cancer registry records of women diagnosed with ovarian cancer in NSW in 1993–1996 to hospital separation records, women experienced a higher risk of death if they were first admitted to a public hospital other than a public principal referral hospital rather than to a principal referral hospital or a private hospital or if they were treated in that admission by a practitioner other than a gynaecologist, surgeon or oncologist rather than by one of these more appropriately specialised practitioners (Tracey and Armstrong, personal communication). These results suggest that the outcome of care for ovarian cancer in NSW could be improved by consistently ensuring early referral to a relevantly specialised practitioner or major referral centre, as recommended in published guidelines [23].

While regional variation in cancer survival has been reported from many other countries, such as the USA [2, 24], Canada [4], England [25], Finland [26], Scotland [3, 27], Italy [28] and Denmark [29], and place of residence has been found to be an important determinant of survival for a number of different cancer types, including breast [2–4], lung [25, 29], colon, rectum, uterus and prostate [2], we know of no previous analysis that has been specifically oriented towards identifying the cancers incident within a particular region for which improvements in cancer care should be given priority because of the probable existence and size of the gains in survival that could be made. Dickman *et al*. [1] and Gibberd *et al*. [10] have elucidated the principles on which our analysis is based and we have taken their work further forward by extending the EB gamma-Poisson model to analysing variation in regional relative survival ratios and by including the stage of the cancer at diagnosis to control for that source of potential variation. We plan to use a more complete description of the results of this work as the basis for targeted improvement of cancer services in NSW.

Acknowledgements

We would like to thank the NSW Central Cancer Registry for providing the data. The NSW Central Cancer Registry is funded by the NSW Department of Health and managed by The Cancer Council New South Wales. Bruce Armstrong's research is supported by a University of Sydney Medical Foundation Program Grant.

References

1. Dickman PW, Gibberd RW, Hakulinen T (1997) Estimating potential savings in cancer deaths by eliminating regional and social class variation in cancer survival in the Nordic countries. *J Epidemiol Commun Health* **51**: 289–298.
2. Farrow DC, Samet JM, Hunt WC (1996) Regional variation in survival following the diagnosis of cancer. *J Clin Epidemiol* **49**: 843–847.
3. Twelves CJ, Thomson CS, Dewar JA, Brewster DH (2001) Variation in survival of women with breast cancer: Health Board remains a factor at 10 years. *Br J Cancer* **85**: 637–640.
4. The Canadian Institute for Health Information. Location plays role in cancer survival: study. Available at: http://www.cbc.ca/stories/2002/05/30/cancer_report020530, accessibility verified June 13, 2002.
5. Cole P, Morrison AS (1980) Basic issues in population screening for cancer. *J Natl Cancer Inst* **64**: 1263–1272.
6. Black WC, Welch HG (1993) Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. *N Engl J Med* **328**: 1237–1243.
7. Jacobson B, Mindell J, McKee M (2003) Hospital mortality league tables: question what they tell you-and how useful they are. *BMJ* **326**: 777–778.
8. Efron B, Morris C (1975) Data analysis using Stein's estimator and its generalizations. *J Am Stat Assoc* **70**: 311–319.
9. Christiansen CL, Morris CN (1997) Improving the statistical approach to health care provider profiling. *Annal Int Med* **127**: 764–768.
10. Gibberd R, Pathmeswaran A, Burtenshaw K (2000) Using clinical indicators to identify areas for quality improvement. *J Qual Clin Practice* **20**: 136–144.

11. Spiegelhalter DJ, Myles JP, Jones DR, *et al.* (1999) An introduction to Bayesian methods in health technology assessment. *BMJ* **319**: 508–512.
12. Brenner H, Soderman B, Hakulinen T (2002) Use of period analysis for providing more up-to-date estimates of long-term survival rates: empirical evaluation among 370,000 cancer patients in Finland. *Int J Epidemiol* **31**: 456–462.
13. Ederer F, Axtell LM, Cutler SJ (1961) The relative survival rate: a statistical methodology. *Natl Cancer Inst Monograph* **6**: 101–121.
14. Chiang CL (1968) *Introduction to Stochastic Processes in Biostatistics*. New York: John Wiley.
15. Ederer F, Heise H (1959) Instructions to IMB 650 programmers in processing survival computations. *Methodological Note No. 10, End Results Evaluation Section*. Bethesda, MD: National Cancer Institute.
16. Voutilainen ET, Dickman PW, Hakulinen T (2000) *SURV2: Relative Survival Analysis Program. Software Manual (Version 2.02β)*. Helsinki: Finnish Cancer Registry.
17. Suissa S (1999) Relative excess risk: an alternative measure of comparative risk. *Am J Epidemiol* **150**: 279–282.
18. Cancer Strategies Group (2001) *Priorities for Action in Cancer Control 2001–2003*. Canberra: Commonwealth of Australia, pp. 9–12.
19. Howley P, Gibberd R (2003) Using hierarchical models to analyse clinical indicators: a comparison of the gamma-Poisson and beta-binomial models. *Int J Qual Health Care* **15**: 919–929.
20. Australian Council on Healthcare Standards (2003) *Determining the Potential to Improve the Quality of Care,* 3rd edn. ACHS Clinical Indicator Results for Australia and New Zealand 1998–2001. Sydney: The Australian Council on Healthcare Standards.
21. Supramaniam R, Smith DP, Coates MS, Armstrong BK (1999) *Survival from Cancer in New South Wales in 1980 to 1995*. Sydney: NSW Cancer Council.
22. Clinical Governance Unit (2002) *The National Colorectal Cancer Care Survey. Australian Clinical Practice in 2000*. Melbourne: National Cancer Control Initiative.
23. Accounts Commission for Scotland (1998) *Fighting the Silent Killer: Optimising Ovarian Cancer Management in Scotland*. Edinburgh: Accounts Commission for Scotland.
24. Goodwin JS, Freeman JL, Mahnken JD, Freeman DH, Nattinger AB (2002) Geographic variations in breast cancer survival among older women: implications for quality of breast cancer care. *J Gerontol A Biol Sci Med Sci* **57**: M401–M406.
25. Cartman ML, Hatfield AC, Muers MF, Peake MD, Haward RA, Forman D (2002) Lung cancer: district active treatment rates affect survival. *J Epidemiol Commun. Health* **56**: 424–429.
26. Karjalainen S (1990) Geographical variation in cancer patient survival in Finland: chance, confounding, or effect of treatment? *J Epidemiol Community Health* **44**: 210–214.
27. Campbell NC, Elliott AM, Sharp L, Ritchie LD, Cassidy J, Little J (2000) Rural factors and survival from cancer: analysis of Scottish cancer registrations. *Br J Cancer* **82**: 1863–1866.
28. Gatta G, Buiatti E, Conti E, *et al.* (1997) Variations in the survival of adult cancer patients in Italy. *Tumori* **83**: 497–504.
29. Madsen FF, Norskov B, Frolund L, Hanash JA (2002) Lung cancer: survival rate differences in Danish counties. Survival analysis of 33,838 patients during the period 1984–1998. *Ugeskr Laeger* **164**: 483–487.

ELSEVIER

European Journal of Cancer 41 (2005) 2715–2721

European Journal of Cancer

www.ejconline.com

A population-based study from New South Wales, Australia 1996–2001: Area variation in survival from colorectal cancer

Xue Q. Yu [a,*], Dianne L. O'Connell [a], Robert W. Gibberd [b], Bruce K. Armstrong [c]

[a] *Cancer Epidemiology Research Unit, The Cancer Council New South Wales, P.O. Box 572, Kings Cross, Sydney, NSW 2011, Australia*
[b] *Health Service Research Group, Faculty of Health, University of Newcastle, Newcastle, NSW 2308, Australia*
[c] *School of Public Health, The University of Sydney, Sydney, NSW 2006, Australia*

Received 11 April 2005; received in revised form 16 May 2005; accepted 20 May 2005
Available online 17 October 2005

Abstract

In this study, we have investigated the impact of area of residence on survival from colon and rectal cancer. Relative survival and relative excess risk of death from cancer were calculated for each of 17 health areas in New South Wales, Australia. There were statistically significant differences in survival across areas for both cancers after adjusting for demographic factors. The variation remained for colon cancer but was reduced for rectal cancer after adjustment for spread of disease at diagnosis. This persistent variation in colon cancer survival suggests that variation in treatment contributes to it, and there is separate evidence for such variation. Of the 7186 patients whose deaths within five years were attributable to colorectal cancer, 784 could have had their survival increased to more than five years if the excess risk of death in all areas was reduced to the 20th centile of its distribution. Estimates such as this can assist in prioritising improvements in cancer services.

Keywords: Colorectal cancer; Regional variation; Relative survival; Australia

1. Introduction

Over the last two decades, important improvements in survival for colorectal cancer have been observed. These improvements may be attributable to earlier diagnosis, improved treatment or both. New and improved surgical techniques and adjuvant therapy developed in the early 1990s have probably played an important role [1,2]. However, these developments may not have been applied universally in clinical practice and this may be reflected in geographical variation in colorectal cancer outcomes.

Geographic variation in survival from colorectal cancer has been reported in many countries [3–5]. Survival from colorectal cancer was found to vary markedly between European countries and between states of the USA [3,4]. Variation in survival from colorectal cancer across districts in southern England was found to persist after adjusting survival rates for stage of disease, hospital size and surgery type [5]. A number of factors make it difficult to interpret this observed geographical variation. It is well established that the prognosis of colorectal cancer is strongly associated with spread of disease at diagnosis and treatment. But it is not easy to disentangle the effect of treatment from that of early diagnosis unless stage of disease at diagnosis can be controlled in the analysis. This has rarely been done in population-based studies of cancer outcome [6].

This study aimed to investigate the influence of place of residence at diagnosis of colorectal cancer on survival, while adjusting for demographic and clinical factors such as age, sex, length of follow-up and spread

* Corresponding author. Tel.: +61 2 9334 1851; fax: +61 2 9334 1778.
E-mail address: xueqiny@nswcc.org.au (X.Q. Yu).

0959-8049/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2005.05.018

of disease at diagnosis (a measure of stage) by using data from an Australian population-based cancer registry.

2. Patients and methods

2.1. Study population

Data were provided by the New South Wales (NSW) Central Cancer Registry, a population-based cancer registry which covers the whole state of NSW, Australia with a population of approximately 6.6 million. Notification of cancer has been a statutory requirement for all NSW public and private hospitals, radiotherapy departments and nursing homes since 1972, and for pathology departments since 1985 [7]. Only first occurrences of primary colorectal cancer in people between 15 and 89 years of age at diagnosis were included. Cases notified by death certificate only or first identified at post-mortem were excluded from analyses. All patients diagnosed during 1992–2000 were followed for survival up to 31 December 2001.

