Uveal melanoma in England: trends over time and geographical variation

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Hospital admission rates for uveal melanoma in England: annual rates per 100,000 population with 95% confidence intervals, shown as annual rates, 1999 to 2010
43x27mm (300 x 300 DPI)

Hospital admission rates for uveal melanoma in the Oxford Record Linkage Study (ORLS): annual rates per 100,000 population with 95% confidence intervals, shown as annual rates, 1979 to 1998. The temporary increase in rates of treatment episodes observed in the early 1990s might be partly explained by the introduction of diode laser thermotherapy as a primary treatment for uveal melanoma. This modality was used in the ORLS area during this period, but in 1997 all primary treatments for uveal melanoma were taken on by the National Ocular Oncology Centres.

42x26mm (300 x 300 DPI)

Age- and sex-specific mean annual hospital admission rates for uveal melanoma (people-based rates) in England per 100,000 population, 2001 to 2010. (A) Male; (B) Female
38x23mm (300 x 300 DPI)

Map of mean annual hospital admissions rates for newly diagnosed melanoma across England from 1999 to 2010, showing rates for each local authority area with expansions for Manchester, West Midlands and London, with quintiles of rates from highest (darkest shading) to lowest (lightest shading). (A) Uveal melanoma; (B) Cutaneous melanoma
73x43mm (300 x 300 DPI)

Scatter plot in which each point represents a local authority area, with the area’s mean annual admission rate for newly diagnosed uveal melanoma (1999-2010) plotted against the area’s index of multiple deprivation (IMD) score
60x35mm (300 x 300 DPI)

Title

Uveal melanoma in England: trends over time and geographical variation

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ABSTRACT

Aims

Uveal melanoma is the commonest primary intraocular malignancy in adults, and leads to death in around half of patients. The aim was to report on trends over time and geographical variation in rates of uveal melanoma in England.

Methods

Analysis of admissions for uveal melanoma, using linked English national hospital episode statistics (HES), available from 1999-2010, and the Oxford record linkage study (ORLS), prior to that, from 1979-1998.

Results

The annual rate of people admitted in England with a new record of uveal melanoma remained stable at around 1.0 people per 100,000 population from 1999-2010. Annual ORLS incidence rates were also stable from 1979-1998. Proportions of new uveal malignancies in adults for 2006-10 were 88% (382 people/year) choroidal and 12% (52) ciliary body/iris. Incidence rates increased with increasing age and were higher in males than females. Geographical analysis showed variation across local authorities (LAs) in incidence rates, from 0.1 to 1.9 people per 100,000 population per year. Incidence rates at the LA level were inversely correlated with the proportion of black ($r=-0.18$) or Indian individuals ($r=-0.13$) in each LA, were weakly correlated with LA levels of social deprivation ($r=0.08$), and were not correlated with southerly latitude.

Conclusion

The annual incidence of uveal melanoma in England has remained stable over the past decade. This contrasts with the rising incidence of cutaneous melanoma. Our data do not support the possibility that ultra-violet light exposure contributes to the pathogenesis of uveal melanoma.

INTRODUCTION

Uveal melanoma is the commonest primary intraocular malignancy in adults¹, and one of the most important causes of mortality in ophthalmic practice. Of malignant ocular neoplasms in adults, around 90% are melanomas^{1,2}; of these, the large majority (around 85%) arise from the uveal tract^{1,3,4}. In particular, approximately 90% of intraocular melanomas involve the choroid, while the rest arise from the ciliary body or iris⁵. Choroidal melanomas lead to death in around 50% of patients, most commonly from metastatic disease affecting the liver⁵.

In the past, uveal melanoma was usually treated by enucleation⁶⁻⁸. However, recent trends in management have seen fewer patients undergoing primary enucleation³; alternative therapies now include brachytherapy, proton beam radiotherapy, trans-scleral local resection, endoresection and trans-pupillary thermotherapy¹. In addition, uveal melanoma in the United Kingdom (UK) is now managed through four designated ocular oncology centres; this network was established in order to improve survival and quality of life for patients with suspected ocular cancer by providing highly specialised services⁹.

