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Survival trends of cancer among the south Asian and non-south Asian population under 30 years of age in Yorkshire, UK

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ABSTRACT

INTRODUCTION: Several studies have shown differences in survival trends between ethnic groups across adults with cancer in the UK. It is unclear whether these differences exist exclusively in the older adult population or whether they begin to emerge in children and young adults.

METHODS: Subjects (n=3534) diagnosed with cancer under 30 years of age in Yorkshire between 1990 and 2005 were analysed. Differences in survival rates for diagnostic subgroups were estimated by ethnic group (south Asian or not) using Kaplan–Meier estimation and Cox regression.

RESULTS: When compared to non-south Asians (all other ethnic groups excluding south Asians) a significant increased risk of death was seen for south Asians with leukaemia (hazard ratio (HR) = 1.75; 95% confidence interval (CI) = 1.11 to 2.76) and lymphoma (HR=2.05; 95%CI=1.09 to 3.87), whereas south Asians with solid tumours other than central nervous system tumours had a significantly reduced risk of death (HR=0.50 95%CI=0.28 to 0.89). This was independent of socioeconomic deprivation.

CONCLUSION: We found evidence of poorer survival outcomes for south Asians compared to non-south Asian children and young adults with leukaemia and lymphoma, but better outcomes for south Asian children and young adults with other solid tumours. This needs to be explained, and carefully addressed in the on-going development of cancer services.

Keywords: Cancer; Epidemiology; Ethnicity; Paediatric; Survival

INTRODUCTION

Cancer survival rates for children and young adults across Europe have improved markedly over recent decades, yet outcomes for certain types of cancers have been shown to vary by gender, age, treatment, place of care, geographical location and deprivation [1-4].

Within the UK, survival trends vary according to ethnic group across the adult age range. Worse survival rates from breast cancer have been observed amongst non-south Asian women (65-67% 5-year survival) compared to south Asian women (70-73% 5-year survival) [5-6]. However, it is unclear whether survival differences by ethnic group in the UK exist exclusively in the older adult population or whether they begin to emerge in childhood or young adults. Survival rates for UK childhood cancer have shown few consistent patterns with ethnicity, although south Asians with acute lymphoblastic leukaemia (ALL) had a significantly higher risk of death compared to White children in one study [7], and a non-significantly higher risk in two studies [8-9]. In the US, the overall five year cancer survival rate of Hispanic children (72%) was found to be lower than for White children (84%), whilst another study shows Black children with ALL had poorer survival than White children (75% vs. 85%) [10-11]. However, this could be as a result of differences in socio-economic status affecting access to health care services in the US. Recent studies in Europe and England have reported on survival trends of teenage and young adult (TYA) cancer, however none have focused on differences by ethnic group [1,12].

This study utilises high quality population-based data on children and young adults diagnosed with cancer between 1990 and 2005 in combination with a validated method of ethnicity assignment based on name analysis and linked hospital episode statistics (HES) data [13]. The specific aim was to investigate for the first time in the UK

differences and trends in cancer survival by ethnic group (south Asian or not) across the childhood (0–14) and young adult (15–29) age ranges.

MATERIALS AND METHODS

Case Data

The data used for this study cover a 16 year period from 1990 to 2005 including all children and young adults under the age of 30, living in the former Yorkshire Regional Health Authority who were diagnosed with cancer other than skin carcinomas and melanomas. Cases were extracted from the population-based Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP) [13].

Diagnoses were categorised into groups according to the International Classification of Childhood Cancer (ICCC); this histologically based classification scheme was chosen in preference to the site based classification used for adults [14], as the majority of our cases (54%) are aged 18 and under. In order to retain statistical power, diagnoses were grouped into four main categories; leukaemia, lymphoma, central nervous system (CNS) tumours, and other solid cancers, corresponding to ICCC codes I, II, III, and IV–XII. Biennial proactive follow-up of cases was carried out to ascertain each individual's vital status, with a censoring date of 31st December 2009 so that all cases had a potential follow-up period of at least four years.

The former Yorkshire region contained 11% of all south Asians under the age of 30 in England (Census, 2001) compared to only 7.4% of all 0–29 year old non-south Asians.

Assignment of Ethnic Group

Ethnicity was assigned as either south Asian (i.e. of Pakistani, Indian, or Bangladeshi origin) or non-south Asian (all other ethnicities) primarily via two name analysis programs (Nam

Pehchan and SANGRA) and secondly through an independent validation with linked inpatient HES data [13,15-16].