Spread of cancer at diagnosis is obtained by the Registry from statutory notification forms and from pathology reports and classified as localised (confined to tissue or organ of origin), locally advanced (spread to adjacent organs or tissues), regional (spread to regional lymph nodes), distant (distant metastases) or unknown stage (no information available). Coding was done either by medical coders in the hospitals who notified the registry, or by medical coders in the registry who used pathology, in-patient and additional reports to determine stage. During the period of this study, the State of NSW was divided into 17 geographically defined Area Health Services; nine covered the major urban areas with larger populations ranging from 270 000 to 750 000 and eight were rural areas with populations ranging from 50 000 to 250 000. The assignment of cancer patients to an Area Health Service was based on their place of residence at the time of diagnosis.

An indicator of socio-economic status (SES) was also used in the analysis. It is a summary measure of educational and occupational levels of communities derived from the 1996 population Census [8]. An area with a high score on this index would have high concentrations of people with higher education and people employed in the higher skilled occupations and *vice versa*. The index values for each Local Government Area (LGA) in NSW were grouped into quintiles. The residential address recorded at the time of diagnosis was used to allocate each case to an LGA and to its corresponding SES quintile.

2.2. Data analysis

Variation in stage distribution between areas was assessed for colon and rectal cancers separately.

As information on cause of death may not be accurate in the Registry data, we computed relative survival to correct for mortality from competing causes of death. Five-year relative survival was estimated for each Area Health Service using a modified period analysis. The period method has been described in detail elsewhere and is based on calendar year of survival rather than year of diagnosis (cohort method) [9,10]. It focuses on a recent time interval (1996–2001) in which each patient's survival experience is observed and excludes short-term survival of patients diagnosed before the start of the interval (diagnosed 1992–1995 and dying before 1996) but includes their long-term survival within the period. Short-term survival of more recently diagnosed patients (those diagnosed between 1996 and 2000) was included. The survival time was measured from the month of diagnosis to the date of death or censoring and was grouped into annual intervals. Observed and expected survival was estimated using standard life table methods [11,12]. All-cause mortality data obtained from the Australian Bureau of Statistics and the NSW population by single year of age, sex and area of residence were used to construct the life tables for each Area Health Service.

A Poisson regression model [13] was used to examine variation in survival due to place of residence at diagnosis after adjustment for other potential determinants of survival. For this purpose, age at diagnosis was divided into four groups: 15–44 years, 45–59 years, 60–74 years and 75–89 years. Spread of disease at diagnosis was classified into five categories: localised, locally advanced, regional, distant and unknown stage. Other variables included in the model were patients' sex and length of follow-up.

Data from individual records were aggregated to yield one observation for each category of the variables included in the model, and then a generalised linear model with a Poisson error structure based on grouped data using exact survival time was fitted for colon and rectal cancers separately. The relative excess risk (RER) of death derived from this model is the ratio of the excess risk of death in a given area (the excess minus the expected on the basis of the area-specific life table) to that in a reference category (in this case the State average risk of excess death) after controlling for other factors included in the models. A RER of less than one for a given area indicated that the risk in that area was lower than that of the State average and *vice versa*. All analyses were done using SAS version 8.2, and the procedure GENMOD was used to fit the models and assess the prognostic effects of the variables on relative survival.

To estimate how much variation in survival between areas was due to variation in the extent of the disease and how much to variation in treatment, we fitted two models; one with and the other without spread of disease as a covariate, and then compared the estimates

from the two models [14]. Variation in area-specific RERs of death from the model excluding spread of disease should reflect effects of variation in both diagnosis and treatment. That from the model including spread of disease should reduce the degree of variation in RER due to differences in spread of disease, subject to the accuracy of spread of disease as a measure of stage at diagnosis.

As many studies have identified SES as a moderate risk factor for colorectal cancer survival, we added it to the model without spread of disease to investigate its impact on the between area variation in RERs.

To stabilise the estimates of area-specific risk, we applied an Empirical Bayes method to obtain shrunken estimators. The methods are described elsewhere [15]. Briefly, we assume that the area-specific excess risks follow a gamma distribution and variation of the gamma distribution (σ) was estimated using the SAS procedure NLIN. We specified the initial σ value as one (1) with bounds of 0.0001–3, and estimated its value. The standard errors of the shrunken RERs were calculated and used to estimate the 95% confidence intervals (CI) using the normal approximation. The hypothesis of no area variation (*i.e.*, $\sigma = 0$) was tested by comparing the statistic calculated as the ratio of σ and its standard error ($z = \sigma/\mathrm{SE}(\sigma)$) with the standard normal distribution. A *P*-value of less than 0.05 from the hypothesis test was taken to indicate statistically significant area variation in the RERs for the given cancer.

To show how important the factors underlying area variation in survival might be, we estimated the number of patients whose survival time could be extended to beyond five years after diagnosis, if the overall excess risk of death in NSW following a diagnosis of colorectal cancer could be reduced to the 20th centile of the distribution of excess risks across the areas; three of the areas were below the 20th centile [15,16]. This was done in separate categories for spread of disease at diagnosis with the three advanced stage categories grouped together as non-localised.

3. Results

There were 17678 patients with colon cancer and 10283 with rectal cancer included in this analysis. The numbers in individual Area Health Services varied from 75 males and 59 females with colon cancer, and 52 males and 21 females with rectal cancer in the least populous Health Service; to 1210 males and 1211 females with colon cancer, and 828 males and 588 females with rectal cancer in the most populous. The age and sex distribution of colon and rectal cancers reported to the NSW Central Cancer Registry in a recent year are available at http://www.nswcc.org.au/editorial.asp?pageid=263.

There was statistically significant variation between areas in the proportions of localised tumours and unknown stage tumours ($P < 0.0001$ for both colon and rectal cancer) (Table 1). Four areas (South Western Sydney, Mid Western, New England and Far West) had lower proportions of localised colon cancers (as a proportion of those of known stage) and two areas (Far West and Illawarra) had lower proportions of localised rectal cancer. Far West also had a higher proportion of unknown stage rectal cancer. It is the largest and most sparsely populated of the areas with the highest

Table 1
Stage distribution of colon and rectal cancer by NSW Areas Health Services 1996–2001

Area Health Service	Colon cancer			Rectal cancer		
	Localised stage % of known stages	Unknown stage % of all stages	Number of all stages	Localised stage % of known stages	Unknown stage % of all stages	Number of all stages
Central Sydney	34.9	9.2	1161	40.1	13.4	731
Northern Sydney	31.2	8.3	2421	43.9	10.5	1292
Western Sydney	35.6	9.3	1348	43.3	9.9	840
Wentworth	33.5	9.8	529	47.5	12.1	338
South Western Sydney	26.9	9.2	1475	38.4	12.7	850
Central Coast	34.2	17.7	1063	43.9	16.8	591
Hunter	30.5	11.4	1731	40.6	15.0	919
Illawarra	29.7	13.5	1097	35.1	16.6	669
South Eastern Sydney	30.5	8.1	2262	38.1	12.2	1416
Northern Rivers	32.3	11.0	942	42.3	16.2	463
Mid North Coast	33.1	12.8	1013	46.7	13.7	568
New England	27.6	16.1	479	43.9	17.7	277
Macquarie	36.6	11.5	278	47.2	16.3	129
Mid Western	27.5	12.6	508	40.5	16.7	264
Far West	28.1	14.9	134	33.9	23.3	73
Greater Murray	35.1	15.4	708	42.5	18.5	482
Southern	32.7	9.3	529	41.4	15.7	381
New South Wales	31.6	10.9	17678	41.4	13.8	10283

proportion of Indigenous Australians in its population, thus high proportions with late diagnosis of cancer would not be unexpected [17].

The relative excess risks for colon cancer varied significantly by age group ($P < 0.0001$) and spread of disease at diagnosis ($P < 0.0001$). RERs for rectal cancer varied significantly by age group ($P < 0.0001$), sex ($P = 0.01$) and spread of disease at diagnosis ($P < 0.0001$). The goodness of fit for the Poisson models of both colon and rectal cancer without spread of disease at diagnosis as a covariate was poor ($P < 0.0001$). After adding spread of disease, the goodness of fit was much better: $P = 0.36$ for colon cancer and $P = 0.56$ for rectal cancer.

After adjustment for age at diagnosis, sex, and length of follow-up, there was statistically significant area variation in RER for colon ($P = 0.006$) and rectal ($P = 0.049$) cancers. The shrunken RERs ranged from 0.91 to 1.11 for colon cancer and from 0.90 to 1.07 for rectal cancer (Tables 2 and 3). There was also significant variation in RERs for colon cancer ($P = 0.015$) and to a

Table 2
Five-year relative survival, shrunken relative excess risk (RER) due to colon cancer with and without adjustment for disease stage at diagnosis and 95% confidence intervals (CI), by NSW Area Health Services 1996–2001

Area Health Service	Five-year relative survival (%)	RER[a] without adjustment for stage and its 95% CI		RER[a] with adjustment for stage and its 95% CI	
Central Sydney	60.0	1.01	(0.92–1.10)	1.04	(0.94–1.13)
Northern Sydney	63.4	0.91	(0.84–0.97)	0.92	(0.86–0.99)
Western Sydney	58.7	1.03	(0.95–1.12)	1.06	(0.97–1.15)
Wentworth	60.9	1.01	(0.90–1.13)	1.05	(0.93–1.17)
South Western Sydney	58.3	1.07	(0.99–1.16)	1.04	(0.96–1.13)
Central Coast	62.4	0.97	(0.88–1.06)	0.98	(0.89–1.08)
Hunter	61.0	1.02	(0.94–1.10)	1.03	(0.95–1.12)
Illawarra	64.0	0.93	(0.85–1.02)	0.93	(0.84–1.02)
South Eastern Sydney	61.4	0.96	(0.89–1.03)	0.95	(0.88–1.02)
Northern Rivers	62.6	0.95	(0.86–1.05)	0.95	(0.86–1.05)
Mid North Coast	62.8	0.95	(0.86–1.05)	0.98	(0.88–1.07)
New England	53.9	1.11	(0.99–1.23)	1.12	(1.00–1.25)
Macquarie	66.1	0.95	(0.83–1.07)	0.99	(0.86–1.13)
Mid Western	53.8	1.11	(0.99–1.23)	1.13	(1.00–1.25)
Far West	63.7	0.99	(0.86–1.13)	0.97	(0.83–1.11)
Greater Murray	59.5	1.04	(0.93–1.14)	1.09	(0.98–1.20)
Southern	59.3	1.02	(0.91–1.13)	1.02	(0.91–1.14)
New South Wales	61.3	1.00		1.00	

[a] Adjusted for age, sex, and length of follow-up with the state average risk as the reference.

