

Patterson MJ, Sutton RJ, Forrest I, Sharrock R, Lane M, Kaufmann A, O'Donnell R, Edmondson R, Wilson BT, Curtin N. [Assessing the function of homologous recombination DNA repair in malignant pleural effusion \(MPE\) samples](#). *British Journal of Cancer* 2014, 111(1), 94-100.

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DOI link to article:

<http://dx.doi.org/10.1038/bjc.2014.261>

Date deposited:

05/10/2015

Embargo release date:

27 May 2015



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Socio-economic patterning in the incidence and survival of males aged 15-24 years diagnosed with non-seminoma testicular cancer in northern England

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Running head: Incidence and survival of males with testicular cancer

Keywords: Socio-economic Factors; Epidemiology; Incidence; Survival; Testicular Neoplasms

Abstract

Purpose: Previous research from developed countries has shown a marked increase in the incidence of testicular cancer in the past fifty years. This has also been demonstrated in northern England, along with improving five-year survival. The present study aims to determine if socio-economic factors may play a role in both aetiology and survival from non-seminoma testicular cancer.

Materials and Methods: We extracted all 214 cases of non-seminoma testicular cancer diagnosed in males aged 15-24 years during 1968-2006 from the Northern Region Young Persons' Malignant Disease Registry, which is a population-based specialist regional registry. Negative binomial regression was used to examine the relationship between incidence and both the Townsend deprivation score (and component variables) and small-area population density. Cox regression was used to analyse the relationship between survival and both deprivation and population density.

Results: Decreased incidence was associated with living in areas of higher household overcrowding for young adults aged 20-24 (relative risk [RR] per 1% increase in household overcrowding=0.79; 95% confidence interval [CI] 0.66 to 0.94) but no association was detected for young people aged 15-19. Community-level household unemployment was associated with worse survival (hazard ratio per 1% increase in household unemployment=1.04; 95% CI 1.00 - 1.08).

Conclusions: This study has shown that increased risk of non-seminoma testicular cancer in teenage and young adult males may be associated with some aspect of more advantaged living. In contrast, greater deprivation is linked with worse survival prospects. The study was ecological by design and so these area-based results may not necessarily apply to individuals.

1. Introduction

Testicular cancer is relatively rare, accounting for less than two percent of all malignancies in males, mainly affecting younger men [1,2]. Since the 1960's, the incidence of testicular cancer has risen markedly in developed countries. However, more recently the incidence of non-seminoma testicular cancer, which tends to affect a younger age group, has reached a plateau [3-5]. The magnitude and uniformity of the observed increases, together with the finding of space-time clustering [6,7], suggests a role for environmental or lifestyle factors in aetiology.

Despite the rise in incidence, survival from testicular cancer has greatly improved in recent years and far exceeds survival from other carcinomas [1,7-9]. In general, survival for most adult cancers has been found to be significantly lower in more deprived areas [10]. A previously published review considered 63 studies that examined the role of socio-economic status on the incidence and survival from testicular cancer: overall more advantaged socio-economic status was associated with greater incidence and better survival [11]. However, one case-control study from the UK found no association between socio-economic status and risk of testicular cancer [12]. Another study from the UK of all testicular cancer (diagnosed up to 2001) found worse survival associated with greater deprivation [13]. However, the possible roles that socio-economic factors may play in determining survival have not been hitherto explored for young males (aged 15-24 years) with non-seminoma testicular cancer in the UK.

In view of previous findings, the aim of this study was to assess geographical variation in incidence and survival of cases of non-seminoma testicular cancer that might arise as a result of environmental or lifestyle factors related to area-level population density and area-level socio-economic deprivation. The following *a priori*

hypotheses were tested: a primary factor influencing geographical heterogeneity of incidence of non-seminoma testicular cancer is modulated by differences occurring in (i) less and more densely populated areas of residence; and (ii) less and more socio-economically deprived areas of residence; and survival from non-seminoma testicular cancer is modulated by differences occurring in (iii) less and more densely populated areas of residence; and (iv) less and more socio-economically deprived areas of residence. These were tested using data from the Northern Region Young Persons' Malignant Disease Registry (NRYPMDR).

