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

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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

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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.

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