Table 3
Five-year relative survival, shrunken relative excess risk (RER) due to rectal cancer with and without adjustment for disease stage at diagnosis and 95% confidence intervals (CI), by NSW Area Health Services 1996–2001

Area Health Service	Five-year relative survival (%)	RER[a] without adjustment for stage and its 95% CI		RER[a] with adjustment for stage and its 95% CI	
Central Sydney	60.2	1.00	(0.91–1.10)	1.00	(0.91–1.09)
Northern Sydney	64.8	0.90	(0.82–0.98)	0.93	(0.86–1.01)
Western Sydney	58.9	1.04	(0.94–1.14)	1.04	(0.95–1.13)
Wentworth	64.4	0.97	(0.86–1.08)	1.01	(0.90–1.11)
South Western Sydney	58.5	1.06	(0.96–1.16)	1.05	(0.96–1.14)
Central Coast	59.1	1.00	(0.90–1.11)	1.01	(0.91–1.10)
Hunter	57.1	1.07	(0.97–1.16)	1.04	(0.96–1.13)
Illawarra	62.0	0.99	(0.89–1.09)	0.99	(0.90–1.08)
South Eastern Sydney	61.1	0.98	(0.90–1.06)	0.95	(0.88–1.02)
Northern Rivers	62.4	0.95	(0.85–1.06)	0.97	(0.88–1.07)
Mid North Coast	64.7	0.95	(0.85–1.05)	0.99	(0.90–1.09)
New England	64.3	0.98	(0.87–1.10)	1.01	(0.91–1.12)
Macquarie	53.3	1.04	(0.92–1.17)	1.05	(0.93–1.16)
Mid Western	58.6	1.04	(0.92–1.16)	1.03	(0.92–1.13)
Far West	55.0	1.02	(0.89–1.15)	1.02	(0.91–1.13)
Greater Murray	62.9	0.97	(0.87–1.08)	0.99	(0.89–1.08)
Southern	60.0	1.02	(0.91–1.13)	1.00	(0.91–1.10)
New South Wales	61.6	1.00		1.00	

[a] Adjusted for age, sex, and length of follow-up with the state average risk as the reference.

Table 4
Number of lives that might be extended beyond five years after diagnosis by degree of spread for colon and rectal cancer in NSW, 1996–2001

Cancer type	Number of excess deaths	Sigma (σ)[a]	SE(sigma)	P-value[†]	Number of lives might be extended[b]	% of number of excess deaths
Localised tumours						
Colon	279	0.55	0.10	<0.0001	180	64.5
Rectum	321	0.27	0.10	0.005	82	25.4
Non-localised tumours						
Colon	3722	0.09	0.04	0.014	251	6.8
Rectum	1888	0.04	0.07	0.548	59	3.1
Unknown stage tumours						
Colon	564	0.27	0.09	0.002	128	22.7
Rectum	412	0.19	0.06	0.002	84	20.5

[a] σ is the standard deviation of the gamma distribution of area-specific risks and indicates the size of the area variation for a given cancer.
[b] Estimated from the model containing age, sex, length of follow-up and stratified by spread of disease at diagnosis.
[†] P-value for test of area variation equal to 0.

lesser extent for rectal cancer ($P = 0.08$), across SES categories, after adjustment for age, sex and length of follow-up. For both, the RERs for the lower four categories of SES, relative to the highest, ranged from 1.03 to 1.15 with little trend across them. Adjustment for SES produced little change in the range of RERs for colon cancer across areas (from 0.91–1.11 to 0.93–1.09 with an increase in P-value from 0.006 to 0.02) but narrowed the range for rectal cancer appreciably (from 0.90–1.07 to 0.97–1.03 with an increase in P-value from 0.049 to 0.48). Adjustment for spread of disease at diagnosis similarly did not appreciably change the variation for colon cancer (RER 0.92–1.13, $P = 0.004$) but reduced that for rectal cancer (RER 0.93–1.05, $P = 0.16$) (Tables 2 and 3).

Area variation in RERs, estimated from the model containing age group, sex, length of follow-up and stratified by spread of disease at diagnosis, was greatest for localised cancers, as indicated by the comparatively large values for σ, least for non-localised cancers and intermediate for cancers of unknown stage (Table 4). Variation was greater for colon than rectal cancer in each stage category.

Our estimate of the number of patients with colon cancer whose survival time might be increased to more than five years (559) was higher than that for patients with rectal cancer (225) due to the larger number of excess deaths and the greater area variation for colon cancer (Table 4). The most lives that might be extended were in patients with non-localised colon cancer (251) while the highest estimated proportion of lives that might be extended was for localised colon cancer (64.5%), because of the larger variation between areas in this category ($\sigma = 0.55$).

4. Discussion

Relative excess risk of death following a diagnosis of colon cancer and rectal cancer in NSW varied between Area Health Services by 20% and 17%, respectively. Controlling for spread of cancer at diagnosis had little impact on inter-area variation in RERs for colon cancer (21% after adjustment) but reduced it to 12% for rectal cancer, thus suggesting that variation in extent of disease between areas contributed slightly to the variation in outcome for rectal cancer.

The significant variation in RERs for colon cancer between areas after adjustment for spread of disease suggests that differences in the application of treatments of known effectiveness contribute to variation in outcome. While SES of the patient's area of residence also contributed to variation in RERs between areas, we did not adjust for its effects when examining the effect of adjustment for stage of disease on variation in RERs; because it is probably a contributor to variation in treatment quality rather than a confounder of it [18]. In this regard, it is relevant to note the recent results of Lemmens and colleagues from the Netherlands, which showed that use of adjuvant chemotherapy for stage III colon cancer was less in people of lower SES, and in older people [19].

A recent report on patterns of care for colorectal cancer in NSW throws some light on the possibility that treatment variation contributed to variation in outcome [20]. There is level I evidence that post-operative adjuvant chemotherapy improves outcome of node positive colon cancer [21]. In NSW in 2000, 31% of colon cancer patients received post-operative chemotherapy; 31% or more of patients received it in six of the eight Area Health Services in which the RER was less than or equal to 1.0 but in only three of nine areas in which the RER was greater than 1.0 [20].

Variation in surgical experience may also have contributed to variation in outcomes for colon cancer. A number of studies have found that outcomes for colorectal cancer patients is better when patients are treated by surgeons with higher case volumes and specialist expertise [22–25].

The capacity to adjust for the effect of spread of cancer on survival depends on the accuracy of the data. Information on spread of cancer at diagnosis was obtained from hospital medical record departments and radiotherapy notifiers and its quality may vary between areas. This may reduce the capacity to adjust for its effect on area variation in survival. More accurate data on spread of cancer at diagnosis would be highly desirable but are rarely available at the population level. It is noteworthy, though, that when spread of disease at diagnosis was added to the statistical models, the fit of the models improved dramatically.

Our adjustment for cancer stage at diagnosis is by rather crude categorical measures and we cannot adjust for possible stage migration within each of these stage categories, as might be indicated, for example, by number of lymph nodes examined histopathologically if we had these data [26]. Thus, there may be residual effects due to differences in the extent of disease within stage. Information about patients is limited on population-based cancer registries and no treatment information is collected by the registry, thus the data themselves do not allow us to point a direct link between the poor outcomes and differences in treatments. However, we know from other data that some patients received suboptimal cancer therapy [20].

The estimated number of lives that might be extended beyond five years after diagnosis offers a tool to health authorities to set priorities for treatment improvement. In this case non-localised colon cancer is the area of potentially greatest gain from improved treatment, with an estimated 251 lives over five years (50 a year) extendable by shifting the State average risk to the 20th centile. Some of this gain could almost certainly be achieved by ensuring that guidelines for adjuvant treatment of node-positive colon cancer are fully implemented and consistently followed in all Area Health Services [21]. This could require improved access to medical oncology services in rural and remote areas of the State [14] as well as improved uptake of guidelines by treating practitioners. As radiotherapy centres are located in metropolitan areas in NSW [14], patients living in rural and remote areas have relatively poorer access to the standard of cancer treatment services available to their metropolitan counterparts [27]. For localised colon cancer the estimated number of extendable lives over five years was also comparatively high at 180. Surgery is the critical treatment modality for these cancers and it may be here that low surgical caseloads in some areas may be contributing to poorer outcome [22–25]. This would, however, be a challenge to address. Surgical services are undersupplied outside major centres in rural and remote Australia and population density is too low to be able to support any substantial degree of surgical sub-specialisation [28].

Studying variation in RERs of death within five years of diagnosis of cancer, with use of Empirical Bayes methods to shrink RER estimates and adjustment for spread of cancer at diagnosis, can help identify cancers for which better application of treatment guidelines might improve outcome. Estimates of the numbers of lives that could be extended if the State average risk was reduced to the 20th centile of the distribution may assist in setting priorities for treatment improvement.

Conflict of interest statement

None declared.

Acknowledgements

We thank the NSW Central Cancer Registry for providing the data. Bruce Armstrong's research is supported by a University of Sydney Medical Foundation Program Grant.

References

1. Faivre-Finn C, Bouvier-Benhamiche AM, Phelip JM, *et al*. Colon cancer in France: evidence for improvement in management and survival. *Gut* 2002, **51**, 60–64.
2. Coleman MP, Rachet B, Woods LM, *et al*. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *Br J Cancer* 2004, **90**, 1367–1373.
3. Gatta G, Capocaccia R, Sant M, *et al*. Understanding variations in survival for colorectal cancer in Europe: a EUROCARE high resolution study. *Gut* 2000, **47**, 533–538.
4. Farrow DC, Samet JM, Hunt WC. Regional variation in survival following the diagnosis of cancer. *J Clin Epidemiol* 1996, **49**, 843–847.
5. Kim YE, Gatrell AC, Francis BJ. The geography of survival after surgery for colo-rectal cancer in southern England. *Soc Sci Med* 2000, **50**, 1099–1107.
6. Osnes K, Aalen OO. Spatial smoothing of cancer survival: a Bayesian approach. *Stat Med* 1999, **18**, 2087–2099.
7. Tracey E, Supramaniam R, Chen W. *Cancer in New South Wales: incidence and mortality 2001*. Sydney, The Cancer Council New South Wales, 2003.
8. Australian Bureau of Statistics. Information paper: 1996 Census Socio-Economic Indexes For Areas (SEIFA). Canberra, ABS; 1998.
9. Brenner H, Gefeller O. An alternative approach to monitoring cancer patient survival. *Cancer* 1996, **78**, 2004–2010.
10. Brenner H, Gefeller O. Deriving more up-to-date estimates of long-term patient survival. *J Clin Epidemiol* 1997, **50**, 211–216.
11. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. *Natl Cancer Inst Monogr* 1961, **6**, 101–121.
12. Chiang CL. *Introduction to stochastic processes in biostatistics*. New York, John Wiley, 1968.
13. Dickman PW, Sloggett A, Hills M, *et al*. Regression models for relative survival. *Stat Med* 2004, **23**, 51–64.
14. Jong KE, Smith DP, Yu XQ, *et al*. Remoteness of residence and survival from cancer in New South Wales. *Med J Aust* 2004, **180**, 618–622.