2. Materials and methods

2.1 Case data

Data were included for all patients with non-seminoma testicular cancer, aged 15–24 years at time of diagnosis, registered during the period 1968 to 2006 by the Northern Region Young Persons' Malignant Disease Registry (NRYPM DR). This is a specialist registry which has recorded all cases of cancer in children and young adults since its establishment in 1968. It covers the former Northern Region of England, with the exclusion of Barrow-in-Furness (Cumbria). The region is ethnically homogeneous with fewer than 2% from minorities [14-16]. There are low rates of migration into or out of the region [17-19]. The registry currently holds details on over 7000 cases of cancer and is housed within the regional specialist centre for this age-group at the Newcastle upon Tyne Hospitals NHS Foundation Trust. Data on children (aged 0 – 14 years) have been obtained prospectively since 1968. Data on teenagers and young adults (aged 15 – 24 years) have been collected retrospectively for the years 1968 – 1985 and prospectively since then [20]. Although registration is not mandatory, cases are identified from a number of sources, including consultants, death certificates and hospital admissions records. Registry data are regularly cross-checked with regional and national cancer registries, thus ensuring a high level of accuracy and completeness. Data held include demographic details as well as diagnosis and treatment. The registry is exempted (originally under Section 60 of the UK Health and Social Care Act 2001, which has now been superseded by Section 251 of the National Health Service Act 2006) from the need to obtain patient consent for recording and analysis of data.

2.2. Population data

In this study, analyses were performed at the small-area census ward level. The populations of wards, aged 15-24 years, ranged from 45 to 4396 (median = 463). During the study period there were four censuses. There were also widespread boundary changes throughout this time, especially at small-area level. To derive population estimates, allowing for these perturbations, the data were apportioned from the original boundary systems to using the small-area boundaries that applied at the time of the 2001 census [21].

2.3. Demographic data

Census ward demographic characteristics were derived from the censuses. These characteristics were population density (persons resident per hectare) and the Townsend score for area-based level of deprivation [22], which is a combination of four census measures: unemployment (as a percentage of those aged 16 years and over who are economically active) and non-car ownership, non-home ownership and household overcrowding (each as a percentage of all households). A time series of Townsend deprivation scores was constructed by allocating these four constituent measures from the 1971, 1981, 1991 and 2001 censuses to the time periods for cancer diagnosis that were closest, i.e. 1968-1975, 1976-1985, 1986-1995 and 1996-2006 respectively, for the 2001 census geography [23]. Increasingly negative Townsend scores represent lower area deprivation (better). Increasingly positive scores represent higher deprivation (worse). Population density was derived using the apportioned populations and then dividing by the areal extent of the 2001 wards.

2.4. Statistical analysis

Age-specific incidence rates per million person years were calculated based on mid-year population estimates for males only from the study region obtained from the Office for National Statistics. Age-standardised incidence rates (ASR) were calculated based on the standard world population [24]. Temporal trends for incidence were assessed using Poisson regression with the logarithm of population as an offset.

There was evidence of extra-Poisson variation: 95.0% of age group specific ward cells had zero counts. Therefore, incidence was modelled at census ward level using negative binomial regression in STATA. The number of cases observed in each census ward was the dependent variable and the logarithm of the underlying population was used as the offset. The ecological (independent) variables were the census-derived ward characteristics, which were allocated to the 2001 census geography [23]. Analysis of overall survival was performed using Cox regression modelling.

For both incidence and survival, a series of multivariable models were fitted including the following independent variables: age (categorized in two groups as: 15-19 and 20-24 years), population density and the Townsend score (as a composite). The following components of the Townsend score were included in separate models that did not include the composite score: unemployment, non-car ownership, non-home ownership and household overcrowding. The interactions between age and the Townsend score (and its components) were also considered for inclusion in the models. Each variable in turn was removed and compared using a likelihood ratio test. Thus, the effect of each variable was assessed by calculating differences in residual deviances and comparing with a chi-square distribution with degrees of freedom (df) equal to the difference in residual degrees of freedom. Model fit was

assessed using the residual deviance for incidence models and minus twice log-likelihood for survival models together with the Akaike information criterion (AIC). Linearity assumptions were tested by including quintiles of significant continuous variables as ordinal variables in the models.

