CUTANEOUS MELANOMA AND PRECURSOR LESIONS

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Preface

In recent years much progress has been made in knowledge and understanding of the biology of cutaneous melanoma. In this respect etiological factors, prognostic factors, antigen expression of melanoma cells, immune response and mechanisms of metastasis formation have to be mentioned. It is the purpose of this book to give a review on fundamental aspects, diagnosis and prognosis, and treatment of cutaneous melanoma and precursor lesions. Moreover, previously unpublished new data are presented.
A post-graduate Boerhaave course "Cutaneous Melanoma and Precursor Lesions" was held at Leiden University on 12 and 13 April, 1984. The proceedings are contained in this volume.
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Dirk Ruiter, Kees Welvaart and
Soldano Ferrone,
Leiden and Valhalla (NY),
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THE EPIDEMIOLOGY OF MELANOMA

R.M. MacKIE

GENERAL INTRODUCTION

The comments in this chapter on the epidemiology of malignant melanoma refer to all forms of cutaneous malignant melanoma other than lentigo maligna melanoma. The evidence that lentigo maligna melanoma affects a different age group of the population, has a different natural history, and may therefore be due to different balances of aetiological factors has been well stated by the late Vincent McGovern (1). When considering the acral variant of malignant melanoma, it is difficult to incriminate directly the influence of solar radiation, but this, of course, may be an indirect effect, as was stated some years ago now by Lee & Merrill, who postulated the presence of a solar circulating factor (2).

INCIDENCE FIGURES

No figures for the incidence of malignant melanoma are available prior to 1950, as up till this date all cutaneous skin cancer was included under the one category in cancer registries. At this time, however, cutaneous malignant melanoma was separated from basal cell carcinoma and squamous carcinoma, and this coincided with the observation by Lancaster (3) that melanoma incidence appeared to be higher in areas of intense natural sunlight inhabited by white-skinned races. At the present time the highest incidence of melanoma in the world is recorded in Australia and New Zealand. Excellent epidemiological figures are available from the Queensland Melanoma Project Group and also from the Sydney Melanoma Group. The annual incidence of melanoma at the present time in these parts of the world is over 30 new cases per 100,000 per year (4,5). This contrasts with the incidence figures from Scandinavia, which have been kept with great care over a long period of time. The incidence in Norway at the present time, as reported by Magnus (6) and his colleagues, is around 10-12 new cases per 100,000

per year and the evidence would suggest that similar figures apply to the other Scandinavian countries. In North America there are no figures available for the whole country but individual States show very interesting variations in incidence figures. In general, the more northerly situated States on the eastern seaboard have a relatively low incidence of the tumour, while the west coast State of California and the so-called sunbelt States of Arizona (7) and New Mexico (8) have a high incidence of around 28 new cases per 100,000 per year. In the United Kingdom the incidence figures are around 5 new cases per 100,000 per year for both England and Wales and Scotland (9). Figures from Japan (10) suggest that the tumour is relatively rare and put the incidence at around only 2 new cases per 100,000 per year. Few accurate figures are available from the Third World countries on incidence figures of melanoma but the evidence available would suggest that in countries with a predominantly dark-skinned population the incidence is very low indeed.

EVIDENCE OF CHANGING INCIDENCE

At the present time evidence from Australia, from Scandinavia and from the sunbelt States in North America all suggests that the incidence of malignant melanoma is rising relatively rapidly. Studies over the past 30 years in Scandinavia suggest that the incidence of the tumour is doubling over a decade in these countries, and in Australia a similar rate of increase is seen. In the sunbelt States the rate of increase in incidence is even more dramatic, with a trebling over a decade in the case of Arizona and a quadrupling in the case of New Mexico. If figures like these are extrapolated forward to the year 2000, and one assumes the same rate of increase as is currently seen, melanoma will become one of the commoner forms of malignancy and may be as common in some parts of the world as breast cancer.

