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RISK OF CUTANEOUS MELANOMA ASSOCIATED WITH A FAMILY HISTORY OF THE DISEASE

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In a combined analysis of 2952 melanoma patients and 3618 controls from 8 case-control studies in white populations the risk of cutaneous melanoma was 2.24-fold higher (95% CI, 1.76–2.86) in subjects who reported at least one affected first-degree relative than in subjects who did not. There was no evidence for heterogeneity in the relative risk between the studies, which were from a wide range of latitudes and hence degrees of sun exposure. The effect of family history on melanoma risk was independent of age, naevus count, hair and eye colour, and freckling. There was no evidence for a relationship between family history and primary site of melanoma but there was some suggestion that the familial patients were more likely to have superficial spreading melanoma or lentigo maligna melanoma than acral lentiginous melanoma or nodular melanoma.

Melanoma has been recognised to arise in a familial context for many years (Norris, 1820; Cawley, 1952; Greene and Fraumeni, 1979). Families with multiple cases of melanoma often exhibit the dysplastic naevus syndrome (DNS) (also known as the BK-mole syndrome or the FAMMM syndrome), a syndrome characterised by the familial occurrence of melanoma in combination with multiple dysplastic naevi or atypical moles (Lynch *et al.,* 1978; Clark *et al.,* 1978). However, most studies of familial melanoma and DNS are based on anecdotal reports of high risk families, and there is relatively little systematic evidence about the familial risks of melanoma or DNS. To quantify more precisely the familial risk of melanoma and to analyse the relationship between familial risk and naevus phenotype, we have conducted an overview of 8 case-control studies comprising 2952 cases and 3618 controls.

METHODS

Eight case-control studies were included in this analysis (Cristofolini *et al.,* 1987; Green *et al.,* 1985; Holly *et al.,* 1987; Holman and Armstrong, 1984; B. Langholz, J. Richardson, E. Rappaport, J. Waisman and T. Mack, personal communication; Østerlind *et al.,* 1988; Swerdlow *et al.,* 1986; Walter *et al.,* 1990). They are identified hereafter in this report by the first author of the original publication. These studies were a subset of studies originally collected to examine the relationship between naevi and melanoma risk and are described in detail by Bliss *et al.* (1995). Eligible studies were case-control studies of cutaneous melanoma, for which data collection was complete by the end of 1989 and was comparable in cases and controls, which included a physical examination of naevi by a trained individual, and, for the purpose of this analysis, additionally included questionnaire data on family history of melanoma. In all studies information about melanoma in relatives was obtained by interviewing the case or control, but was not verified using other sources. Data from individual subjects were available for all studies. Subjects were classified as having a positive family history of melanoma if they reported one or more affected first-degree relatives. Some studies also collected information on more distant relatives but this information is unlikely to be complete and has not been analysed. Since it is not possible to distinguish between those subjects who have no family history of melanoma and those who are unaware of an affected relative, subjects with missing family history information were treated as having no family history of the disease. In the Swerdlow study the questions on family history referred to any skin cancer and for 5 cases and 4 controls it could not be ascertained whether the relative had melanoma or non-melanoma skin cancer; these individuals were assumed to have no family history.

Stratum-matched conditional logistic regression was used to estimate the effect of family history on melanoma risk in each study (Breslow and Day, 1980). Individual matching within studies was ignored and all studies were stratified by age in 5 year intervals, by sex, and in one study (Swerdlow) by interview centre. All data were then combined and study was added as a stratification variable. Heterogeneity between studies was tested by fitting an interaction term between study and family history. Naevus measures varied between studies with respect to the type and size of skin lesions that were included as "naevi"; therefore adjustment for number of naevi was made within each study by including number of naevi as a stratification variable. Naevus count on the arms was used for analysis in all studies, although definition of the arm and whether one or both arms were counted again varied between studies. In 6 of the 8 studies the number of naevi was grouped as follows: 0, 1–4, 5–9 or ≥ 10 naevi; in 2 studies, Green and Cristofolini, exact naevus counts were not recorded so we were limited to using the categories in which the data had been collected. To test for an interaction between family history and naevi we added an interaction term between the variable log (number of naevi + 1) and family history. To estimate the effect of family history on melanoma risk after adjustment for other covariates (hair colour, eye colour, or freckles), each study was analysed separately and a pooled relative risk for family history was calculated from an inverse variance weighted average of the log (relative risk) estimates from the individual studies.