Statistical Analysis

Survival rates were examined overall and by major histological subtype to determine differences by ethnic group. Deprivation scores for address at diagnosis were derived using the Townsend index based on the 2001 Census. This electoral ward based measure of material wealth was derived as a composite score based on levels of unemployment, non-home ownership, over-crowding, and non-car-ownership [17].

Differences were initially assessed using Kaplan–Meier (KM) estimation and univariate log–rank tests. Cox regression modelling was used to assess the independent impact of ethnic group on the survival time for all cancers combined and in each of the four main diagnostic groups adjusting for age, sex, year of diagnosis, deprivation, and stage of disease. A test for linearity was used to determine whether age and year were appropriately modelled as continuous variables. To differentiate between the independent effect of ethnicity and the potentially confounding effect of socioeconomic status, deprivation was adjusted for within each Cox model. Deprivation was analysed as a continuous variable using Townsend scores.

Stage at diagnosis was included in the analysis; instances where data on stage were unavailable were imputed using ordered logistic regression. White blood cell count was used as a proxy for stage when modelling leukaemia survival rates and missing values were imputed using linear regression. White blood cell count was log transformed to an approximately normal distribution. Missing data on stage was assumed to be missing at random, as opposed to missing completely at random after interrogation of missing data patterns and comparisons of individuals with observed and missing data. Separate imputation models were created for all cancers combined and each main diagnostic group.

Each imputation model included the following variables; gender, age, year of diagnosis, deprivation level, ethnicity, treatment type, diagnostic group/subgroup, and relapse status. Interactions tested within the main analysis were also included within the imputation model (deprivation and ethnicity) [18]. Additionally, the Nelson–Aalen (NA) estimate of the cumulative hazard function and censoring indicator were included in the imputation model, to avoid underestimation of stage and survival time [19-20]. A total of 65 imputations were completed for each diagnostic group. The results of each imputation were modelled individually using Cox regression and combined parameter estimates were calculated using Rubin's rules [21]. All imputation methods were implemented in Stata 11 using multiple imputation by chained equations (MICE) [22-23].

Hazard ratios (HR) were taken from the Cox regression models and reported for each covariate. In order to retain power, we considered separate Cox models for each major diagnostic group so that they adhered to the general rule of ten or more deaths per covariate [24]. Schoenfeld residuals were used to assess the Cox proportional hazards assumption for each imputation [25]. Random scatters around zero on plots of the residuals against the rank survival time by covariate validated these assumptions [26]. Furthermore, Monte Carlo (MC) standard errors were calculated to measure the level of uncertainty in all estimated quantities of each model, and the c-index measure of discrimination was used to assess predictive performance [27-28]. For each model estimate, MC errors were sufficiently small so that statistical significance remained unaltered at the upper and lower bounds and predictive power was above 70% in all cases. Results from a complete-case analysis were compared to those from the multiple imputation analysis (see supplementary material). There were no important differences in terms of the direction of effects; however, there was an overall improvement in the precision of the analysis indicated by a reduction in standard errors.

RESULTS

A total of 3534 children and young adults were registered with cancer between 1990 and 2005 whilst living in the former Yorkshire region, of which 275 (7.8%) were south Asian (Table 1). We observed a total of 896 (27%) non-south Asian deaths compared to 80 (29%) south Asian deaths over the study period. The overall five year survival rate for both groups together was 75% (95% confidence interval (CI) 74–76%).

Figure 1 contains univariate KM survival estimates for each main diagnostic group. Log-rank tests indicated no difference in survival rates between south Asians and non-south Asians for all cancers combined ($p=0.27$), lymphoma ($p=0.23$), CNS tumours ($p=0.55$), or other solid tumours ($p=0.29$). A significant difference was observed for leukaemia ($p=0.02$), with south Asians exhibiting consistently lower survival rates. The five year survival rate for south Asians with leukaemia was 60% (95%CI 47% to 71%) compared to 70% (95%CI 67% to 74%) for non-south Asians. Univariate log-rank tests showed evidence of a significant difference in survival between diagnostic groups ($p=0.001$).

KM estimates comparing 0–14 and 15–29 year olds by diagnostic group showed 15–29 year olds had significantly lower survival rates for leukaemia ($p=0.001$) and other solid tumours ($p=0.001$) but very little difference in survival rates for all cancers combined or lymphoma. No differences in survival rates were observed by gender.