REASONS FOR CHANGING INCIDENCE OF MALIGNANT MELANOMA

All theories concerning the rise of incidence of malignant melanoma, which is seen on a world basis, relate to exposure to ultraviolet light. The epidemiological method of cohort study, a careful analysis of the incidence of tumours in individuals born in successive decades, shows clearly that the rate of increase is associated with possible changes in

cultural habits occurring at some time after 1930 (11). This, of course, coincides with a period of much greater relaxation with regard to exposure of skin to natural sunlight and since this time this trend has continued unabated. In 1984, there are very few areas of the body that can be regarded as habitually covered sites in the case of a young, healthy individual who enjoys sunny vacations. The evidence that exposure of the skin to sunlight is an important aetiological factor is also strengthened by the fact that areas such as the sunbelt States in North America and Australia are areas of very high solar insulation and coincide with the highest incidence rates for melanoma on a world basis. Studies on a geographical basis also show clearly an inverse relationship between melanoma incidence and distance from the Equator.

In the past decade the suggestion has been made that the rising incidence is due not only to changing cultural habits with regard to sunlight exposure, but also to a change in the quality of ultraviolet light reaching the earth's surface. It has been postulated (12) that changes in the ozone layer in the atmosphere due to pollution from supersonic aircraft and from refrigerator exhaust is allowing a greater proportion of potentially damaging ultraviolet light to reach the earth's surface, and is thus contributing to the changing incidence of malignant melanoma. A lot of this information is theoretical rather than factual, and is based on complex mathematical models relating possible changes in ozone layer characteristics. The models in general do not agree with each other but nevertheless the possibility that this qualitative change is contributing to the rising incidence must not be discounted.

At the present time, the action spectrum for ultraviolet damage on the melanocyte leading to malignant change is not established, but it is assumed from all circumstantial evidence that this lies in the UVB range (290-320 nm). There is current concern about the possible role of appliances emitting UVA (320-360 nm) in the aetiology of malignant melanoma (13) and it may well be that ultraviolet light in these wavelengths has an additive effect on the UVB wavelengths. More information, however, is needed before the recent introduction of sunbeds and photochemotherapy can be incriminated in the current rise of malignant melanoma.

PATIENT CHARACTERISTICS

One of the conundrums in relating the rising incidence of malignant melanoma to sunlight exposure is the fact that the majority of patients with non-lentigo maligna melanoma do not have outdoor occupations (14) and are in the 40-60 age range. This is in contrast to patients who suffer from squamous cell carcinoma, who are generally over the age of 60 and have a history of outdoor occupation. The role of cumulative lifetime sun exposure in the aetiology of squamous cell carcinoma is relatively well established. We must therefore postulate a different mechanism for the action of ultraviolet light on the melanocyte by comparison with that on the keratinocyte. A number of recent studies have suggested that short, sharp episodes of ultraviolet exposure, on occasion leading to burning (15), may be more important in the incidence of malignant melanoma than cumulative lifetime sun exposure. Thus the average melanoma patient is an individual who enjoys recreational rather than occupational sun exposure and who has a history of sunburn in the five years preceding his malignant melanoma. This history may indicate that the majority of melanoma patients have skin type one or skin type two (patients who tan either never or rarely in the sun and who burn very readily). This, of course, is the type of patient who tends to travel to the Mediterranean once or twice a year from Scandinavia and to expose his normally covered skin to an intensity of sunlight to which phylogenetically he is totally unadapted.

There appears to be very little occupational risk associated with the development of malignant melanoma, with the exception of two recent papers, one showing a slightly higher incidence of the tumour in veterinarians resident in the State of California (16), and one showing a higher incidence in employees of the Livermore Laboratory (17). Both of these observations have prompted intense study of similar occupational groups in other parts of the world, but as yet no other study has emerged suggesting that individuals in this type of occupation in other geographic areas are similarly at increased risk. A recent publication by Beral *et al.* (18) suggested that amongst females who were being studied for a possible association between ingestion of the oral contraceptive and melanoma, exposure to fluorescent lighting, either at work or in the home, was a risk factor. This is a new observation and requires confirmation.