To test whether the effect of a family history on melanoma risk differed with respect to either site of primary melanoma or histological subtype, the presence or absence of family history in the cases was used as the outcome variable and the effects of melanoma site and histological subtype were fitted and compared with a model with no effect. All significance tests were based on likelihood ratio tests and are two-sided.

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RESULTS

Table I shows the number of cases and controls with a first-degree family history of melanoma. In the 2 studies conducted in Australia (Holman and Green), where melanoma rates are highest, the proportions of both cases and controls with a family history of melanoma were predictably high. The highest proportion of subjects reporting a positive family history, however, occurred in the Southern Ontario study (Walter). Since incidence rates are considerably lower in Southern Ontario than in Australia or California, this was unexpected. It is possible that there was a particular tendency towards over-reporting of a positive family history in this study since the questionnaire refers to malignant moles in relatives as opposed to melanoma, and other skin cancers or non-malignant moles may have been included.

All studies were consistent with an increased risk of melanoma in subjects with a positive family history of the disease, although in some of the studies the effect was not significant. When all the data were pooled there was no evidence for heterogeneity of risk between studies ($p = 0.40$). The pooled estimate for the relative risk of melanoma for those with a positive family history versus those with no family history was 2.24 (95% CI, 1.76–2.86). There was, however, a significant difference between the relative risks estimated for males and females ($p = 0.001$). The pooled estimate for the relative risk of melanoma in men associated with a positive family history was 3.65 (95% CI, 2.45–5.44) compared with 1.60 (95% CI, 1.17–2.19) in women. This difference in relative risk was primarily due to a difference in the proportions of male and female controls who reported a positive family history, which were 2.0% and 3.9%, respectively. There was little difference in the proportions of male and female cases who reported a positive family history (7.4% of male cases, 6.6% of female cases).

Overall the relative risk associated with a positive family history in subjects under 50 years old was 2.26 (95% CI, 1.61–3.16) compared with 2.23 (95% CI, 1.58–3.17) in subjects aged 50 and over.

Table II shows the relative risk by type of affected first-degree relative. The relative risk associated with having at least one affected sibling (2.87) was higher than the risk associated with having an affected parent (1.85) or an affected offspring (2.26) but the difference was not significant ($p = 0.13$, for comparison between siblings and other first-degree relatives).

In 6 of the studies (all but Cristofolini and Walter) it was possible to examine the relative risk by number of affected relatives. The relative risk associated with having 2 or more affected first-degree relatives was 5.56 (95% CI, 1.59–19.47) compared with a relative risk of 2.18 (95% CI, 1.59–3.00) for subjects with only one affected relative.

TABLE II – RELATIVE RISK OF MELANOMA ASSOCIATED WITH TYPE OF AFFECTED RELATIVE[1]

Relative	No affected relatives		One or more affected relatives[2]		Relative risk (95% CI)
	Cases	Controls	Cases	Controls	
Parent[3]	2,743	3,347	106 (3.7)	66 (1.9)	1.85 (1.35, 2.54)***
Sibling[3]	2,763	3,378	86 (3.0)	35 (1.0)	2.87 (1.92, 4.30)***
Offspring[4]	2,171	2,279	24 (1.1)	11 (0.5)	2.26 (1.09, 4.65)*

[1]Analysis by conditional logistic regression, stratum matched for age, sex, and study.–[2]Values in parentheses are percents.–[3]All studies except Cristofolini.–[4]All studies except Cristofolini, Osterlind, and Swerdlow.–*$p < 0.05$.–***$p < 0.001$.