Cox Regression

Data on stage of disease at diagnosis was missing in 66% overall, 66% for lymphoma cases, 28% for CNS tumours, and 69% for other solid tumours. Additionally, white blood cell count was missing for 57% amongst leukaemia cases. There were no missing data in any of the other variables within the analysis. Missing values for stage of disease (and white blood cell count in case of leukaemia) were imputed.

The results of the Cox proportional hazards modelling for all cancers combined and each main diagnostic group are given in Table 2, where each parameter estimate is mutually adjusted for all other covariates listed in the appropriate column. Overall for all cancers combined, there was no evidence of a significant difference in survival between south Asians and non-south Asians. However, significant differences in survival by ethnic group were observed amongst those with leukaemia, lymphoma, and other solid tumours. South Asians with leukaemia were 1.8 times more likely to die than non-south Asians, this difference was more apparent for 15–29 year olds (almost twice as likely), but was a consistent finding across diagnostic subgroups. South Asians with lymphoma were more than twice as likely to die compared to non-south Asians and this difference was most apparent amongst 0–14 year olds, and was observed consistently for both Hodgkin’s disease (HD) and non-Hodgkin’s lymphoma (NHL). Ethnicity did not demonstrate any independent effect on survival time amongst those with CNS tumours. For other solid tumours, south Asians were less likely to die by 50% compared to non-south Asians. This difference was particularly evident for sympathetic nervous system tumours, bone tumours, and sarcomas.

We observed no significant differences in survival rates by gender for any diagnostic group.

For all cancers combined, CNS tumours, and other solid tumours, there was a two to three percent significant increased risk of death for each single year in increase of age at diagnosis. We observed that older TYA diagnosed with leukaemia (aged 15–19, 20–24, and 25–29 at diagnosis) were twice as likely to die compared to those in the youngest age group (0–4 years old). For lymphoma 10–14 year olds were half as likely to die compared to 25–29 year olds. No significant differences were observed between the other age categories amongst this diagnostic group.

Almost all diagnostic groups showed a consistent improvement in survival over time apart from other solid tumours. Significant improvements in survival since 1990 were observed for lymphoma and leukaemia (five and six percent per year respectively).

There was no significant independent effect on survival by level of deprivation except for those diagnosed with lymphoma, such that increasing deprivation is associated with better survival rates. Since the south Asian population tends to live in more deprived areas, interactions between ethnicity and deprivation were tested in each model; however they were not statistically significant.

For all cancers combined, leukaemia, CNS tumours, and other solid tumours survival rates were significantly lower in patients presenting with a more advanced stage of disease. There was no significant difference in survival rates of those with lymphoma according to stage of disease.

DISCUSSION

Our findings relate to a novel population-based study examining survival trends in relation to ethnic group encompassing the childhood, teenage and young adult age range. We observed significantly poorer survival outcomes for south Asians with leukaemia and lymphoma compared to non-south Asians, but improved survival for south Asians with other non-CNS solid tumours. The Yorkshire region is representative nationally in terms of its socioeconomic and demographic profile, and therefore our results can be easily generalised to the rest of the UK population [29]. Furthermore, an estimated 60% of the south Asian population within the study region originates from Mirpur in rural Pakistan, making it one of the few regions in the UK that allows for detailed analysis of a relatively homogeneous south Asian population [30].

A few UK studies, including one from Yorkshire, have found evidence of survival inequalities occurring between ethnic groups in children under the age of 16 years [8-9]. However, our results describing the independent effects on survival of being south Asian ethnic origin, provide an important benchmark from which to judge the impact of the National Institute for Health and Clinical Excellence Improving Outcomes Guidance (IOG) for Children and Young People, due to be implemented by 2011 [31]. The public health implications and necessity to understand reasons for these discrepancies in survival are especially pertinent as we expect a three-fold increase of young people to be diagnosed with cancer who are of south Asian origin over the next 10-20 years [13].