PHENOTYPIC CHARACTERISTICS

In most parts of the world the sex incidence for patients with melanoma is roughly equal. The significant exception to this rule appears to be the U.K., where the incidence is two females to one male. This does not appear to apply to the rest of Europe and has caused much interest and speculation. It has been suggested by Lee & Storer (19) that this is due to an endocrine factor influencing the development of melanoma, which is only seen in areas of relatively low solar exposure and which is masked in higher incidence areas associated with intense solar exposure. Studies relating the incidence of melanoma to racial type show that Caucasian white-skinned individuals who have emigrated to sunnier climates are at greatest risk. This is clearly seen in the Australian figures, where those who have migrated from Scotland and Ireland appear to be at even greater risk than other European emigrants. There is similar evidence from the State of Israel (20) and in both Australia and Israel there is evidence to suggest that the risk of melanoma increases with the number of years spent in the new country. This observation is somewhat at odds with the earlier comments suggesting that cumulative, lifetime sun exposure is not the main way in which sunlight is involved in the development of malignant melanoma. The New Mexico study (8) shows clearly that the very rapid rise in incidence of melanoma in that State over the past decade is confined solely to the white settlers, the so-called Anglos, in contrast to the Spanish and Mexican Indian population, who show little if any rise. Figures from other parts of the United States, such as Connecticut, comparing the incidence of melanoma in the white-skinned Americans and in the Negro population, show clearly that this is a disease of the white-skinned races. Melanoma in Negroes is rare and a high proportion of these tumours is found on the soles of the feet. In the past it has been suggested that this was due to the trauma of walking barefoot, but the urbanised Negro who is shod in the same way as his Caucasian counterpart still develops the tumour on this site.

Numerous studies have shown that amongst the Caucasian population it is the individual with reddish-fair hair, with blue eyes (21), and with a fair skin that freckles easily, tans poorly and has a tendency to burn, who is at greatest risk. This particular phenotype has in the past been dubbed Celtic, but a more appropriate term for this group of individuals

is, in fact, Caledonian (22).

THE ASSOCIATION BETWEEN MOLES AND MELANOMA

At the present time there is intense interest in the association between benign melanocytic naevi and their malignant counterparts. Melanocytic naevi can be divided somewhat arbitrarily into three main groups. The first is the congenital naevi, which are either present at birth or arise very shortly thereafter. The second are the majority of acquired naevi, which develop around puberty and which are common and normal on the average Caucasian skin, with a mean of around 30 such lesions in early adult life. The third recently recognised variety is the so-called dysplastic naevus, which is a larger acquired melanocytic naevus with certain clinical and pathological features, and a documented increased risk of conversion to malignant melanoma.

The risk of malignant change within a congenital naevus has been studied over many years and the bulk of the work here is related to the so-called giant, or garment, congenital naevi. The most authoritative work in this area is that by Lorentzen *et al.* (23), who studied a cohort of affected patients for 60 years and from this estimated a lifetime risk of malignant change within such lesions of 4%. More recently attention has been focussed on small congenital naevi and Rhodes *et al.* (24) have suggested that as many as 19% of all malignant melanomas have histological features suggesting origin in a congenital naevus. This is an unexpectedly high figure and certainly requires confirmation. As far as acquired naevi are concerned, the bulk of these lesions are not pre-malignant. However, between 25% and 40% of all melanomas have evidence, on histological study, of having arisen in association with a pre-existing acquired naevus. This figure is probably higher in the areas of highest incidence around the world.

A recent paper (25) suggests that this association is associated with a better prognosis for the individual patient, but once again requires confirmation.

The dysplastic naevus patient requires to be subdivided into a number of categories. At the present time, both familial and sporadic forms of this condition are recognised. Affected patients generally have large numbers of 'large, ugly moles' on their trunk and moles on slightly unusual sites, such as the scalp, buttocks and breasts. A

number of them develop multiple superficial spreading melanomas which are said to have a relatively good prognosis. There is currently intense interest in these lesions and many studies are going on to determine their true incidence and the true risk of malignant melanoma developing in affected individuals.

