PERSPECTIVE

Risk factors for intraocular melanoma and occupational exposure

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Ocular melanoma is an uncommon cancer. Age standardised incidence ranges from 0.4 to 1.2 cases per 100 000 within Europe and from 0.1 to 2.3 worldwide (figures from WHO and International Agency for Research on Cancer (IARC)). Only one report[1] suggests any change over decades.[2–6] However, incidence data from the USA show a decrease over the period 1973–89.[7]

The behaviour of intraocular melanoma varies with site. Tumours located in the iris form 10% of eye melanomas[8] and usually have low grade histology with a good prognosis.[9] Local excision is effective in most such cases although some may require enucleation, and metastasis is seen in only 3% of cases. In contrast, melanoma of choroid or ciliary body has a poor prognosis, although late metastasis after removal of the primary tumour is common. Metastasis is haematogenous and 1 year survival after liver metastasis not higher than 10%.[10] Raivio[8] in Finland observed that survival rates at 5, 10, and 15 years were 65%, 52%, and 46% respectively. Among the 12% of patients surviving at least 20 years, 21% developed metastasis thereafter. Treatment of metastatic disease by chemotherapy has been disappointing with less than 1% response rates to systemic DTIC based chemotherapy.[11] Prognosis therefore reflects the development of metastasis uninfluenced by treatment, although recent developments hold some hope of progress.[12 13]

Twenty years ago "many of the difficulties in diagnosing choroidal melanomas which clinicians confronted in the past [had] been eliminated".[14 15] The past two decades have seen advances in classification, now widely accepted,[16] and continuing refinement of prognostic factors influencing outcome in these patients.[17–20] However, despite a number of studies of risk factors for intraocular melanomagenesis, the cause of this tumour is far from clear.

During the 1980s, with increased interest in epidemiology generated by higher frequency of skin melanoma, additional and more detailed investigations were conducted either by reviewing groups of patients[21–23] or by conducting specifically designed case-control studies,[24–29] allowing these groups to test hypotheses related to exposure to various environmental factors. Most of the publications during this period show a positive association with pre-existing naevi or melanocytosis, light eye, hair, and skin complexion and a null or weak association with hormonal factors and earlier malignancy. In 1986 a large clinical trial, the Collaborative Ocular Melanoma Study,[30 31] started in the United States and Canada, including patients until 1994. This large scale study has been designed to provide important information regarding the choice of treatment, as well as natural history, quality of life, and pathology findings.[32]

Potential risk factors

A familial history of uveal melanoma[33–43] and pre-existing naevi[44–48] have been postulated as predisposing factors. A large range of risk factors have been investigated (for example, sex related factors,[27 29 49–51] social class, and socioeconomic factors,[1 8 52–54] lightness of complexion and hair,[53] eye colour,[23 24 55] sunlight exposure,[25 56–59] smoking,[60] viruses,[61 62] chemicals,[63] links with other cancers[28 64–69]), but no causative agent has been recognised.

Following advances in understanding of the pathogenesis of skin melanoma,[70] several studies investigated the role of ultraviolet light,[56 58] finding a positive association (relative risk (RR) significantly higher than 3). However, these results remain controversial[53 71–73] and the recent drop in incidence in the United States is further evidence that this is not a major factor.[7] Furthermore, dosimetry studies suggest that only 1–2% of incident radiation in the ultraviolet B range reaches the back of the eye.[74]

Several studies have addressed the possible importance of genetic factors, following the demonstration of genetically determined predisposition in other cancers.[75–86] Clear evidence of a genetic component in uveal melanoma is the unbalanced racial risk with a strong predominance among white people and an absence among dark skinned people.[7 87] There is a clear racial predisposition which follows the same pattern as cutaneous melanoma. Familial predisposition has been known to occur since 1892 following Silcok's report of uveal melanoma in three successive generations. However, such families are rare and although many familial reports have been published since then, it is clear that genetic factors are only part of the aetiological process. A specific genetic alteration, if any, would probably only explain a small proportion of disease, as has been shown for BRCA1 and BRCA2 in breast cancer. Currently, the data therefore suggest that environmental risk factors do exist, but that these are yet to be demonstrated.