Key observations were the statistically significant two-fold increased risk of death for south Asians with leukaemia and lymphoma in contrast to non-south Asians, as well as the significantly higher risk of death for non-south Asians with other solid tumours compared to south Asians. For other solid tumours this difference was seen across all ages, whereas for leukaemia it was most apparent amongst 15–29 year olds, and for lymphoma it appeared to be limited to patients aged 0–14 years; in all instances the effect remained significant even after adjustment for deprivation. For lymphoma, there was also an unexpected independent lower risk of death for individuals from more deprived areas. This may be due to subtle differences in the socioeconomic distribution between Indians, Pakistanis and Bangladeshis, or the use of an area based measure which may not necessarily reflect socioeconomic status at an individual level.

In relation to survival and age at diagnosis, the data revealed that older patients, especially those aged 15–29 years, were significantly more likely to die than children under 15 years of age even after allowing for diagnostic group and stage/white cell count (acting as a proxy for stage) in the regression models. This increased mortality risk was seen for all cancers combined, leukaemia, CNS, and other solid tumours. Taken together with the increased risk of death associated with ethnicity, our results infer that south Asian patients aged 15–29

years with leukaemia would be four times more likely to die than non-south Asian children, under the assumption of multiplicative effects from the Cox regression modelling. Part of the explanation for lower survival rates seen in older children and young adults could be due either to differences in the biological or molecular characteristics of tumours occurring in this age group or the reported smaller proportion of older TYA patients (19% in 2006/2007) enrolled onto clinical trials than their childhood cancer counterparts (51% in 2006/2007) [32]. Efforts are underway in the UK to ensure all TYA have the opportunity to enter trials where appropriate and are treated within Principal Treatment Centres (PTC) so that individuals can be treated and followed-up within an environment with appropriate age and/or site-specific expertise.

Limitations of our work included the relatively small number of south Asians in our study and therefore some lack of statistical power. Furthermore, stage at diagnosis was missing in two-thirds of cases overall. However, multiple imputation was considered the best available option. Failure to include stage at diagnosis in the multivariate analysis could lead to bias in the results, whereas multiple imputation avoids discarding non-missing stage data or case wise deletion. Imputation for this level of missing values was considered acceptable because values were imputed for only one variable due to the availability of complete case data for all other variables included in the analysis. The use of multiple imputation is fast becoming an accepted statistical technique for handling missing data [33-34]. It has led to an improvement in precision of our estimates compared to a complete-cases analysis indicated by a reduction in standard errors by 44% on average.

Importantly, survival rates showed a consistent improvement over the study period for leukaemia and lymphoma. However, such an improvement was not observed for all cancers combined, CNS tumours, or other solid tumours.