Trends in the incidence of uveal melanoma have been examined previously for various countries in one large study¹⁰, but only up until 2000. No recent study has examined trends in the rate of patients diagnosed with uveal melanoma in England, or investigated geographical variation within England. Our aims were to analyse trends over time and geographical variation in uveal melanoma.

METHODS

Annual rates of patients diagnosed with uveal melanoma in England were calculated from record-linked Hospital Episode Statistics (HES) for the years 1999 to 2010, using methods described previously¹¹. Similarly, annual rates were calculated for the former Oxford Regional Health Authority (ORHA) area using data from the Oxford Record Linkage Study (ORLS) for the years 1979 to 1998, as described previously¹¹. We refer to years by calendar period, i.e. 2010 means 1st January 2010 to 31st December 2010.

HES data cover all day case and inpatient admissions in NHS hospitals in England, as well as those funded by the NHS for treatment elsewhere. ORLS data comprise computerised abstracts of HES for all patients resident and treated in several districts within the former ORHA area (covered population about 1.9 million from 1979-1986, 2.5 million from 1987); both datasets also include day case admissions. These datasets have been described previously¹¹. In order to analyse separately numbers of admissions versus numbers of people, rates were calculated distinguishing episodes of care and individuals treated by means of record linkage. For the count of people, individuals were counted once only at the first ever record of uveal melanoma, and not for any subsequent admissions (if any) for uveal melanoma. English national population denominators for each calendar year were obtained from the Office for National Statistics. Age-standardisation was performed as previously described¹².

English national HES were analysed to produce a geographical profile of people admitted for uveal melanoma by government office region (GOR) and by local authority (LA) area between 1999 and 2010. These geographical data refer to the residential location of patients, i.e. where patients live rather than where they are admitted or treated. The data were used to construct maps showing the person-based admission rate (first occurrence only) per 100,000 resident population for each GOR or LA, expressed as average annual rates, as described previously¹¹. Age-standardisation was performed as previously described¹². The admission rate for each LA was plotted against its score for the index of multiple deprivation (IMD 2004)¹³. The IMD is a measure of socio-economic deprivation, which we used at the level of the LA¹¹. In addition, the admission rate for each LA was plotted against the proportion of individuals in that LA according to ethnicity, using data from the Office for National Statistics 2001 Census: black (as self-reported in the census), Indian, and those born outside the UK. Finally, a map was constructed showing the person-based admission rate (first occurrence only) by LA for cutaneous melanoma.

The diagnostic codes used to identify patients with uveal melanoma from the datasets were: 190.6 (malignant neoplasm of choroid) and 190.0 (malignant neoplasm of ciliary body / iris) in the International Classification of Diseases, 9th revision (ICD-9), and C69.3 (malignant neoplasm of choroid) and C69.4 (malignant neoplasm of ciliary

body / iris) in ICD-10. The diagnostic code used to identify patients with cutaneous melanoma was: C43 (malignant melanoma of skin) in ICD-10.

RESULTS

Admission rates over time

English national rates of uveal melanoma are shown in Figure 1. The annual rate of people admitted with a new record of uveal melanoma has remained stable at around 1.0 people per 100,000 population from 1999 to 2010. Over the same period, the annual rate of all admissions for uveal melanoma has generally remained stable at around 1.3 episodes per 100,000 population. Hence there were approximately 30% more admissions for uveal melanoma as there were people newly diagnosed with uveal melanoma.

ORLS rates of uveal melanoma are shown in Figure 2. The annual rate of people admitted with a new record of uveal melanoma remained stable, though at a lower level than that for England, from 1979 to 1998. In general, the annual rate of all admissions for uveal melanoma closely followed the person-based rate.

Numbers of individuals and site of uveal melanoma

For the most recent national data analysed (2006-10), the total number of people aged 15 years and above admitted to hospital in England with a new record of uveal malignancy was 2171 over the five years, i.e. around 430 per year. Of these 2171 people, 1912 (88%) had choroidal malignancy and 259 (12%) had ciliary body / iris malignancy.