15. Yu XQ, O'Connell DL, Gibberd RW, *et al*. Estimating regional variation in cancer survival: a tool for improving cancer care. *Cancer Causes Control* 2004, **15**, 611–618.
16. Gibberd R, Hancock S, Howley P, *et al*. Using indicators to quantify the potential to improve the quality of health care. *Int J Qual Health Care* 2004, **16**(Suppl. 1), i37–i43.
17. Condon JR, Barnes T, Armstrong BK, *et al*. Stage at diagnosis and cancer survival for Indigenous Australians in the Northern Territory. *Med J Aust* 2005, **182**, 277–280.
18. Kelley E, Moy E, Stryer D, *et al*. The national healthcare quality and disparities reports: an overview. *Med Care* 2005, **43**, I3–I8.
19. Lemmens VE, van Halteren AH, Janssen-Heijnen ML, *et al*. Adjuvant treatment for elderly patients with stage III colon cancer in the southern Netherlands is affected by socioeconomic status, gender, and comorbidity. *Ann Oncol* 2005, **16**, 767–772.
20. Armstrong K, O'Connell DL, Leong D, *et al*. *The New South Wales colorectal cancer care survey – Part 1 surgical management*. Sydney, The Cancer Council New South Wales, 2004.
21. National Health and Medical Research Council. Guidelines for the Prevention, *Early detection and management of colorectal cancer*. Canberra, AGPS; 1999.
22. Hodgson DC, Fuchs CS, Ayanian JZ. Impact of patient and provider characteristics on the treatment and outcomes of colorectal cancer. *J Natl Cancer Inst* 2001, **93**, 501–515.
23. Meagher AP. Colorectal cancer: is the surgeon a prognostic factor? A systematic review. *Med J Aust* 1999, **171**, 308–310.
24. Smith JA, King PM, Lane RH, *et al*. Evidence of the effect of 'specialization' on the management, surgical outcome and survival from colorectal cancer in Wessex. *Br J Surg* 2003, **90**, 583–592.
25. McArdle CS, Hole DJ. Influence of volume and specialization on survival following surgery for colorectal cancer. *Br J Surg* 2004, **91**, 610–617.
26. Ciccolallo L, Capocaccia R, Coleman MP, *et al*. Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery. *Gut* 2005, **54**, 268–273.
27. Australian Institute of Health and Welfare and Australasian Association of Cancer Registries. *Cancer survival in Australia 1992–1997: geographic categories and socioeconomic status*. Canberra: AIHW; 2003.
28. Australian Institute of Health and Welfare.*Health in rural and remote Australia*. Canberra: AIHW; 1998.

Int. J. Cancer: **119,** 894–900 (2006)

Trends in survival and excess risk of death after diagnosis of cancer in 1980–1996 in New South Wales, Australia

Xue Q. Yu[1]*, Dianne L. O'Connell[1], Robert W. Gibberd[2], Alan S. Coates[3,4] and Bruce K. Armstrong[4]

[1]*Cancer Epidemiology Research Unit, The Cancer Council New South Wales, Australia*
[2]*Faculty of Health, University of Newcastle, Australia*
[3]*The Cancer Council Australia, Australia*
[4]*School of Public Health, The University of Sydney, Australia*

Survival from almost all cancers has improved during the last 30 years. There is debate over the reasons for the improvement. We examined trends in survival for 28 cancers from 1980 to 1996 in New South Wales (NSW), Australia, with adjustment for disease spread at diagnosis. NSW Central Cancer Registry data were used to estimate 5-year relative survival and relative excess risk of death for patients diagnosed in 1980–84, 1985–88, 1989–92 and 1993–96. Statistical significance of variation in excess deaths between periods of diagnosis was assessed using Poisson regression, with adjustment for age, sex, duration of follow-up, histology and spread of disease at diagnosis. There were statistically significant falls in excess deaths for 20 of the cancers with a 25% fall for all cancers combined. Cancers of the prostate, liver, thyroid, breast, gallbladder, body of uterus, rectum, cervix and ovary had falls of >30%. The falls varied by spread of disease; the largest being in localised and regionally spread tumours. Overall survival, when unadjusted for spread of cancer, generally fell in parallel with that in the specific categories of spread, which implies that stage migration did not contribute importantly to survival trends. While acknowledging the limitations of incomplete data on stage of cancer at diagnosis, we conclude that falls in excess deaths in NSW from 1980 to 1996 are unlikely, for many cancers, to be attributed to earlier diagnosis or stage migration; thus advances in cancer treatment have almost certainly contributed to them.

Key words: trend; relative survival; cancer registry; epidemiology; stage migration

Survival from almost all cancers has improved, for some markedly, during the last 30 years. Notable successes include childhood leukaemia, testicular cancer and Hodgkin's disease, in which survival improvement has been mainly due to the introduction of more effective treatments.[1–3] Between 1975–79 and 1995–2000 in the USA, 5-year-survival from female breast cancer increased from 75 to 88% and that for colorectal cancer from 50 to 64% (men) and 52 to 63% (women): these improvements were attributed to both earlier detection and more effective treatment of cancer.[4] There has been debate, however, over the extent to which improved treatment has contributed to the trend in survival.[5] By extrapolating trends in cancer mortality in the USA, Bailar and Gornick argued that newer cancer therapies have produced few real benefits and concluded that recent decreases in cancer mortality were due mainly to falling incidence or earlier detection.[6]

In this study, we examined time trends in excess risk of death within 5 years of diagnosis from 1980 to 1996 in patients with one of the 28 cancers, in New South Wales (NSW), Australia using data from a population-based cancer registry. To try to exclude impacts of earlier detection, we examined the trends in excess risk of death, with adjustment for a measure of disease spread at diagnosis, along with histological type of cancer, age and sex. In doing so, we also assessed possible effects of stage migration, a shift with time in the stage distribution of a cancer towards apparently higher stage disease because of more complete identification of disease spread. This shift produces an artificial increase in survival in each stage category because of the removal of more advanced disease from earlier stage categories and its transfer as relatively less advanced disease into later stage categories.[7] Taking confounding trends in stage and the possibility of stage migration into account allows an interpretation of the trends in excess risk of death in terms of changes in disease management.

Material and methods

Data

Data for patients diagnosed with any of the 28 major cancers during 1980–96 were obtained from the population-based NSW Central Cancer Registry. Notification of cancer has been a statutory requirement for all NSW public and private hospitals, radiotherapy departments and nursing homes since 1972, and for pathology departments since 1985.[8] The Central Cancer Registry generally has high standards of data completeness, quality and follow-up; the data are accepted by the International Agency for Research on Cancer for publication in Cancer Incidence in Five Continents.[9] Individuals with the first occurrence of a primary cancer between 15 and 89 years of age were included. Cases notified by death certificate only or first identified at postmortem were excluded from the analysis of survival, but included in the calculation of age–sex standardised incidence rates. These cases were 1.8% of the total and were relatively constant over time, except for an increase to 3.3% in 1985–88 caused by lack of Registry resources to investigate them. Data on the population and population mortality used to calculate relative survival and age and sex standardised incidence rates were obtained from the Australian Bureau of Statistics, which conducts Australia's quinquennial population census and collates national death data.

All cases diagnosed from 1980 to 1996 were followed to December 2001 to determine survival status. Identifiers from each were compared with those of all records of deaths in the State Register of Deaths and the National Death Index from their date of diagnosis to 31st December 2001 to find a matching death record, if present. This passive approach to follow-up may fail to ascertain all deaths and may incorrectly link some incidence and death records. A study investigating its completeness and accuracy found loss to follow-up to be uniform from 1980 to 1993 and estimated the resulting overestimation of relative survival to be a maximum of 2%.[10] The end of follow-up was the date of death for those who died within five years of diagnosis or five years after diagnosis for those who survived the first 5 years.

All information on primary cancer site and histology was coded according to the International Classification of Diseases for Oncology, second edition (ICDO-2).[11] Data on spread of disease at diagnosis were provided by hospital medical record departments and radiotherapy notifiers, and classified into four broad categories: localised, regional (including adjacent organs and regional lymph nodes), distant and unknown to the Registry. This summary classification of stage is used by a number of major cancer registries around the world, including registries in the Surveillance, Epidemi-

This study was funded by The Cancer Council NSW Australia.
***Correspondence to:** Cancer Epidemiology Research Unit, The Cancer Council New South Wales, PO Box 572, Kings Cross NSW 1340, Australia. Fax: +61-2-93341778. E-mail: xueqiny@nswcc.org.au
Received 8 August 2005; Accepted 18 January 2006
DOI 10.1002/ijc.21909
Published online 20 March 2006 in Wiley InterScience (www.interscience.wiley.com).

ology, and End Results (SEER) program in the USA. While not as detailed as the standard TNM staging system, it can be applied to most cancers occurring in whole populations.[12] Degree of spread was not applicable to staging for Hodgkin's disease, non-Hodgkin lymphoma, multiple myeloma, leukaemia and brain cancer, and no other staging data were available for them. Because of the importance of spread of disease in our analysis and the possibility of stage migration, we tabulated changes in the distribution of spread in 1980–96 for the sites for which it was available, with regional and distant spread combined as nonlocalised disease.

Statistical methods

Relative survival and relative excess risk of death. Cancer patients were followed for five years after diagnosis and relative survival was estimated using the cohort method. Relative survival is the ratio of the observed proportion surviving in a group of patients to the expected proportion that would have survived in a comparable group of people from the general population.[13] Observed survival was estimated using the life table method.[14] The expected survival from the general population was calculated using all cause mortality for the NSW population by single year of age, sex and calendar year.[15]

The excess risk of death after diagnosis of a cancer is the risk of death above what would have been observed if the population death rates had been applied to the cancer patients. To analyse trends in excess risk of death, four time periods were defined: 1980–84, 1985–88, 1989–92 and 1993–96. Grouping the dates of diagnosis in periods of a few years increases the likelihood that cancer patients diagnosed within a period followed similar treatment protocols and had similar access to screening. The period 1980–84 preceded compulsory reporting of cancer to the Cancer Registry by pathology laboratories, which was introduced in 1985.

Statistical modelling of excess risk of death. To determine the change in survival over time after adjustment for possible confounders, we fitted a Poisson regression model for excess deaths from each type of cancer.[16] The model included time period of diagnosis, age group at diagnosis (15–44, 45–59, 60–74 and 75–89 years), year of follow-up since diagnosis, sex (where applicable), histological type (based on ICDO-2 and with the less common histological types grouped together) and spread of disease at diagnosis (where applicable) as independent variables. We then fitted another model by adding the interaction of spread of cancer by period of diagnosis to the main effects model for cancers to which spread of disease at diagnosis was applicable. Finally, we compared the difference between the deviance from this model with that from the main effects model to determine whether addition of the interaction produced a statistically significant difference in model deviance ($p < 0.05$), using the chi-square test. If the difference was statistically significant, we then carried out further analyses to examine the differences in trends across categories of spread of cancer.