For the analysis of incidence, relative risks (RRs) and associated 95% confidence intervals (CIs) are reported. For the analysis of survival, hazard ratios (HRs) and associated 95% CIs are reported. All p -values were two-sided and statistical significance was taken as $p < 0.05$ throughout the analyses.

3. Results

The study included 214 cases of non-seminoma testicular cancer diagnosed aged 15 – 24 years. There were 70 cases of non-seminoma testicular cancer aged 15 – 19 years and 144 cases aged 20 – 24 years. The ASR over the study period was 24.49 per million persons per year (95% CI 21.21 to 27.78) for all males aged 15 – 24 years. Case numbers, crude rates and ASRs by age-group, period and sub-type are given in Table 1.

Small area analysis based on ward level data was carried out for non-seminoma cases aged 15-24 years. The analysis of deviance and AIC showed that the incidence rate was higher for males aged 20-24 ($p < 0.001$). After adjustment for age, the model fit was significantly improved by the addition of Townsend deprivation ($p = 0.002$) and also for its components: unemployment ($p = 0.049$), overcrowding ($p < 0.001$), non-car ownership ($p = 0.008$) and non-home ownership ($p = 0.011$). Table 2 gives a comparison of the goodness-of-fit of the different models, assessed using AIC. Model 5 shows that a statistically significant decreased risk was associated with higher levels of overcrowding (RR for one percent increase in level of household overcrowding = 0.85; 95% CI 0.79 to 0.93). Additional analysis by quintile of household overcrowding as a linear or non-linear variable (models 9 & 10) did not improve model fit. The best fitting model 11 had an interaction between age and overcrowding such that for cases aged 20-24 years the incidence was lower in areas with more overcrowded households (RR for one percent increase in level of household overcrowding = 0.79; 95% CI 0.66 to 0.94) but not age 15-19 (Table 3).

The survival depends on time period and a univariate analysis shows that five year overall survival rates increased markedly from 35.7% (95% CI 21.7 to 49.9) in 1968-77 to 80.7% (95% CI 67.9 to 88.8) in 1978-87 (Figure 1). The increases were

then smaller with 86.9% (95% CI 75.5 to 93.2) in 1988-97 and 97.9% (95% CI 86.1 to 99.7) in 1998-2006.

Univariate Cox regression models (Table 4) confirmed that time period was a significant factor ($p < 0.001$). Neither age ($p = 0.959$) nor population density affected the risk of death ($p = 0.522$). After adjustment for time period it was found that there was no significant association with Townsend deprivation ($p = 0.417$) nor with components of deprivation: overcrowding ($p = 0.626$), non-car ownership ($p = 0.471$) and non-home ownership ($p = 0.944$). An increased risk of death, however, was associated with unemployment (model 6) ($p = 0.053$). Model 11 which included an interaction between time period and unemployment did not significantly fit better than model 6 ($p = 0.679$). Therefore model 6 was judged to be the best fitting model. This model shows that a one percent increase in unemployment rate increased the hazard ratio by 4.3% (HR=1.043; 95% CI 1.003 - 1.083).

4. Discussion

This study has specifically analysed socio-economic and demographic patterning in incidence and survival from non-seminoma testicular cancer in young males. The study has been made possible by the availability of highly accurate and complete cancer registration data from a specialist population-based registry (the NRYPMR), together with corresponding census population and socio-demographic data. This study has two main findings: (a) decreased risk of non-seminoma testicular cancer was associated with living in areas of greater household overcrowding; and (b) worse survival from non-seminoma testicular cancer was associated with living in areas of greater unemployment. Although there was a marked increase in survival in the earlier time periods, the association of worse overall survival with residence in areas of greater unemployment remained unchanged for all periods. It was not possible to analyse cancer-specific survival as such data were not available. However, the vast majority of deaths in this young age-group will have been due to cancer.

Other studies of patients aged 15-24 years, using the same database from the northern region of England, have identified a male-specific increase in the incidence of non-melanotic skin cancer, a male-specific decrease for lymphomas and female-specific increases for osteosarcoma, thyroid cancer and melanoma [25,26]. Survival has improved for most other cancers and for both males and females [27]. For melanoma, there was higher incidence for females, but no difference in survival between the sexes. Greater affluence was associated with higher incidence of melanoma, but also with better survival [28].