Rates by age group, sex and geographical area

English national rates of uveal melanoma were analysed by age and sex over two time periods (2001-5 and 2006-10), and are presented in Figure 3. Rates were similar across the two time periods studied. In both men and women, rates were generally higher with increasing age and were highest in the 70-79 year old age group. Rates were consistently higher for men than for women in age groups beginning at 50 years. The rate ratio comparing men and women increased with age, reaching 3:2 in the age group ≥ 80 years.

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English national rates of uveal melanoma were also analysed for geographical variation at the level of the GOR and LA area, based on residential locations of all patients. The annual rate of people newly diagnosed showed a significant variation between GORs, ranging from 0.64 (95% CI 0.57-0.70) to 1.14 (1.06-1.21) people per 100,000 population per year in 1999-2010. The lowest rates were found in Yorkshire and Humber and the East Midlands, with highest rates in the North West and North East (see Table).

Figure 4A shows a geographical profile of the annual rate of people newly diagnosed with uveal melanoma by LA. LAs showed a large variation in melanoma rates, ranging from 0.09 (0.00-0.48) to 1.86 (1.09-2.99) people per 100,000 population per year in 1999-2010. The rate of melanoma by LA was inversely correlated with the proportion of people in each LA who were black ($r=-0.18$, $p=0.001$), the proportion who were Indian ($r=-0.13$, $p=0.006$), and the proportion who were born outside the UK ($r=-0.13$, $p=0.02$). The rate of melanoma by LA showed positive but weak correlation with the index of multiple deprivation ($r = 0.08$) (see Figure 5). However, the rate of melanoma by GOR and LA showed no evidence of an increasing gradient with southerly latitude (where increased sunlight exposure might be expected).

For comparison, Figure 4B shows a geographical profile by LA of the annual rate of people newly diagnosed with cutaneous melanoma. In this case, the rate of melanoma did demonstrate evidence of an increasing gradient with southerly latitude: although the trend was not entirely consistent, highest rates were generally found in southerly areas.

DISCUSSION

The HES data demonstrate that the national annual incidence of uveal melanoma has remained stable in England over the past decade at around 1.0 people per 100,000 population. The ORLS data have the advantage of containing linked data from the outset, and suggest that the annual incidence of uveal melanoma was also stable in England over the previous two decades. While ORLS rates and HES rates both demonstrate fairly stable values within their time frames, it is worth noting a difference in incidence rates between the two (approximately 0.2 versus 1.0 people per 100,000 population, respectively). This might be explained by genuine

geographical differences, i.e. lower incidence rates in the ORLS area compared to the national average, for example because of ethnic composition. Other possible reasons might include referral of Oxford patients to centres outside the Oxford Region (where data were not captured for the ORLS); and the effects of reorganisation of ophthalmic oncology services in the UK, with the establishment in 1997 of four designated ocular oncology centres⁹. For example, this increased specialisation may have led to improvements in accuracy of coding and reporting rates.

Our data are consistent with previous studies of the incidence of uveal melanoma. Stang and colleagues used data from cancer registries to calculate crude and age-standardised incidence rates of uveal melanoma in a variety of countries for the period 1983-1997¹⁰: the crude incidence rate for England was 0.7 per 100,000 population, while that for Scotland was 0.9, France 0.6, Italy 0.5 and the United States of America (USA) 0.6 (Caucasian population) and 0.03 (Afro-Caribbean population).

Using more recent data, Lockington and colleagues estimated the annual incidence of choroidal melanoma in Scotland at 0.7 per 100,000 from 1994-2008²⁰. Singh and colleagues recently reported the results of a large study of uveal melanoma in the USA from 1973 to 2008²¹: the mean age-adjusted annual incidence of uveal melanoma was 0.5 per 100,000 population, and did not change significantly over the study period. Burr and colleagues conducted a study of uveal melanoma in England from 1986-1999 using cancer registry data, but this analysis focussed on survival rates rather than incidence trends¹. In their report, most malignant ocular tumours (86%) were melanomas, and median age at diagnosis for adults with uveal melanoma was 64 years, with men representing 52% of cases¹.