The modelling methods we used are described in detail by Dickman et al.[17] Briefly, data from individual records were aggregated to yield a count of deaths for each combination of the variables included in the model, and then a generalised linear model with a Poisson error structure based on aggregated data using exact survival time (person-years) was fitted for each cancer. This model quantifies the extent to which the excess risk of death in a given period differs from the excess risk of death in the reference period (1980–84) after controlling for the factors included in the model. The relative excess risk of death (RER) in the period 1980–84 was set to a value of 1. A RER of less than 1 in another period indicates that the excess risk of death in that period was less than that in the reference period, and vice versa. Ninety-five per cent confidence intervals (CIs) for the RERs were calculated using the estimated coefficients and standard errors from the Poisson models. The statistical significance of each variable in the model was determined by the log-likelihood ratio test with a *p*-value of <0.01 taken to indicate statistical significance. All analyses were done using SAS version 8.2 and the procedure GENMOD was used to fit the models and assess the effects of the variables on excess risk.

Trends in incidence rates. To estimate trends in incidence, which we reported to give context to the survival trends, we calculated annual age-sex standardised incidence rates for the resident population in NSW during the period 1980–96 for each of the 28 cancers. These rates were expressed per 100,000 of the population, and age and sex were adjusted by the direct method to the Australian estimated residential population of 2001. Trends in incidence were summarized by calculating the annual percent change in age-standardised incidence rates over the 17 years for each cancer. The annual percent change was estimated by fitting a Poisson regression model to the natural logarithm of the rates, with calendar year as a continuous independent variable. The assumption of a linear trend was reasonable for all cancers except for melanoma and prostate cancer in which there have been sizeable short-term perturbations in the long-term trend.[8]

Results

A total of 343,034 newly diagnosed cancers were included in this analysis, with the commonest cancers being breast (41,476), lung (39,769) and prostate (37,374) (Table I). Age-standardised incidence of most cancers increased during the period 1980–96. The largest annual percent increases were for cancers of the prostate, liver and thyroid, and mesothelioma, and the largest falls were for cancers of the stomach, cervix and bladder. The incidence of prostate cancer showed a dramatic rise between 1990 and 1994, followed by a fall after 1994.[8] The Registry's report on cancer incidence in 2003[8] is available at http://www.cancerinstitute.org.au/cancer_inst/statistics/pdfs/IncidenceMortalityReport2005.pdf.

TABLE I – AGE AND SEX STANDARDISED INCIDENCE RATES (PER 100,000) AND AVERAGE ANNUAL PERCENT CHANGE, WITH THE CORRESPONDING 95% CI, FOR 28 CANCERS, IN NSW, AUSTRALIA, 1980–96

Cancer type	Number of new cases	Age-standardised incidence rates[1]	Average annual percent change 1980–96	95% CI
Lip	3,562	9.0	2.51	0.85, 4.19
Head and neck	12,553	28.3	0.00	−0.58, 0.58
Oesophagus	4,167	10.5	1.21	0.54, 1.88
Stomach	10,354	22.5	−2.66	−3.11, −2.21
Colon	32,414	80.6	0.56	0.19, 0.93
Rectum	17,688	44.5	0.94	0.57, 1.32
Liver	1,891	6.7	7.91	6.48, 9.36
Gallbladder	2,709	6.6	0.29	−0.63, 1.23
Pancreas	8,091	19.8	0.04	−0.43, 0.51
Lung	39,769	90.7	−0.56	−0.78, −0.33
Melanoma	32,316	84.4	3.06	2.15, 3.97
Mesothelioma	1,634	5.1	5.11	4.14, 6.08
Connective tissue	2,088	4.6	−0.16	−1.25, 0.93
Breast	41,476	113.9	2.71	2.30, 3.13
Cervix	5,957	11.6	−1.63	−2.22, −1.04
Body of uterus	5,793	14.0	0.93	0.27, 1.60
Ovary	5,375	12.1	−0.30	−0.87, 0.27
Prostate	37,374	146.1	7.09	5.46, 8.75
Testis	2,314	5.4	2.68	1.79, 3.57
Bladder	12,139	25.2	−2.90	−3.63, −2.16
Kidney	9,053	24.3	2.79	2.24, 3.33
Thyroid	3,438	10.2	4.92	3.86, 5.99
Brain	5,404	12.8	1.08	0.62, 1.55
Hodgkin's disease	1,856	3.7	−0.76	−1.49, −0.03
Non-Hodgkin lymphoma	12,688	34.8	3.04	2.68, 3.41
Multiple myeloma	4,229	11.0	1.09	0.38, 1.81
Leukaemia	9,365	23.5	0.48	−0.04, 1.00
Unspecified	17,337	40.2	−0.49	−1.03, 0.05

[1]Age and sex adjusted to the Australian estimated residential population of 2001.

TABLE II – PROPORTION OF SPREAD OF DISEASE AT DIAGNOSIS BY PERIOD OF DIAGNOSIS FOR 23 MAJOR CANCERS DIAGNOSED IN NSW, AUSTRALIA, 1980–96[1]

Cancer type	Localised				Non-localised				Unknown			
	1980–84	1985–88	1989–92	1993–96	1980–84	1985–88	1989–92	1993–96	1980–84	1985–88	1989–92	1993–96
Lip	81.0	72.4	69.7	62.7	7.2	6.9	6.6	5.6	11.8	20.8	23.7	31.7
Head and neck	47.1	45.3	41.9	30.8	36.8	36.2	36.3	39.5	16.0	18.5	21.8	29.7
Oesophagus	34.8	42.0	38.5	27.4	42.3	36.0	35.7	37.9	22.9	22.0	25.8	34.7
Stomach	24.7	25.2	23.5	17.1	59.2	57.3	60.1	59.9	16.1	17.5	16.4	23.0
Colon	33.7	30.8	30.4	23.7	55.5	57.5	60.9	63.8	10.8	11.7	8.7	12.4
Rectum	42.3	39.4	38.2	30.9	47.9	49.5	51.9	52.8	9.8	11.2	9.9	16.2
Liver	49.6	39.1	37.7	23.6	32.7	23.5	22.5	18.7	17.7	37.3	39.7	57.8
Gallbladder	24.3	25.0	23.6	17.3	64.5	57.5	56.1	49.9	11.3	17.5	20.2	32.8
Pancreas	14.3	16.4	16.5	9.6	68.5	56.1	56.0	52.6	17.2	27.5	27.5	37.8
Lung	23.2	30.3	26.4	17.0	49.8	44.7	44.6	46.8	27.0	25.0	29.0	36.2
Melanoma	82.9	87.3	88.2	89.0	9.6	7.5	8.1	6.8	7.5	5.2	3.7	4.2
Mesothelioma	28.8	42.7	35.9	19.6	49.2	18.6	21.7	21.6	22.0	38.7	42.4	58.8
Connective tissue	53.8	55.6	48.2	34.3	27.0	21.8	18.9	16.0	19.2	22.5	32.9	49.7
Breast	47.3	47.9	49.3	51.0	37.6	37.8	37.8	33.5	15.1	14.3	12.9	15.4
Cervix	57.0	67.3	63.7	50.7	31.3	24.9	28.6	25.9	11.7	7.8	7.7	23.4
Body of uterus	67.9	69.4	65.7	61.5	17.2	17.8	20.8	21.3	14.9	12.8	13.5	17.2
Ovary	28.2	27.4	24.4	16.0	61.1	58.7	65.4	70.0	10.7	13.9	10.2	14.0
Prostate	59.0	52.5	51.1	40.6	21.8	21.4	16.6	10.0	19.3	26.1	32.3	49.4
Testis	59.1	65.5	66.6	60.5	20.4	23.5	23.1	21.2	20.4	11.0	10.4	18.3
Bladder	77.8	71.7	65.9	47.2	11.6	11.6	15.3	15.4	10.6	16.7	18.8	37.4
Kidney	51.2	49.8	50.1	44.3	38.5	38.8	36.0	35.1	10.3	11.4	13.9	20.6
Thyroid	64.9	59.0	62.7	51.7	25.4	28.6	24.3	24.9	9.7	12.4	13.1	23.4
Unspecified	0.7	1.4	1.2	0.8	95.6	88.6	89.4	87.4	3.7	10.0	9.4	11.8

[1]Brain cancers, non-Hodgkin lymphoma, Hodgkin disease, multiple myeloma and leukaemia are not included in this table because classification of stage at diagnosis on the basis of spread of disease at diagnosis does not apply to them.

TABLE III – RELATIVE EXCESS RISK (RER) DURING THE FIRST 5-YEARS AFTER DIAGNOSIS, WITH ADJUSTMENT FOR AGE, SEX, SPREAD OF CANCER, YEARS SINCE DIAGNOSIS AND HISTOLOGICAL TYPE FOR 28 CANCERS DIAGNOSED IN 1980–96 AND FOLLOWED TO 2001, IN NSW, AUSTRALIA