CONCLUSION AND COMMENT

In the past 15 years pathologists have worked intensively on aspects of prognosis relating to the pathology of malignant melanoma and it is now relatively easy to prognosticate with a high degree of accuracy for the individual patient. During this time the incidence of melanoma has continued to rise at an alarming rate. There is therefore a great need during the next 20 years for intense and accurate epidemiological studies to try to pinpoint risk factors which will enable sensible and informed public education campaigns to be mounted.

REFERENCES

1. McGovern VJ. 1982. The nature of melanoma. Journal of Cutaneous Pathology 9, 61-82.
2. Lee JAH, Merrill JM. 1970 Sunlight and the aetiology of malignant melanoma. Medical Journal of Australia 2, 846-851.
3. Lancaster HO. 1956. Some geographic aspects of the mortality from melanoma in Europeans. Medical Journal of Australia 2, 1082-1087.
4. Greene A. 1982. Incidence and reporting of cutaneous melanoma in Queensland. Australian Journal of Dermatology 23, 105.
5. Little JH, Holt J, Davis N. 1980. Changing epidemiology of malignant melanoma in Queensland. Medical Journal of Australia 1, 66-91.
6. Magnus K. 1977. Incidence of malignant melanoma of the skin in the five Nordic countries: significance of solar radiation. International Journal of Cancer 20, 477-485.
7. Schreiber MM, Bozzo PD, Moon TE. 1981. Malignant melanoma in Southern Arizona: increasing incidence and sunlight as an etiologic factor. Archives of Dermatology 117, 6-11.
8. Pathak DR, Samet JM, Howard CA, Key CR. 1982. Malignant melanoma of the skin in New Mexico 1969-1977. Cancer 50, 1440-1446.
9. MacKie RM, Hunter JAA. 1982. Cutaneous malignant melanoma in Scotland. British Journal of Cancer 46, 75-80.
10. Seiji M, Takahashi M. 1975. Plantar malignant melanoma. Journal of Dermatology, Tokyo 4, 163-170.
11. Klepp O, Magnus K. 1979. International Journal of Cancer 23, 482-486.
12. Climatic Impact Committee NRC. 1975. Environmental aspects of stratospheric flight. Washington, DC, NAS.

13. Retsas S. 1983. Sunbeds and melanoma. British Medical Journal 286, 892.
14. Lee JAH, Strickland D. 1980. Malignant melanoma: social status and outdoor work. British Journal of Cancer 41, 757-763.
15. MacKie RM, Aitchison TC. 1982. Severe sunburn and subsequent risk of melanoma. British Journal of Cancer 46, 955-960.
16. Faral E, Jackson EW, Klauber MR. 1966. Mortality in Californian veterinarians. Journal of Chronic Diseases 19, 293-308.
17. Dickson D. 1980. Melanoma increase in radiation laboratories. Nature 287, 475.
18. Beral VE. 1982. Malignant melanoma and exposure to fluorescent lighting at work. Lancet ii, 290-292.
19. Lee JAH, Storer BE. 1980. Excess of malignant melanomas in women in the British Isles. Lancet ii, 1337-1339.
20. Anaise D, Steinitz R, Hur NM. 1978. Solar radiation: a possible aetiological factor in malignant melanoma in Israel. A retrospective study (1960-1972). Cancer 42, 299-304.
21. Elwood JM, Gallagher RP, Hill GB, Spinelli JJ, Pearson JCG, Threlfall W. 1984. Pigmentation and skin reaction to sun as risk factors for cutaneous melanoma: Western Canada Melanoma Study. British Medical Journal 288, 99-102.
22. MacKie EW, MacKie RM. 1984. Red-haired Celts are better termed Caledonians. American Journal of Dermatopathology. In press.
23. Lorentzen M, Pers M, Bretteville-Jensen G. 1977. The incidence of malignant change in giant pigmented naevi. Scandinavian Journal of Plastic and Reconstructive Surgery 11, 163-167.
24. Rhodes AR, Sober AJ, Day CL, Melski JW, Harrist TJ, Mihm Jr MC, Fitzpatrick TB. 1983. The malignant potential of small congenital naevocellular naevi. Journal of the American Academy of Dermatology 6, 230-241.
25. Friedmann RJ & 14 others. 1983. Favourable prognosis for malignant melanomas associated with acquired melanocytic naevi. Archives of Dermatology 119, 455-462.