The incidence of cutaneous melanoma in England is known to have increased significantly in recent years, most likely through increased sunlight exposure¹⁹. Our geographical data on cutaneous melanoma support this idea, in that some evidence was found for an excess in incidence in southerly regions with more sunlight. The rise in cutaneous melanoma stands in stark contrast to the stable incidence reported here for uveal melanoma. Unlike for cutaneous melanoma, the potential role of ultra-violet light exposure in uveal melanoma remains controversial^{17,18}. Interestingly, our data on geographical variation for uveal melanoma do not show any evidence of a general

excess in incidence in southerly regions, so do not support the idea that ultra-violet light exposure is involved in uveal melanoma pathogenesis.

Our age- and sex-specific data for England from 2001-10 show the extent to which the annual incidence of uveal melanoma increases with age, for example from 0.3 (15-49 years) to 3.0 (70-79 years) people per 100,000 population in men (2006-10). Incidence rates were also substantially higher for men than for women. Very few recent data are available in the published literature comparing age- and sex-specific incidence rates of uveal melanoma in Europe. However, our findings are largely in agreement with those reported by Bergman and colleagues for Sweden (1960-1998), where the annual incidence of uveal melanoma increased with age from around 1 (45-54 years) to 3 (75-84 years) cases per 100,000 population, and was significantly higher in older age groups for men than for women²². Age-adjusted incidence rates of uveal melanoma have also been consistently higher for men than for women in the USA from 1973 to 2008²¹.

Population-based rates of uveal melanoma showed variation between different geographical areas, i.e. according to where patients live. This variation is not attributable to differences in age structure between areas: the rates are age-standardised. The variation may be explained partly by differences in ethnic composition across different areas, as risk of uveal melanoma is known to be higher in individuals with fair complexion and light iris colour^{10,23}. For example, Stang and colleagues found that the incidence of uveal melanoma in the USA was 20 times higher in the Caucasian population than in the Afro-Caribbean population¹⁰. Our data provide evidence of geographical variation according to ethnic composition at the level of the LA area, i.e. lower incidence in areas with higher proportions of black people, Indian people, and those born outside the UK. By contrast, there is no strong evidence of increased rates in or around the three ophthalmic oncology centres in England (in Liverpool, Sheffield and London); while the Liverpool LA area has a high rate (1.49 people per 100,000 population per year), LAs around London and Sheffield are close to the national mean. The variation did show a weakly positive correlation with level of social deprivation.

Very little information is present in the published literature on the effect of socioeconomic deprivation on risk of uveal melanoma. One study in Scotland reported that the distribution of choroidal melanoma in Scotland (in 1994-2008) was similar between different socioeconomic groups²⁰. In addition, no significant differences were present between treatment groups (enucleation versus proton beam radiotherapy versus plaque radiotherapy) in the median Scottish IMD, suggesting that patients with higher levels of socioeconomic deprivation did not necessarily seek medical attention later²⁰. It is worth mentioning that the rate of enucleation is lower in Scotland than the rest of the United Kingdom; it may be that patients in Scotland receive medical attention earlier partly because of the availability of free optometrist consultations, subsidised by the Scottish Executive²⁰. Nevertheless, one large study of patients in England and Wales reported that there was no statistically significant variation in survival from uveal melanoma by poverty level¹. Examining potential variation in incidence rates by poverty level was outside the scope of this paper.