Occupational exposure and eye melanoma: investigation of potential risk factors

Most environmental risk factors can be investigated by occupational exposure analysis, but the rarity of uveal melanoma has prevented many studies of this subject. However, there is some evidence that this may be important. Albert *et al*[63] reported a significant excess of choroidal melanoma among the white workers in a chemical industry in West Virginia. However, this observation is incidental, as the point of interest was the incidence of disease rather than a search for aetiological factors. Since then, various chemicals have been reported to induce ocular melanocytic tumours in animals,[9 88] including nickel, platinum, radium, and some other compounds.

Table 1 Relative risk estimates for measuring the association between eye melanoma and industries according to the industry classification system (from Ajani et al[90])

Occupation exposure cross linkage system (OEC)		*Bureau of census classification system (BOC)*	
Agriculture, forestry, fishing	2.02	1.52	Agriculture, forestry, and fisheries
Construction	0.49	0.53	Construction
		1.18	Manufacturing
Paper and wood	1.04		
Glass, clay, and stone	1.32		
Metal	4.42		
Machinery	0.33*		
Transportation methods, ship building, aircraft	0.67	1.23	Transportation, communications, and other public utilities
		1.08	Wholesale trade
		1.21	Retail trade
		0.60	Finance, insurance, and real estate
		0.88	Business and repair services
		0.71	Personal services
Food and tobacco	1.33		
Textile	0.77		
Chemicals, drugs, and paints	0.24		
Rubber, plastic, and synthetics	0.50		
Leather	3.06		
Medicine and science	0.73		
Entertainment and recreation	0.82	3.02	Entertainment and recreation services
		0.55	Professional and related services
		1.06	Public administration
Art	1.03		
		1.61	Others
Other occupations with few chemical exposures	1.35		

*Significant at p<0.05.

Several occupational clues to aetiology appeared when Swerdlow,[1] using the UK Registrar General classification with 26 occupation orders, reported a significant excess of proportional registration ratio in three categories: electrical and electronic workers, administrators and managers, and technical workers and artists. Results from a subsequent Canadian study conducted between 1979 and 1981 with 65 eye melanoma cases and their age and sex matched controls were published by Gallagher *et al*[24] As well as host factors, sun exposure variables and medical factors, occupation and chemical exposure were investigated, using a detailed occupational history. No individual occupation appeared to be at significantly elevated risk, but when grouped, a predominantly indoor managerial group ("government workers") had an odds ratio (OR) of 3.5 (p=0.006) after controlling for hair and eye colour. No indication of elevated risk was found for other occupational groups, including chemical, electrical, or electronic workers.

In 1990, Vagero *et al* [89] using cancer registration data in England and Wales analysed the occupation of 662 patients with ocular melanoma, using an age adjusted proportional registration ratio (PRR, a comparison of the proportion of all cancers which melanomas constitute in a particular occupation with the corresponding proportion in all occupational groups combined, adjusted for age). Information about occupation was coded according to the 1970 OPCS (Office of Population Censuses and Survey) classification system. Only significant results are noted here: for men, an excess incidence was found in clerical workers, PRR=1.4 (95% CI 1.0–1.8), in accordance with Gallagher's report.[24] Top rank occupations with highest PRR were among male athlete sportsmen (a priori not known for indoor activities) and electrical engineers, and among female commercial travellers and kitchen hands. If occupations for men and women were combined, scientists (PRR=2.2, NS), judges (PRR=1.9, NS), and teachers (PRR=1.8, 95% CI 1.2–2.5) had the highest risk.