Cancer type	5-year RSR[1] 1993–96 (%)	RER[2] and 95% CI				*p*-value
		1980–84	1985–88	1989–92	1993–96	
Lip	93.1	1.00	0.87 (0.52–1.47)	0.61 (0.36–1.04)	0.72 (0.43–1.19)	0.28[3]
Head and neck	55.6	1.00	0.93 (0.86–1.01)	0.87 (0.81–0.95)	0.78 (0.72–0.85)	<0.0001[3]
Oesophagus	15.4	1.00	0.85 (0.77–0.94)	0.75 (0.68–0.83)	0.70 (0.63–0.77)	<0.0001[4]
Stomach	23.8	1.00	0.93 (0.87–1.00)	0.88 (0.82–0.94)	0.82 (0.77–0.88)	<0.0001[4]
Colon	60.0	1.00	0.84 (0.80–0.89)	0.80 (0.76–0.85)	0.71 (0.68–0.75)	<0.0001[4]
Rectum	59.4	1.00	0.86 (0.80–0.92)	0.75 (0.70–0.81)	0.67 (0.62–0.71)	<0.0001[4]
Liver	11.4	1.00	0.71 (0.60–0.85)	0.73 (0.62–0.87)	0.55 (0.47–0.65)	<0.0001[3]
Gallbladder	19.5	1.00	0.83 (0.73–0.93)	0.78 (0.69–0.88)	0.61 (0.54–0.69)	<0.0001[4]
Pancreas	5.3	1.00	0.85 (0.79–0.91)	0.94 (0.88–1.01)	0.86 (0.80–0.92)	<0.0001[4]
Lung	12.5	1.00	0.94 (0.91–0.97)	0.90 (0.87–0.93)	0.82 (0.79–0.84)	<0.0001[4]
Melanoma	90.9	1.00	0.82 (0.73–0.93)	0.72 (0.64–0.81)	0.72 (0.64–0.81)	<0.0001[3]
Mesothelioma	4.9	1.00	0.88 (0.74–1.04)	0.87 (0.74–1.02)	0.92 (0.79–1.07)	0.35[3]
Connective tissue	63.0	1.00	1.08 (0.86–1.35)	1.11 (0.89–1.39)	1.05 (0.84–1.30)	<0.0001[4]
Breast	85.0	1.00	0.88 (0.82–0.94)	0.76 (0.71–0.81)	0.61 (0.57–0.65)	<0.0001[4]
Cervix	73.1	1.00	1.03 (0.91–1.18)	0.78 (0.68–0.89)	0.68 (0.59–0.78)	<0.0001[3]
Body of uterus	79.2	1.00	0.79 (0.66–0.94)	0.66 (0.55–0.79)	0.61 (0.51–0.72)	<0.0001[3]
Ovary	37.3	1.00	1.03 (0.93–1.14)	0.84 (0.76–0.92)	0.68 (0.62–0.75)	<0.0001[4]
Prostate	86.9	1.00	1.09 (1.01–1.19)	0.95 (0.87–1.03)	0.54 (0.49–0.59)	<0.0001[4]
Testis	95.5	1.00	0.72 (0.42–1.23)	0.51 (0.31–0.84)	0.63 (0.38–1.04)	0.05[3]
Bladder	62.5	1.00	1.06 (0.96–1.18)	1.08 (0.97–1.21)	1.13 (1.02–1.26)	0.14[3]
Kidney	57.4	1.00	0.86 (0.78–0.94)	0.85 (0.77–0.93)	0.73 (0.67–0.80)	<0.0001[4]
Thyroid	93.5	1.00	0.81 (0.57–1.14)	0.63 (0.44–0.89)	0.58 (0.42–0.81)	<0.0001[3]
Brain[5]	17.9	1.00	0.88 (0.80–0.96)	0.94 (0.86–1.02)	0.86 (0.79–0.94)	0.003[3]
Hodgkin's disease[5]	77.3	1.00	1.13 (0.86–1.48)	0.99 (0.74–1.33)	0.85 (0.63–1.15)	0.26[3]
Non-Hodgkin lymphoma[5]	53.6	1.00	0.94 (0.86–1.02)	0.92 (0.85–0.99)	0.86 (0.80–0.93)	0.002[3]
Multiple myeloma[5]	31.9	1.00	0.95 (0.85–1.07)	0.91 (0.82–1.02)	0.86 (0.77–0.97)	0.07[3]
Leukaemia[5]	38.2	1.00	0.84 (0.78–0.92)	0.74 (0.68–0.80)	0.82 (0.76–0.88)	<0.0001[3]
Unspecified	11.0	1.00	1.06 (1.01–1.11)	1.04 (0.99–1.09)	1.10 (1.05–1.15)	<0.0001[4]
All cancer	*59.6*	*1.00*	*0.92 (0.91–0.94)*	*0.86 (0.85–0.88)*	*0.75 (0.74–0.76)*	*<0.0001*[4]

Values in parentheses represent 95% CI.
[1]Five-year relative survival for the period 1993–96.–[2]RER for the period of 1980–84 as reference (set to 1.0). Each model included age group at diagnosis, sex, year since diagnosis, period of diagnosis, histological type and spread of cancer.–[3]*p*-value for the main effect of period for cancer types with nonsignificant interaction term for period by stage.–[4]*p*-value for the interaction of period by stage for cancer types with significant interaction term for period by stage.–[5]Classification of stage by spread of cancer not applicable for these cancers.

There were substantial changes in the distribution of the cancers by spread of disease at diagnosis over the period of study (Table II). The proportion with localised disease fell for all but three cancer types—melanoma, breast cancer and testicular cancer—and the proportion with unknown stage increased for all except these same three cancer types. The proportions with regional and distant disease fell for 15 cancer types (including melanoma and breast cancer) and increased for 8 types, the most substantial being in cancers of the

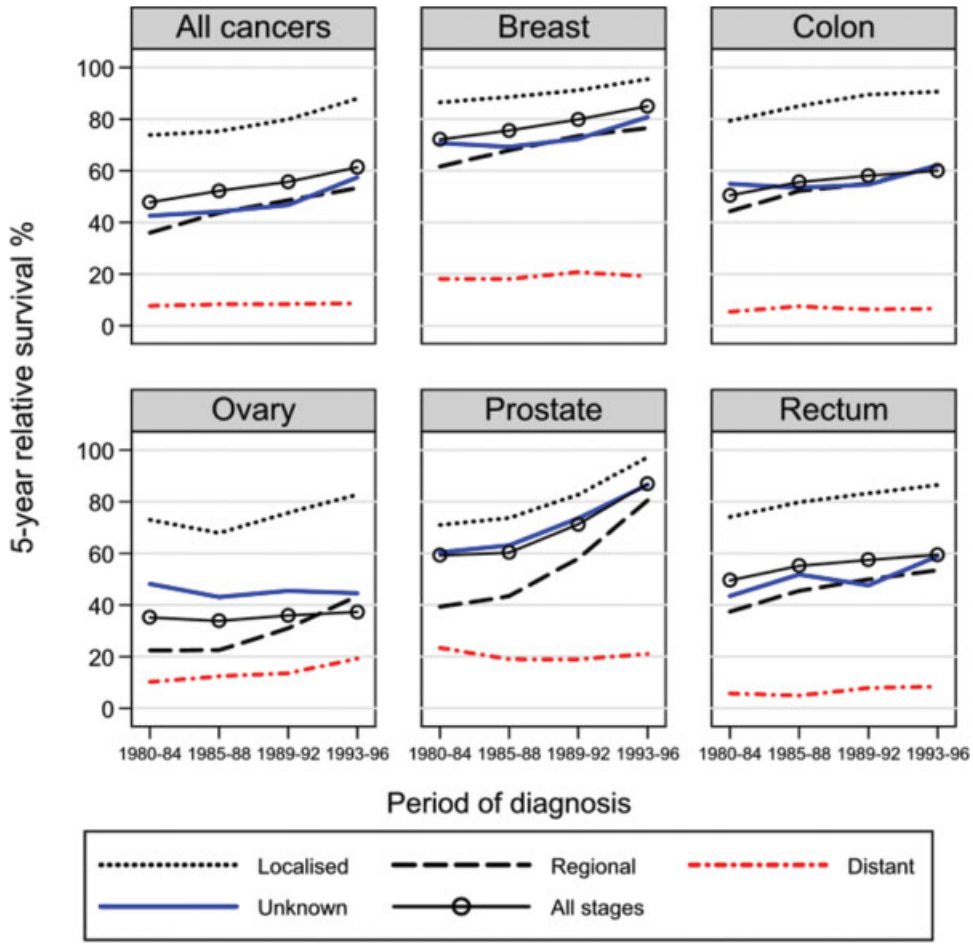

FIGURE 1 – Trends in 5-year relative survival by spread of cancer for all cancers combined and cancers of the breast, colon, ovary, prostate and rectum (New South Wales, Australia, 1980–96).

colon, rectum and ovary (5 percentage points or more). The increase in the proportion of cancers of unknown stage occurred mainly in 1993–96 and, to a much less extent, in 1989–92 for 13 of the 20 cancer types in which an increase occurred. These increases were probably largely due to a change from paper-based to electronic notification of cancer from some hospitals, introduced from 1992, which meant that some information on stage provided through manual notification was no longer available to the Registry. In the remaining 7 cancer types, the increase was more gradual across the whole period of observation, indicating that additional factors, unknown to us, were influencing completeness of stage information reported to the Registry for these cancers.

The excess risk of death fell over time for most cancers except cancers of the connective tissue and unspecified site, for which it rose significantly ($p < 0.0001$), and cancer of the bladder, where the increase was not statistically significant (Table III). For all cancers together, the excess risk of death fell by a relative 25%. The most dramatic falls were in cancers of the liver, prostate and thyroid, with the excess risk of death in the latest period being less than 60% of that in the earliest period. Other notable falls were for cancers of the oesophagus, rectum, gallbladder, breast, cervix, uterus and ovary.

There were nonsignificant falls in excess risk of death from cancers of the lip and testis, mesothelioma, Hodgkin's disease and multiple myeloma. The CIs about the RERs of less than unity for cancers of the lip and testis diagnosed in 1993–96 were wide and included the point estimate of 0.75 for RER of all cancers together. These were among the least frequent of the cancers studied and were in the 3 least fatal; thus real downtrends in excess risk of death for these cancers are possible, but our data had limited statistical power to detect them with any certainty. Hodgkin's disease and multiple myeloma shared with non-Hodgkin lymphoma a 14–15% reduction in excess risk of death between 1980–84 and 1993–96, which was statistically significant for the latter.

The trend in excess risk of death was significantly heterogeneous among categories of spread of disease for 13 of the 23 cancers for which disease stage was available. Some patterns are shown in terms of trends in 5-year relative survival in Figure 1. For all cancers combined and cancers of the colon, breast and prostate, the main trends in 5-year relative survival were increases in the localised, regional and unknown categories, with no improvement for distant cancers. For cancer of the rectum, the 5-year relative survival increased in all categories though much less so for cancers with distant spread. For ovarian cancer, the increase in survival was evident in cancers that were localised, regional or distant but hardly at all in unknown spread or all degrees of spread together (unadjusted for degree of spread); this strongly suggests that stage migration caused the apparently increased survival in the individual degree of spread categories (Fig. 1).

There was also evidence of stage migration in the pattern of change in the degree of spread with time for cancer of the ovary: the proportion of localised cancers fell, that of regionally and distant spread cancers increased correspondingly and that of unknown spread cancers changed little. Cancers of the colon, rectum, head and neck, and body of uterus showed similar patterns of change in degree of spread. For colon and rectal cancers, however, overall survival, unadjusted for spread of disease, paralleled the trends in survival in the individual spread of cancer categories, thus ruling out substantial stage migration (Fig. 1). For cancers of the head and neck and body of uterus, the uptrend in overall survival was modest relative to that in individual categories of degree of spread (data not shown), thus suggesting some stage migration.

Discussion

We found that excess risk of death after diagnosis for 20 of the 28 categories of cancer type, adjusted where possible for degree of spread of cancer (cancer stage) at diagnosis, fell significantly, between 1980 and 1996 in New South Wales. These results are consistent with the beneficial effects of newer cancer therapies on cancer survival but incomplete data on degree of spread and its increase with time may limit the confidence with which this conclusion can be drawn.

Our data are population-based and thus represent the experience of a general population of people with cancer, not one that has been selected by referral to a particular hospital or expert centre. We were able to take some account of trends in stage, which many population-based studies cannot because stage data are not collected by the relevant cancer registry. Our observations are also based on large numbers of patients and deaths and thus can give quite precise estimates of trends for many different cancers.