While this study demonstrates that hospital data such as HES and ORLS are useful in the analysis of trends in uveal melanoma, there are several limitations to this study. As with cancer registry data, hospital data rely on accurate coding and reporting of clinical information, e.g. correct anatomical subtype of ocular melanoma. In this study, we included malignant neoplasm of the choroid, ciliary body and iris only, i.e. truly uveal malignancies. We excluded malignant neoplasm of the retina in order to avoid inappropriate inclusion of retinal tumours such as retinoblastoma or astrocytoma. It is possible that this approach may have missed some cases of choroidal melanoma which were misclassified as retinal malignancies, but previous reports have shown that specification of anatomical subtypes has improved over time in England, perhaps following the reorganisation of services towards specialised ocular oncology centres¹. One disadvantage of HES and ORLS data is that ICD categories do not currently encode histological information for uveal malignancies; for example, they do not distinguish between choroidal melanoma versus another malignant choroidal neoplasm.

In addition, HES datasets contain record linkage only from 1998; we therefore used ORLS data to complement HES data, as ORLS datasets have consistently used record linkage since their introduction¹¹. ORLS has the disadvantage of relatively small

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numbers for less common conditions such as uveal melanoma (and hence confidence intervals are wide). However, our data have face validity: in particular, our incidence rate is similar to that in the published literature, as are our age- and sex-specific incidence rates. Finally, one important advantage of linked hospital data is that it is possible to correlate individual patients with different operations or procedures. For example, we plan to analyse trends over time in the rate of patients with choroidal melanoma undergoing enucleation as opposed to plaque radiotherapy or other newer treatment modalities.

In conclusion, the annual incidence of uveal melanoma in England has remained stable over the past decade at around 1.0 case per 100,000 population. This contrasts with the rising incidence of cutaneous melanoma. The incidence of uveal melanoma shows significant regional variation, which may be explained partly by differences in ethnic composition. However, unlike cutaneous melanoma, no excess incidence was seen in the south of England. This supports the established teaching that aetiology of uveal melanoma is unrelated to ultra-violet light exposure.

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Conflicts of interest

None to declare.

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Contributorship statement

TDK had the idea for the paper. MJG and DY performed data acquisition and analysis. TDKL and MJG interpreted the data, and wrote and revised the paper. MJG is guarantor.

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Ethical approval

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Ethical approval for analysis of the record linkage study data was obtained from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176).

Confidential: For Review Only

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Table. Uveal melanoma by government office region (GOR): person-based admission rate (indirectly standardised) per 100,000 population by GOR for 1999-2010, sorted from highest to lowest, accompanied by 95% confidence intervals.

Government Office Region (GOR)	Annual admission rate per 100,000 population	95% confidence interval	
North West	1.14	1.06	1.21
North East	1.02	0.91	1.14
South West	0.92	0.85	1.00
West Midlands	0.86	0.79	0.94
South East	0.84	0.79	0.90
East of England	0.83	0.76	0.90
London	0.75	0.69	0.82
East Midlands	0.68	0.61	0.76
Yorkshire and Humber	0.64	0.57	0.70

Legends to figures

Figure 1. Hospital admission rates for uveal melanoma in England: annual rates per 100,000 population with 95% confidence intervals, shown as annual rates, 1999 to 2010

Figure 2. Hospital admission rates for uveal melanoma in the Oxford Record Linkage Study (ORLS): annual rates per 100,000 population with 95% confidence intervals, shown as annual rates, 1979 to 1998. The temporary increase in rates of treatment episodes observed in the early 1990s might be partly explained by the introduction of diode laser thermotherapy as a primary treatment for uveal melanoma. This modality was used in the ORLS area during this period, but in 1997 all primary treatments for uveal melanoma were taken on by the National Ocular Oncology Centres.

Figure 3. Age- and sex-specific mean annual hospital admission rates for uveal melanoma (people-based rates) in England per 100,000 population, 2001 to 2010. (A) Male; (B) Female

Figure 4. Map of mean annual hospital admissions rates for newly diagnosed melanoma across England from 1999 to 2010, showing rates for each local authority area with expansions for Manchester, West Midlands and London, with quintiles of rates from highest (darkest shading) to lowest (lightest shading). (A) Uveal melanoma; (B) Cutaneous melanoma

Figure 5. Scatter plot in which each point represents a local authority area, with the area's mean annual admission rate for newly diagnosed uveal melanoma (1999-2010) plotted against the area's index of multiple deprivation (IMD) score