Ajani *et al* [90] specifically designed an occupational population based case-control study with 197 cases and twice as many controls. They interviewed the subjects, including questions on constitutional factors, ocular and medical histories, ultraviolet exposure, occupational history and exposure related to work occurring 15 years before the interview. They used two different occupation exposure matrices: the occupation exposure cross linkage system (OEC) (16 categories for industries, nine categories for occupations) and the Bureau of Census classification system (BOC) (13 categories for industries, six categories for occupations). OEC links suspect carcinogens to industry and occupation,[91] which then are used to deduce the agents to which a subject might have been exposed occupationally and to group subjects whose occupational history suggests exposure to a particular agent. This system was used to categorise different exposures into three level groups of exposure. Results from this specific exposure coding found no positive association between any group of exposure and eye melanoma, with two groups (alkylating agents and other organic compounds, NOS), apparently having a significant negative impact on incidence. At the third level (specific agent of exposure) only one product (alicyclic halogens) within the organic compounds group was positively associated with ocular melanoma but this result was not significant (OR 1.95 (95% CI 0.84–4.53)).

Future risk assessment in uveal melanoma

Study design, selection bias, and occupation coding appear to be the three main issues when looking at risk factors for occupational exposure. The choice of study design is always a balance between several contradictory arguments. The ideal, a cohort study among exposed workers (for example, farmers or fishermen), would not be feasible because of the low incidence of this disease. Although wide open to criticism, case-control studies do provide valid OR estimates and present some advantages. Firstly, the cases consist only of the disease of interest (here uveal melanoma), particularly if a standard pathological review is conducted for all eligible cases, and a clear position is adopted for non-histologically confirmed melanoma. Secondly, data may come either from hospital or population based registries and there is no necessity to be exhaustive. However, a limitation of a case-control study is that the number of occupational exposure categories can be greater than the number of cases! The sample size has therefore to be large enough to obtain sufficient numbers in all categories.

Classically, the major limitation of a case-control study is selection bias, usually when selecting controls. Cases and controls must be unbiased with respect to age which is obviously linked with the duration of occupation, whatever

the technical possibilities of statistical adjustment. For a true aetiological factor, cases are expected to be more exposed than the controls, but this may be difficult to verify in some situations. If we assume a dose-response effect, eye melanoma among young cases should be associated either with a strong association with environmental exposure, if any, or with a personal risk factor, or both. The current absence of clear answers from previous studies tells us that there is unlikely to be a strong association with any occupational exposure. Young cases, with a presumed shorter exposure might have other (unknown) aetiological or confounding risk factors, when young controls would not have those personal factors. Even with controls matched for age, selection of an unbalanced number of young cases would therefore lead to an overestimate the role of occupational exposure. With data originating from tumour registries, this issue should not be a problem, since it is (theoretically) possible to check the completeness of registration and therefore to compare the age distribution of included cases with the population age distribution of cases. If data come from referral centres, it is important to verify that there is no bias towards referral of younger cases, as others could be treated locally, either because they are more easily diagnosed and treated by simple enucleation, or because they have a poorer prognosis. For both sources of data, it is worth checking the age distribution of cases.

Ajani's study[90] dealt conclusively with the key issue of occupation coding effect. Comparison of the findings drawn from both systems (Table 1) shows some consistency, supporting both positive (agriculture) and negative (construction) associations. However, the differences present between studies (transportation services, entertainment, and arts) make interpretation difficult and may be related to misclassification of occupational exposure or to variations in the coding systems used.

In addition to coding system problems, the case-control design introduces one other potential source of error. Comparisons are made for groups exposed versus not exposed to a particular occupation at a particular time. Even if one assumes perfect occupation exposure coding, the presence of any agent in the reference group (that is, combining all other exposures) with a similar effect might dilute the effect of the exposure of interest. Ideally, samples should be divided into three groups: occupations certainly exposed, those certainly not exposed, and the occupations exposed to agents with similar or unknown effect. Comparisons could then be made between the exposed and non-exposed groups. However, statistical constraints of study power and occupation coding uncertainties generally do not allow the creation of such categories.

Conclusion

It is clear from this overview of occupational risk factors for uveal melanoma that there are potential link and areas for future studies of exposure can be seen. The role of ultraviolet irradiation remains controversial. The possibility that other forms of radiation and exposure to DNA damaging agents might be important is clearly worth consideration.

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