In summary, we found evidence of poorer survival outcomes of leukaemia and lymphoma associated with those of south Asian ethnic origin; particularly those aged over 15 years with leukaemia and under 15 years with lymphoma. Further work should focus carefully on the implementation and impact of the IOG for Children and Young People examining outcomes between ethnic minority groups across the UK.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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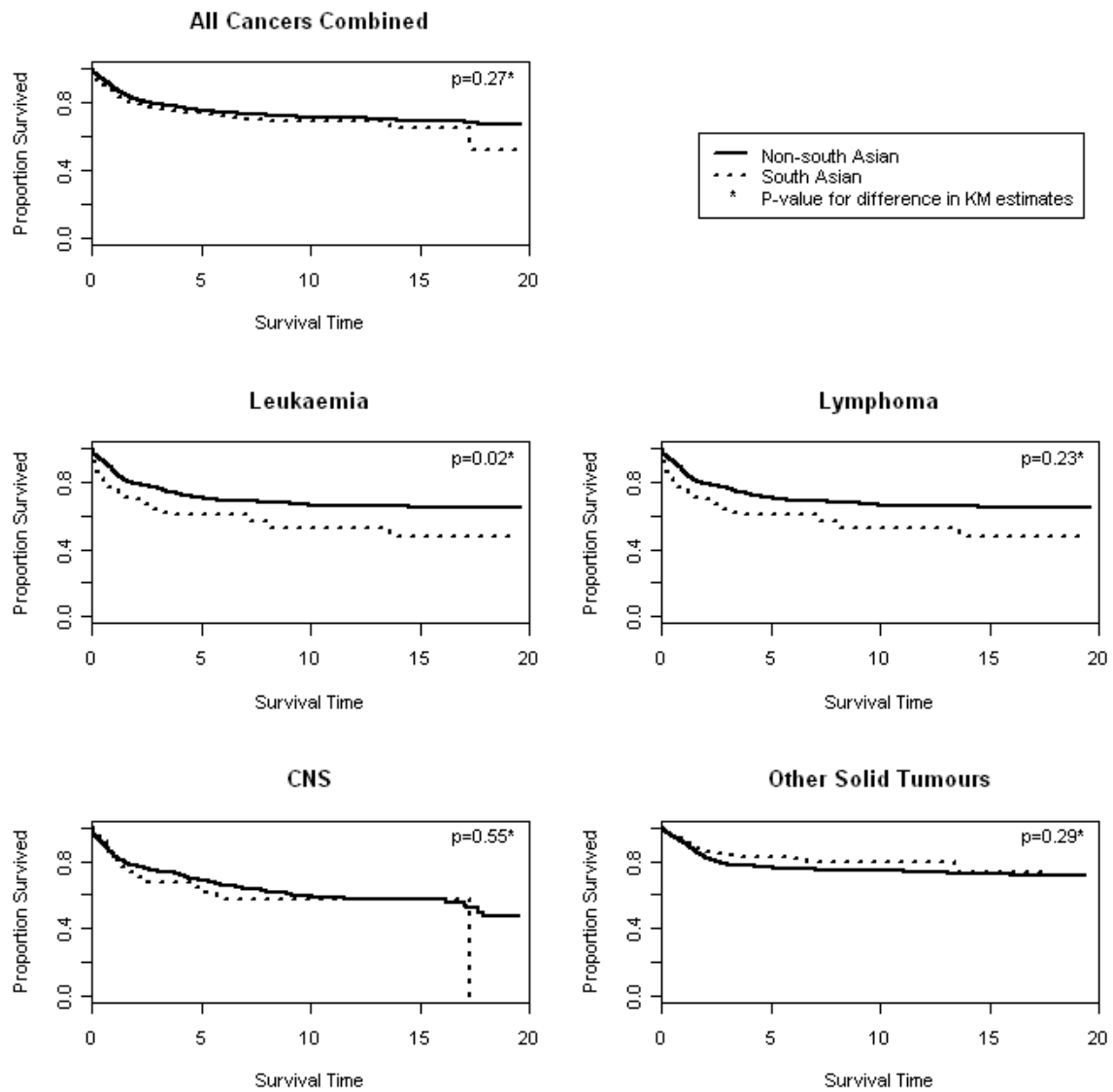
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FIGURE LEGENDS

Figure 1: Kaplan–Meier (KM) estimates comparing south Asians and non–south Asians by diagnostic group



TABLES

Table 1: Number of cases by diagnostic group, age, and gender for those diagnosed with cancer within Yorkshire, 1990–2005

Diagnostic Group	Number of Cases		Total	P-value
	South Asian Cases (column %)	Non-south Asian Cases (column %)		
<i>Leukaemia</i>	66 (24%)	649 (20%)	715	0.040
<i>Lymphoma</i>	71 (26%)	689 (21%)	760	
<i>CNS Tumours</i>	37 (13%)	562 (17%)	599	
<i>Other Solid Tumours</i>	101 (37%)	1359 (42%)	1460	
Age at diagnosis (years)				
0-4	66 (24%)	650 (20%)	716	0.743
5-9	40 (15%)	364 (11%)	404	
10-14	37 (13%)	375 (12%)	412	
15-19	42 (15%)	463 (14%)	505	
20-24	41 (15%)	597 (18%)	638	
25-29	49 (18%)	810 (25%)	859	
Gender				
<i>Male</i>	159 (58%)	1995 (61%)	2154	0.436
<i>Female</i>	116 (42%)	1264 (39%)	1380	
Total	275	3,259	3534	

Table 2: Hazard ratios (HR) and 95% confidence intervals (CI) from a Cox regression model for those diagnosed with cancer in Yorkshire, 1990-2005.

Variable	Model 1: All cancers combined	
	Category	HR (95% CI)
Ethnicity	<i>NSA</i>	1
	<i>SA</i>	0.86 (0.65-1.15)
Gender	<i>Male</i>	1
	<i>Female</i>	1.12 (0.97-1.30)
Age at diagnosis	<i>0-29</i>	1.03 (1.02-1.03)**
Year of diagnosis	<i>1990-2005</i>	0.94 (0.91-0.97)**
Deprivation	<i>Townsend Score</i>	1.02 (0.98-1.07)
Stage of Disease ^a	<i>I</i>	1
	<i>II</i>	2.39 (1.44-3.97)**
	<i>III</i>	7.32 (4.61-11.60)**
	<i>IV</i>	8.20 (5.52-12.16)**
Diagnostic Group	<i>Leukaemia</i>	0.81 (0.59-1.09)
	<i>Lymphoma</i>	0.61 (0.48-0.78)**
	<i>CNS tumours</i>	1.58 (1.31-1.92)**
	<i>Other solid tumours</i>	1