That our data on stage of cancer are incomplete and have become more incomplete with time mean that we cannot rule out entirely the possibility that increased cancer screening or better methods of diagnosis, leading to earlier diagnosis, have contributed to the favourable trends we have observed.[18] In addition to the impacts on cancer mortality that screening and improved diagnosis might have had, both lead-time bias (advancing the date of diagnosis without postponing the time of death) and length bias (detection of slower growing tumours that would not otherwise have been diagnosed or have caused death) could have produced apparent falls in excess risk of death.[19,20] The measure we used to adjust for stage, spread of disease at diagnosis, is a very powerful predictor of survival in our data,[10] but it was missing for more than 10% of most cancer types; this high prevalence of missing data would reduce our ability to control statistically for effects of trends in earlier diagnosis on trends in survival. These issues notwithstanding, the lack, for most cancers, of an increase in the proportion of cases with localised stage (Table II) suggests that these factors were not generally important contributors to apparently improved survival.

Stage migration could also have produced artefactual falls in observed excess risk of death. As suggested earlier, this might explain the whole of the apparent improvement in stage-adjusted survival for ovarian cancer and might have contributed to the falls in stage-adjusted survival for cancers of the head and neck and body of uterus. It was probably not important for other cancers.

There would, perhaps, be greatest concern with inadequate adjustment for stage at diagnosis in cancers for which the proportion of early stage disease increased with time: melanoma, breast cancer and testicular cancer. Introduction of mammographic screening for breast cancer in the 1980s should have reduced the excess risk of death from breast cancers diagnosed in 1980–96.[21] Its effects are probably evidenced in the increasing proportion of localised disease and the somewhat greater downtrend in excess risk for breast cancers than for most other cancers (Table III). However, if screening was the main reason for the reduced excess risk of death, survival improvement should have been most evident in the target age group for screening (50–69 years), whereas it was seen in all age groups (Fig. 2). There is no formal screening program for melanoma in Australia; self and professional skin examination is strongly encouraged and there is evidence of its impact.[22] Here the problem of adequate stage adjustment is even greater: as most melanomas are diagnosed when localised to the skin, a measure of local stage, namely thickness of the melanoma, is a much better indicator of early diagnosis than is clinical stage. We did not use it in this study. Thus we cannot infer benefits from trends in melanoma treatment from our results. While testicular self examination has been promoted in Australia, the trend towards an increase in localised cancer was paralleled by an increase in nonlocalised cancer (Table II) and a fall in cancer of unknown stage. Thus there is no certain trend to earlier diagnosis of testicular cancer and the reduction in excess risk of death for this cancer probably reflects the known improvements in treatment in the 1970s and 80s[2], with the lowest RER in 1989–92 (Table III) consistent with achievement of a minimum in testicular cancer mortality in NSW in this period.[8]

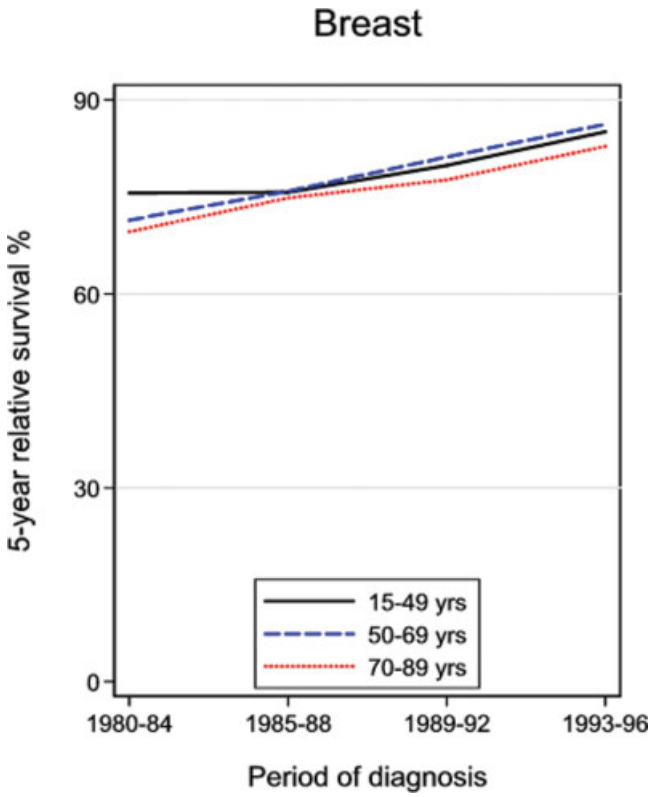

Figure 2 – Trends in 5-year relative survival by age at diagnosis for breast cancer (New South Wales, Australia, 1980–96).

Although there is no formal screening program for prostate cancer in Australia and any trend towards earlier diagnosis of it has probably been masked by the great increase in proportion of cancers of unknown stage, the near 50% apparent fall in excess risk of death from it has probably been caused by the large increase in screening with prostate specific antigen (PSA) testing in Australia in the 1990s, with the associated large increase in prostate cancer incidence.[23] The 5-year relative survival for localised prostate cancers increased from 82.7% in 1989–92 to 97.2% in 1993–96 (Fig. 1). Compared with the model without adjustment for spread of cancer, adjustment increased the RER in 1993–96 from 0.38 to 0.54 (data not shown). Thus, although adjustment for spread of cancer removed more than 40% of the reduction in excess risk for prostate cancer, the recently increased proportion of prostate cancers (49.4%; Table II) with missing spread of disease would probably have prevented full control of the effects of stage shift. The increasing proportion with unknown stage for cancers of the liver and thyroid would similarly reduce our ability to control for stage; these also showed substantial falls in excess risk over the period. The fall in excess risk for liver cancer may be due to its rapidly rising incidence due to chronic viral hepatitis in Australia[8,24] and associated greater detection due to surveillance of infected patients. Thyroid cancer is similarly increasing in incidence[8] and at least some of this is due to greater detection, possibly of lesions with limited potential to advance.[25]

Our results are consistent with those of population-based studies of trends in cancer survival from other countries in which the effects of trends in stage at diagnosis have been considered. The most comprehensive analysis of this type was presented by Dickman et al. using 560,000 cases in 37 categories of cancer type reg-

istered by the Finnish cancer registry, diagnosed in 1955–94 and followed up to 1995.[26] Stage data were available in the same categories as we have used and 22% of all cancers were of unknown stage. Time trends in relative survival were presented only graphically and without adjustment for possible confounding variables. Five-year relative survival from all cancers increased by about 20 percentage points from 1955–64 to 1985–94. Similar uptrends were observed in each category of stage, with the absolute increase being greater in localised and, to a lesser extent, in disease with regional spread than in disease with distant spread. This is similar to the pattern we observed (Fig. 1). A few population-based studies of cancer survival in other countries, limited to colorectal or breast cancers, have taken account of trends in stage at diagnosis. All except one of colorectal cancer, in Singapore, were done in European countries, and all found reductions in fatality or increases in survival, which were apparently independent of trends in stage.[27–31]

How plausible is it that downtrends in excess risk of death that we have observed are due to improvements in cancer management? There are good grounds for believing that such improvements have occurred. Surgical techniques developed during the 1980s and the introduction of adjuvant chemotherapy in the 1990s for colorectal cancer patients may have contributed to their apparently improved outcome.[32] These modalities are now in common use in NSW.[33] The increased use of tamoxifen and adjuvant chemotherapies since the later 1980s should have contributed to the improved survival for breast cancer patients.[18,34,35] These therapies too are in common use in Australia.[36,37] For prostate cancer, increased survival could also be due to changes in treatment practice in the late 1980s and early 1990s when hormonal therapy was introduced for patients with advanced disease and older patients.[38,39] More recently, increasing use of radical prostatectomy in early stage prostate cancer may also have improved outcome.[40]

The approximate 15% fall in excess risk of death from each of Hodgkin's disease, non-Hodgkin lymphoma and multiple myeloma is compatible with 9–16% relative increases in 5-year survival from these cancers between 1980–84 and 1995–97 in data from the US SEER registries.[41] The relatively modest changes for these three related cancers are probably due to the most important therapies that changed outcomes for these diseases, having been already well established in 1980.[42–44]

The small but significant uptrends in excess risk of death from cancers of the connective tissue and unspecified sites might be explained by their falls in incidence over the period of study (Table I) due, perhaps, to increasing classification of better differentiated or less widely spread cancers to more specific sites with more specific histopathological diagnosis or more effective location of the probable site. The statistically nonsignificant uptrend in excess risk for bladder cancer is probably mainly due to a fall in registration of noninvasive tumours of the bladder after 1985, with availability of pathology reports and reduced reporting of bladder papillomata as cancer.[45]

These considerations notwithstanding, there remains justifiable concern about the impact of the increase in the proportion of unknown stage cancers on our adjustment for stage of cancer and especially the possibility that the distribution of stages within this unknown stage group may also have changed with time, a possibility we cannot rule out. There was, however, little correlation (Pearson's correlation coefficient of 0.10) between the size of the change in the proportion of unknown stage between 1989–92 and 1993–96 and the effect of stage adjustment on the RER in 1993–96, which suggests little such bias. Moreover, a comparison of Tables II and III shows that for all cancers for which there was little change in the proportion of unknown stage cancer between 1980–84 and 1989–92, there was still an important reduction in excess risk, with an upper confidence limit for the RER of less than 1.0 in this interval. This was so for cancers of the oesophagus, stomach, colon, rectum, lung, cervix, body of uterus and kidney, for which we suspect no other sources of bias, as well as for melanoma, breast cancer and thyroid cancer, for which we do. Thus for the former set of these, at least, the best explanation for reduced fatality in the period of study is improvement in treatment.

Acknowledgements

We thank the three anonymous reviewers for providing constructive comments, which led to significant improvement in the manuscript. We thank the NSW Central Cancer Registry for providing the data. Bruce Armstrong's research is supported by a University of Sydney Medical Foundation Programme Grant.