The results of the present study suggest that geographical heterogeneity of incidence is modulated by differences occurring in areas with less and more household overcrowding (reflecting a component of area-level socio-economic deprivation). To recap the following *a priori* hypotheses were tested: a primary factor influencing geographical heterogeneity of incidence of non-seminoma testicular cancer is modulated by differences occurring in (i) less and more densely populated areas of residence; and (ii) less and more socio-economically deprived areas of residence; and survival from non-seminoma testicular cancer is modulated by differences occurring in (iii) less and more densely populated areas of residence; and (iv) less and more socio-economically deprived areas of residence. Thus, there was support for prior hypothesis (ii), but not prior hypothesis (i), since incidence was not related to area-level population density. The results also suggest that geographical heterogeneity of survival is modulated by differences occurring in areas with less and more unemployment (again reflecting area-level socio-economic deprivation). Thus, there was support for prior hypothesis (iv), but not prior hypothesis (iii), since survival was not related to area-level population density.

Three methodological caveats must be noted. First, census ward population density and Townsend deprivation scores may not be related to characteristics of individual cases and must only be seen as ecological proxies. These area-level measurements have been allocated to individuals. Caution should be used when extrapolating from grouped data to make inferences about individuals. It is conceivable that there could be unmeasured confounders that exhibit similar patterns of spatial variation [29]. Secondly, case, population and socio-economic and demographic data were analysed using 2001 census boundaries. The possible effects of migration were not taken into account and consequently could have

weakened the results. Thirdly, there is at least a theoretical possibility that delays in diagnosis may be related to the demographic variables that have been analysed.

Hence, it is possible that there has been a differential loss of some cases related to socio-economic and demographic factors.

Older studies have generally reported a higher risk of testicular cancer in men from more advantaged groups, although this was not shown in all reports.

Furthermore, in recent studies this association appears to have diminished. One study found that children of mothers with high socio-economic status had increased risk of non-seminoma testicular cancer [11]. Certain environmental factors have been suggested to be involved in aetiology including occupational exposures to oestrogenic chemicals and maternal exposures to chemicals including polychlorinated biphenyls, hexachlorobenzene and chlordanes [30-33]. Some studies have postulated a link with infections, including the human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Simian virus-40 (SV-40) [34-38]. Exposure to these and other putative environmental factors is likely to be socially determined.

Recent initiatives in UK by the National Cancer Research Institute (NCRI), the National Cancer Intelligence Network (NCIN) and the National Awareness and Early Diagnosis Initiative (NAEDI) have highlighted the need for early diagnosis of cancer to improve survival [39]. Previous studies have shown that lower levels of education and socio-economic status were associated with later stage diagnosis of testicular cancer [11]. Delays in diagnosis may have an adverse effect on outcomes for patients diagnosed with testicular cancer although with high overall survival impact will be limited. Teenage and young adult males present a particularly neglected group of patients, with low use of health-care resources and late presentation [40].

Delays may be 'patient' or 'professional'. Our findings of worse survival linked with social deprivation suggests that either patients from these areas are delaying seeking health advice or general practitioners are slow to refer to a diagnostic centre. Alternatively patients from more deprived areas may be less willing to adhere to treatment protocols. A previous study from the USA by Boscoe and colleagues found similar results for testicular cancer, with higher incidence associated with affluence and worse survival linked with poverty [41]. However, there is a clear distinction in the models of healthcare implementation between the UK and USA. The present study presents results for teenage and young adult males from the UK.

In conclusion, we have found that lower incidence of non-seminoma testicular cancer in teenage and young adult males was observed in areas associated with higher levels of household overcrowding, indicating that increased risk is linked to some aspect of greater affluence. We also found that worse survival was seen in areas with higher levels of unemployment, indicating that survival is linked with some aspect of social deprivation. This suggests that patients from more deprived areas are less likely to seek early diagnosis or are less likely to adhere to treatment regimens.