*Significant at 5% level; **Significant at 1% level; ^aMissing values for stage were imputed. **Abbreviations** CNS: central nervous system; NSA: Non-south Asian; SA: south Asian

Table 3: Hazard ratios (HR) and 95% confidence intervals (CI) from Cox regression models for leukaemia, lymphoma, central nervous system tumours and other solid tumours, 1990–2005

Variable	Model 1a: Leukaemia		Model 1b: Lymphoma		Model 1c: CNS tumours		Model 1d: Other solid tumours	
	Category	HR (95% CI)	Category	HR (95% CI)	Category	HR (95% CI)	Category	HR (95% CI)
Ethnicity	NSA	1	NSA	1	NSA	1	NSA	1
	SA	1.75 (1.10-2.76)*	SA	2.05 (1.09-3.87)*	SA	1.51 (0.82-2.78)	SA	0.50 (0.28-0.89)*
Gender	Male	1	Male	1	Male	1	Male	1
	Female	1.03 (0.79-1.34)	Female	1.21 (0.82-1.80)	Female	1.00 (0.75-1.32)	Female	0.97 (0.69-1.35)
Age at diagnosis ^a	0-4	1	0-4	1.28 (0.65–2.51)	0-29	1.02 (1.01-1.04)**	0-29	1.03 (1.01-1.05)**
	5-9	0.70 (0.44–1.10)	5-9	0.66 (0.30–1.43)				
	10-14	1.11 (0.68–1.80)	10-14	0.46 (0.23–0.92)*				
	15-19	1.91 (1.24–2.96)**	15-19	0.77 (0.47–1.28)				
	20-24	2.62 (1.67–4.13)**	20-24	0.86 (0.55–1.34)				
	25-29	2.56 (1.62–4.03)**	25-29	1				
Year of diagnosis	1990-2005	0.94 (0.92-0.98)**	1990-2005	0.95 (0.91-0.99)*	1990-2005	0.99 (0.96-1.03)	1990-2005	1.01 (0.98-1.04)
Deprivation		1.01 (0.97-1.05)		0.94 (0.89-0.99)*		1.01 (0.96-1.05)		1.03 (0.99-1.08)
Stage of Disease ^b	Log(WCC)	1.26 (1.05-1.51)*	I	1	I	1	I	1
			II	1.06 (0.32–3.50)	II	2.72 (1.50–4.92)**	II	4.73 (1.17-19.04)*
			III	1.47 (0.51–4.28)	III	9.95 (5.29–18.74)**	III	19.11 (6.00-60.82)**
			IV	2.87 (0.93–8.83)	IV	13.72 (7.76–24.26)**	IV	20.10 (6.91-58.44)**
Diagnostic Subgroup	ALL	1	HD	1	Ependymoma	1	Sympathetic NS	1
	AML	1.98 (1.45-2.72)**	NHL	2.49 (1.10-3.84)**	Astrocytoma	2.36 (1.31–4.24)*	Renal	0.35 (0.18-0.68)**
	Other	0.87 (0.49-1.56)			PNET	0.79 (0.42–1.49)	Malignant bone Soft-tissue	0.57 (0.26-1.24)
					Other Glioma	3.68 (1.87–7.23)**	sarcoma	0.73 (0.40-1.32)
					Other	1.34 (0.64–2.81)	Germ cell	0.19 (0.10-0.35)**
							Other	0.45 (0.21-0.96)*

*Significant at 5% level; **Significant at 1% level; ^aLikelihood ratio test indicates evidence of non-linearity of age for leukaemia (p=0.001) and lymphoma (p=0.03); ^bMissing values of stage were imputed, and white blood cell count was used as a proxy for stage in Model1a. **Abbreviations** ALL: acute lymphoblastic leukaemia; AML: acute myeloid leukaemia; CNS: central nervous system; HD: Hodgkin's disease; NHL: non-Hodgkin's lymphoma; NS: nervous system; NSA: non-south Asian; PNET: primitive neuroectodermal tumours; SA: south Asian; WCC: white blood cell count.