THE MOLECULAR BIOLOGY OF CARCINOGENESIS

A.W.M. VAN DER KAMP and N.G.J. JASPERS

It has been generally accepted that the aetiology of tumors can be either viral or non-viral. Oncogenic viruses can induce tumors in specific host species and transform some types of cultured cells in vitro. They may contain DNA as their genetic material (e.g. adenoviruses, or papavo- and herpesviruses) or RNA (retroviruses). Non-viral tumorigenesis is thought to be mediated by mutagenic agents such as radiation or DNA-damaging chemicals. The two research areas, that seemed to be unlinked initially, have converged in the recent years.

Retroviruses can be grouped as slow and fast transforming viruses (1). The fast transforming retroviruses consist of two distinct portions (2): 1) genes necessary for the reproduction of the virus and 2) a gene (or genes) that enables the virus to transform the host cells. The latter part of the genome is responsible for the tumorigenic potential of the virus, and is called the viral oncogene (v-onc). Over the past few years it was demonstrated that the various oncogenes, that have been identified, have a homologous counterpart in the cellular genome, called cellular proto-oncogenes (c-onc) (Table 1) (3). Retroviruses appear to carry an activated version of a cellular proto-oncogene, but the cellular oncogenes themselves can also initiate cell transformation provided they become activated in some way.

The involvement of cellular proto-oncogenes in tumorigenesis has been demonstrated by DNA transfection. By this technique DNA, isolated from one type of cell is introduced into another type (4). If DNA from tumor cells is transfected to non-transformed recipient cells, such as mouse NIH 3T3

Table 1. Cellular Oncogenes

Acronym	Origin	Chromosomal localization in man
abl	Abelson murine leukemia virus	9
B-lym	non-viral	
erbA1	Avian erythroblastosis virus	17
erbB	Avian erythroblastosis virus	
ets	E26 avian leukemia virus	
fgr	Gardner-Rasheed feline sarcoma virus	
fms	McDonough feline sarcoma virus	5
fos	FBJ osteosarcoma virus	6
fps(=fes)	Fujinami (ST feline) sarcoma virus	15
mam	non-viral	
mil(=mht)	MH2- avian sarcoma virus	8
mos	Moloney murine sarcoma virus	8
myb	Avian myeloblastosis virus	6
myc	Avian MC29 myelocytomatosis virus	8
N-myc	non-viral	2
neu	non-viral	
raf-1	3611 murine sarcoma virus	3
Ha-ras1	Harvey murine sarcoma virus	11
Ki-ras2	Kirsten murine sarcoma virus	12
N-ras	non-viral	1
rel	Reticuloendotheliosis virus	
ros	UR II avian sarcoma virus	
sis	Simian sarcoma virus	22
ski	Avian SKV 770 virus	1
src	Rous sarcoma virus	20
yes	Y73 sarcoma virus	

cells, it may cause cellular transformation. The transformed cells produce densely populated colonies ('foci') surrounded by a monolayer of contact inhibited normal cells (5). When these focal cells were inoculated into immunologically compromized mice they gave rise to fibrosarcomas. Mouse NIH 3T3 cells are used, because they show efficient transformation after transfection with exogenous DNA isolated from some tumor cell lines. Gene transfer studies with NIH 3T3 cells have established the presence of transforming DNA sequences in a variety of human tumor types (5-9). Rescue of the tumor DNA from the transformed mouse cells have resulted in the molecular cloning and identification of DNA fragments that are responsible for transformation. For example the transforming DNA sequence from a human bladder carcinoma cell line was identified as the Ha-ras-1 oncogene, the cellular onco-