Acknowledgements

We thank all colleagues from The Northern Region Young Persons' Malignant Disease Registry (NRYPM DR), in particular Cerys Nelson and Gosia Ruiz. The NRYPM DR is funded by the Newcastle Hospitals NHS Foundation Trust. We thank the North of England Children's Cancer Research Fund for financially supporting this research (NB, PJ).

FIGURE CAPTIONS

Figure 1

Five year overall survival of non-seminoma testicular cancer cases by time period of diagnosis

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Table 1

Rates of non-seminoma testicular cancer incidence in northern England by age and period during 1968-2006

	N ¹	Male Population years at risk (000's)	Crude Rate / million	ASR ² (95% CI ³)
Age				
Ages 15 to 19	70	4359.0	16.06	16.06 (12.30, 19.82)
Ages 20 to 24	144	4238.0	33.98	33.98 (28.43, 39.53)
Ages 15 to 24	214	8597.0	24.89	24.49 (21.21, 27.78)

¹N = number of cases

²ASR = Age-standardised rate

³CI = Confidence Interval

Table 2

Comparison of models for non-seminoma testicular cancer in teenage and young adult males

Model	Factor	df ¹	Deviance	AIC ²	contrast	Difference in		p value
						df	deviance	
1	Null	3833	1002.45	0.4077				
2	Age 20-24	3832	921.97	0.3873	2 vs 1	1	80.48	<0.001
3	Age 20-24,townsend	3831	912.52	0.3853	3 vs 2	1	9.45	0.002
4	Age 20-24,unemployment	3831	918.11	0.3868	4 vs 2	1	3.87	0.049
5	Age 20-24,overcrowding	3831	906.73	0.3838	5 vs 2	1	15.25	<0.001
6	Age 20-24,no cars	3831	914.87	0.3859	6 vs 2	1	7.11	0.008
7	Age 20-24,non-ownership	3831	915.47	0.3861	7 vs 2	1	6.51	0.011
8	Age 20-24,population density	3831	921.95	0.3878	8 vs 2	1	0.02	0.876
9	Age 20-24,overcrowding quintiles nonlinear	3828	908.86	0.3859	9 vs 2	4	13.12	0.011
10	Age 20-24,overcrowding quintiles linear	3831	909.92	0.3846	10 vs 2	1	12.05	0.001
11	Age 20-24,overcrowding*age 20-24	3830	900.18	0.3826	11 vs 5	1	6.55	0.011

¹ df = degrees of freedom²AIC = Akaike Information Criterion

Table 3: Effect of age and deprivation on incidence (Model 11)

Factor	Rate Ratio (95% CI)	p-value
Age 20-24	7.33 (4.15,12.94)	<0.001
Overcrowding (%)	1.017 (0.879,1.177)	0.408
Overcrowding(%)*Age 20-24	0.791 (0.661,0.941)	0.001

Table 4

Comparison of Cox regression models for non-seminoma testicular cancer in teenage and young adult males

Model	Factor	Models		difference		P value	AIC ²
		df	compared	G ¹	df		
0	(Null Model)						
1	Time period	3	1 vs 0	54.180	3	<0.001	482.16
2	Age 20-24	1	2 vs 0	0.003	1	0.959	532.34
3	Population density	1	3 vs 0	0.411	1	0.522	531.93
4	Unemployment	1	4 vs 0	21.494	1	<0.001	510.85
5	Townsend	1	5 vs 0	16.566	1	<0.001	515.77
6	Time period,Unemployment	4	6 vs 1	3.738	1	0.053	480.42
7	Time period,Overcrowding	4	7 vs 1	0.237	1	0.626	483.92
8	Time period,Home with no cars	4	8 vs 1	0.520	1	0.471	483.64
9	Time period,Home not owned	4	9 vs 1	0.005	1	0.944	484.16
10	Time period,Townsend	4	10 vs 1	0.660	1	0.417	483.50
11	Time period*Unemployment	7	11 vs 6	1.514	3	0.679	484.91

¹G = 2(log-likelihood of model – log-likelihood of null model)

²AIC = Akaike Information Criterion

Figure 1

Five year overall survival of non-seminoma testicular cancer cases by time period of diagnosis