References

1. Pui CH. Childhood leukemias. N Engl J Med 1995;332:1618–30.
2. Horwich A, Mason M, Hendry W. Testicular tumours. In: Souhami RL, Tannock I, Hohenberger P, Horiot J-C, eds. Oxford textbook of oncology, 2nd ed. New York: Oxford University Press, 2001. 2007–35.
3. Diehl V, Mauch PM, Harris NL. Hodgkin's disease. In: Devita VT, Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and pratice of oncology, 6th ed. Philadelphia, USA: Lippincott Williams and Wilkins, 2001. 2339–87.
4. Jemal A, Clegg LX, Ward E, Ries LA, Wu X, Jamison PM, Wingo PA, Howe HL, Anderson RN, Edwards BK. Annual report to the nation on the status of cancer, 1975–2001, with a special feature regarding survival. Cancer 2004;101:3–27.
5. Kramer BS, Klausner RD. Grappling with cancer—defeatism versus the reality of progress. N Engl J Med 1997;337:931–4.
6. Bailar JC, III, Gornik HL. Cancer undefeated. N Engl J Med 1997; 336:1569–74.
7. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. N Engl J Med 1985;312: 1604–8.
8. Tracey E, Roder D, Bishop J, Chen S, Chen W. Cancer in New South Wales: incidence and mortality 2003. Sydney: Cancer Institute NSW, 2005.
9. Parkin DM, Muir CS. Cancer incidence in five continents. Comparability and quality of data. IARC Sci Publ 1992;45–173.
10. Supramaniam R, Smith DP, Coates MS, Armstrong BK. Survival from cancer in New South Wales in 1980 to 1995. Sydney: NSW Cancer Council, 1999.
11. Percy C, Van Holten V, Muir CS, eds. International classification of diseases for oncology, 2nd ed. Geneva, Switzerland: World Health Organisation, 1990.
12. Muir CS, Percy C. Cancer registration: principles and methods. Classification and coding of neoplasms. IARC Sci Publ 1991;64–81.
13. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr 1961;6:101–21.
14. Chiang CL. Introduction to stochastic processes in biostatistics. New York: John Wiley, 1968.
15. Ederer F, Heise H. Instructions to IMB 650 programers in processing survival computations. Methodological note No. 10, end results evaluation section. Bethesda, MD: National Cancer Institute, 1959.
16. Yu XQ, O'Connell DL, Gibberd RW, Smith DP, Dickman PW, Armstrong BK. Estimating regional variation in cancer survival: a tool for improving cancer care. Cancer Causes Control 2004;15: 611–8.
17. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. Stat Med 2004;23:51–64.
18. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, Mandelblatt JS, Yakovlev AY, Habbema JD, Feuer EJ. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784–92.
19. Cole P, Morrison AS. Basic issues in population screening for cancer. J Natl Cancer Inst 1980;64:1263–72.
20. Black WC, Welch HG. Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. N Engl J Med 1993;328:1237–43.
21. Kricker A, Farac K, Smith D, Sweeny A, McCredie M, Armstrong B. Breast cancer in New South Wales in 1972–1995: tumour size and the impact of mammographic screening. Int J Cancer 1999;81: 877–80.
22. Burton RC, Coates MS, Hersey P, Roberts G, Chetty MP, Chen S, Hayes MH, Howe CG, Armstrong BK. An analysis of a melanoma epidemic. Int J Cancer 1993;55:765–70.

23. Smith DP, Armstrong BK. Prostate-specific antigen testing in Australia and association with prostate cancer incidence in New South Wales. Med J Aust 1998;169:17–20.
24. Law MG, Roberts SK, Dore GJ, Kaldor JM. Primary hepatocellular carcinoma in Australia, 1978–1997: increasing incidence and mortality. Med J Aust 2000;173:403–5.
25. Burgess JR, Dwyer T, McArdle K, Tucker P, Shugg D. The changing incidence and spectrum of thyroid carcinoma in Tasmania (1978–1998) during a transition from iodine sufficiency to iodine deficiency. J Clin Endocrinol Metab 2000;85:1513–7.
26. Dickman PW, Hakulinen T, Luostarinen T, Pukkala E, Sankila R, Soderman B, Teppo L. Survival of cancer patients in Finland 1955–1994. Acta Oncol 1999;38(Suppl 12):1–103.
27. Angell-Andersen E, Tretli S, Coleman MP, Langmark F, Grotmol T. Colorectal cancer survival trends in Norway 1958–1997. Eur J Cancer 2004;40:734–42.
28. Du WB, Chia KS, Sankaranarayanan R, Sankila R, Seow A, Lee HP. Population-based survival analysis of colorectal cancer patients in Singapore, 1968–1992. Int J Cancer 2002;99:460–5.
29. Faivre-Finn C, Bouvier-Benhamiche AM, Phelip JM, Manfredi S, Dancourt V, Faivre J. Colon cancer in France: evidence for improvement in management and survival. Gut 2002;51:60–4.
30. Martijn H, Voogd AC, van de Poll-Franse LV, Repelaer van Driel OJ, Rutten HJ, Coebergh JW. Improved survival of patients with rectal cancer since 1980: a population-based study. Eur J Cancer 2003;39:2073–9.
31. Thomson CS, Brewster DH, Dewar JA, Twelves CJ. Improvements in survival for women with breast cancer in Scotland between 1987 and 1993: impact of earlier diagnosis and changes in treatment. Eur J Cancer 2004;40:743–53.
32. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, Ungerleider JS, Emerson WA, Tormey DC, Glick JH. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990;322:352–8.
33. Armstrong K, O'Connell DL, Leong D, Spigelman AD, Armstrong BK. The New South Wales colorectal cancer care survey, Part 1: surgical management. Sydney: The Cancer Council New South Wales, 2004.
34. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998;351:1451–67.
35. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998;352:930–42.
36. National Breast Cancer Centre. National survey of women with early breast cancer: their perceptions of care (1997). Sydney: National Breast Cancer Centre, 2004.
37. McEvoy SP, Ingram DM, Byrne MJ, Joseph DJ, Dewar J, Trotter J, Harper C, Haworth C, Harvey JM, Sterrett GF, Jamrozik K, Fritschi L. Breast cancer in Western Australia: clinical practice and clinical guidelines. Med J Aust 2004;181:305–9.
38. Akaza H. Adjuvant goserelin improves clinical disease-free survival and reduces disease-related mortality in patients with locally advanced or localized prostate cancer. BJU Int 2004;93:42–6.
39. D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004;292:821–7.
40. Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson SO, Bratell S, Spangberg A, Busch C, Nordling S, Garmo H, Palmgren J, Adami HO, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2005;352:1977–84.
41. Ries LA, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Mariotto A, Feuer EJ, Edwards BK, eds. SEER Cancer Statistics Review, 1975–2002. Bethesda, MD: National Cancer Institute. Based on November 2004 SEER data submission, posted to the SEER website 2005 [accessed July 2005].
42. DeVita VT, Jr, Simon RM, Hubbard SM, Young RC, Berard CW, Moxley JH, III, Frei E, III, Carbone PP, Canellos GP. Curability of advanced Hodgkin's disease with chemotherapy. Long-term follow-up of MOPP-treated patients at the National Cancer Institute. Ann Intern Med 1980;92:587–95.
43. McKelvey EM, Gottlieb JA, Wilson HE, Haut A, Talley RW, Stephens R, Lane M, Gamble JF, Jones SE, Grozea PN, Gutterman J, Coltman C, et al. Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. Cancer 1976;38:1484–93.
44. Alexanian R, Haut A, Khan AU, Lane M, McKelvey EM, Migliore PJ, Stuckey WJ, Jr, Wilson HE. Treatment for multiple myeloma. Combination chemotherapy with different melphalan dose regimens. JAMA 1969;208:1680–5.
45. McCredie M, Stewart J, Smith D, Supramaniam R, Williams S. Observations on the effect of abolishing analgesic abuse and reducing smoking on cancers of the kidney and bladder in New South Wales, Australia, 1972–1995. Cancer Causes Control 1999;10:303–11.

Int. J. Cancer: **119,** 2993 (2006)

Erratum

Yu XQ, O'Connell DL, Gibberd RW, Coates AS, Armstrong BK. Trends in survival and excess risk of death after a diagnosis of cancer in 1980 to 1996 in New South Wales Australia. Int J Cancer 2006;119:894–900.

There were errors in Table I of the article by Yu et al. On page 895, there were errors in the age–sex standardized incidence rates and average annual percent changes in Table I. However, these errors did not change the direction of the trends in incidence or more importantly affect our interpretation of the results. The corrected table is attached.

TABLE I – AGE–SEX STANDARDIZED INCIDENCE RATES (PER 100,000) AND AVERAGE ANNUAL PERCENT CHANGE, WITH THE CORRESPONDING 95% CI, FOR 28 CANCERS, IN NSW, AUSTRALIA, 1980–1996

Cancer type	Number of new cases	Standardized incidence rates for 1993–1996[1]	Average annual percent change 1980–1996	95% CI
Lip	3,562	4.5	2.52	0.86, 4.21
Head and neck	12,553	14.1	0.00	−0.58, 0.58
Oesophagus	4,167	5.2	1.20	0.53, 1.88
Stomach	10,354	11.2	−2.66	−3.11, −2.21
Colon	32,414	40.3	0.56	0.19, 0.92
Rectum	17,688	22.2	0.94	0.57, 1.31
Liver	1,891	3.4	7.89	6.47, 9.33
Gallbladder	2,709	3.3	0.30	−0.63, 1.24
Pancreas	8,091	9.9	0.05	−0.42, 0.52
Lung	39,769	45.2	−0.54	−0.77, −0.31
Melanoma	32,316	42.1	3.05	2.14, 3.96
Mesothelioma	1,634	2.6	5.11	4.14, 6.09
Connective tissue	2,088	2.3	−0.16	−1.25, 0.94
Breast	41,476	113.9	2.72	2.30, 3.13
Cervix	5,957	11.6	−1.63	−2.22, −1.04
Body of the uterus	5,793	14.0	0.93	0.27, 1.59
Ovary	5,375	12.1	−0.30	−0.87, 0.27
Prostate	37,374	146.1	7.09	5.45, 8.75
Testis	2,314	5.4	2.68	1.79, 3.57
Bladder	12,139	12.5	−2.90	−3.63, −2.16
Kidney	9,053	12.1	2.79	2.25, 3.33
Thyroid	3,438	5.1	4.92	3.86, 5.99
Brain	5,404	6.4	1.08	0.62, 1.55
Hodgkin's disease	1,856	1.9	−0.76	−1.50, −0.02
Non-Hodgkin lymphoma	12,688	17.4	3.04	2.68, 3.41
Multiple myeloma	4,229	5.5	1.09	0.37, 1.81
Leukaemia	9,365	11.7	0.48	−0.04, 1.00
Unspecified	17,337	20.1	−0.49	−1.03, 0.06

[1]Age–sex adjusted to the Australian estimated residential population of 2001.

DOI 10.1002/ijc.22271
Published online 16 October 2006 in Wiley InterScience (www.interscience.wiley.com).

Other publications arising from thesis-related work

McKinnon JG, Yu XQ, McCarthy WH, Thompson JF. Prognosis for patients with thin cutaneous melanoma: long-term survival data from New South Wales Central Cancer Registry and the Sydney Melanoma Unit. *Cancer* 2003; 98(6):1223-1231.

Jong KE, Smith DP, Yu XQ, O'Connell DL, Goldstein D, Armstrong BK. Remoteness of residence and survival from cancer in New South Wales. *Med J Aust* 2004; 180(12):618-622.

Yu XQ, O'Connell DL, Forman D. Comparison of cancer survival in UK and Australia: rates are higher in Australia for three major sites. *Br J Cancer* 2004; 91(9):1663-1665.