Adjustment for naevus count within studies had no effect on the association between melanoma risk and family history; the overall relative risk after adjustment was estimated as 2.24 (95% CI, 1.72–2.91). The test for interaction between family history and number of naevi was not significant ($p = 0.52$). In 3 of the studies (Cristofolini, Holly, and Swerdlow) subjects had been examined for the presence of clinically atypical or dysplastic naevi. However, in the Cristofolini and Swerdlow studies none of the cases or controls with atypical naevi reported a family history of melanoma. In the Holly study 4 of the 5 cases with a family history of melanoma also had atypical naevi but a further 63 cases had atypical naevi and no family history, including 24 individuals with more than 5 atypical naevi. There were 24 individuals among the controls who had atypical naevi, all with no family history of melanoma.

Adjustment for other known constitutional risk factors also had no significant effect on the association between melanoma risk and family history. The overall relative risk, after adjustment for naevus count, hair colour, and eye colour within studies, was estimated as 2.15 (95% CI, 1.64–2.82). In 5 studies (Green, Holly, Langholz, Østerlind, and Walter) some measure of freckling was available (see Bliss *et al.*, 1995). After adjustment for naevus count and number of freckles (fitted as a dichotomous variable) the pooled relative risk estimate for family history was 1.83 (95% CI, 1.34–2.49), compared with 2.01 (95% CI, 1.52–2.64) before adjustment.

There was no suggestion of any relationship between family history of melanoma and primary site of melanoma. Eight percent of individuals (35/422) with head and neck melanoma had a positive family history; corresponding proportions for trunk, upper limb, and lower limb melanoma were 7% (83/1,115), 6% (32/548), and 6% (52/839), respectively, (likelihood ratio test, $p = 0.66$). However, there was some suggestion of a difference in familial relative risk by histology (likelihood ratio test, $p = 0.02$). Of the 68 individuals with acral lentiginous melanoma, none reported an affected first-degree rela-

TABLE I – RELATIVE RISK OF MELANOMA ASSOCIATED WITH HAVING A FAMILY HISTORY OF MELANOMA[1]

Study	No family history		Positive family history[2]		Relative risk (95% CI)
	Cases	Controls	Cases	Controls	
Cristofolini	99	204	4 (3.9)	1 (0.5)	7.82 (0.86, 71.31)
Green	210	221	22 (9.5)	11 (4.7)	2.12 (0.99, 4.51)*
Holly	116	135	5 (4.1)	4 (2.9)	1.65 (0.43, 6.41)
Holman	460	492	51 (9.9)	19 (3.7)	2.84 (1.65, 4.87)***
Langholz	715	787	33 (4.4)	13 (1.6)	2.74 (1.42, 5.29)**
Østerlind	460	907	14 (3.0)	19 (2.1)	1.46 (0.72, 2.93)
Swerdlow	177	197	3 (0.6)	0 (0)	—
Walter	510	566	73 (12.5)	42 (6.9)	1.98 (1.33, 2.96)***
Total	2,747	3,509	205 (7.5)	109 (3.1)	2.24 (1.76, 2.86)***

[1]Analysis by conditional logistic regression, stratum matched for age and sex (and study for analysis of the complete data set).–[2]Values in parentheses are percents.–*$p < 0.05$.–**$p < 0.01$.–***$p < 0.001$.

tive; corresponding proportions for superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma were 8% (150/1936), 4% (18/460), and 9% (18/203), respectively. These proportions were similar for each primary site.

DISCUSSION

We have been able to combine data from 8 case-control studies from various white populations to show that an individual's risk of melanoma is increased approximately 2-fold if they have an affected first-degree relative. Since melanoma incidence varies 10-fold between study areas it is interesting that the familial relative risk was similar in all studies, suggesting that genetic susceptibility and sun exposure are likely to act multiplicatively on melanoma risk. The estimated relative risk in men was significantly higher than in women. It seems likely that this is an artefact due to under-reporting of melanoma in the relatives of male controls, since the frequency of a positive family history is similar in male and female cases (7.4% *vs.* 6.6%). If this were the case then the estimated relative risk in women (1.60) would be a better guide to the "true" familial relative risk. An alternative possibility is that female controls over-report melanoma in their relatives (perhaps by confusing melanoma with other skin cancers). If this were the case then the estimated relative risk in men (3.65) would be the better estimate.

We found no evidence that the increased risk of melanoma associated with a family history was stronger at younger ages. This is in contrast to a number of studies of high risk melanoma families (*e.g.,* Greene and Fraumeni, 1979; Greene *et al.,* 1985; Anderson *et al.,* 1967) and is also in contrast to the marked age-at-onset effects observed in the familial risks of other common cancers such as breast and colon cancer. This may reflect bias towards ascertaining younger cases in previous family studies. Alternatively, it may be that very high risk melanoma families exhibit an age-at-onset effect but that these families make only a small contribution to the overall familial risk. Earlier systematic studies which have compared age-at-onset of melanoma in familial patients with non-familial patients have been small and have produced conflicting results (Kopf *et al.,* 1986; Wallace *et al.,* 1971).

Given the known association between melanoma risk and sun exposure, it is conceivable that there might be an interaction between familial risk and melanoma site. For example, genetic influences could be more important for sites which receive little exposure to the sun. However, in line with previous reports (Greene *et al.,* 1985), we found no evidence for any relationship between family history of melanoma and primary site of melanoma.

Previous reports have suggested that superficial spreading melanomas may be over-represented amongst familial cases (Greene and Fraumeni, 1979; Kraemer and Greene, 1985). Although this overview found a higher familial risk amongst superficial spreading melanoma patients than amongst nodular melanoma patients or acral lentiginous melanoma patients, lentigo maligna and superficial spreading melanoma patients exhibited a similar familial risk.

Since the familial relative risk associated with having an affected sibling is not substantially higher than that associated with an affected offspring or parent, the mechanism underlying the familial aggregation of melanoma is likely to involve dominant genes or polygenic effects rather than recessive genes. Evidence to indicate that melanoma can be inherited as an autosomal dominant trait with incomplete penetrance has been provided by the identification of a locus (*MLM*) on chromosome 9p21 which segregates with the disease in some high risk families (Cannon-Albright *et al.,* 1992; Nancarrow *et al.,* 1993). The gene responsible for these families is almost certainly *CDKN2* (*MTS*1), a gene which plays an important role in tumour suppression and is lost or mutated in many cell lines including melanomas. This gene is located in a region consistent with the linkage results (Kamb *et al.,* 1994*a*), and analysis of *CDKN2* in multiple-case melanoma families has uncovered a number of potential predisposing mutations. However, the failure to identify mutations in several families with strong evidence of linkage to the 9p locus (Hussussian *et al.,* 1994; Kamb *et al.,* 1994*b*) suggests that either mutations occur frequently outside the *CDKN2* coding sequence or melanoma susceptibility in some families is controlled by a different gene on 9p21.

The different criteria used to diagnose DNS and its possible high frequency in the general population has led to a rather confusing picture concerning its inheritance. Greene *et al.* (1983) analysed 14 melanoma-DNS families and, whilst they reported that melanoma segregated as an autosomal dominant trait, they found that dysplastic naevi occurred too frequently in the families to fit an autosomal dominant model. Linkage of the combined melanoma-DNS trait was reported to chromosome 1p (Greene *et al.,* 1983; Bale *et al.,* 1989) but subsequent studies have failed to confirm this linkage (Van Haeringen *et al.,* 1989; Cannon-Albright *et al.,* 1990; Kefford *et al.,* 1991; Nancarrow *et al.,* 1992), and some but possibly not all of the families which originally showed linkage to 1p now appear to be consistent with linkage to chromosome 9p (Goldstein *et al.,* 1994). Interestingly, in 9 families with apparent disease-related mutations in *CDKN2* on 9p only 10/33 dysplastic naevi cases carried a mutation, compared with 33/36 of the melanoma cases, suggesting that if the identified mutations are causally related to melanoma they are unlikely to be responsible for the development of dysplastic naevi in these families (Hussussian *et al.,* 1994). To avoid the difficulties inherent in diagnosing DNS, Goldgar *et al.* (1991) modelled the inheritance of total naevus density, a derived phenotype incorporating both number and size of naevi. In families with melanoma and DNS they found some evidence to suggest that a major gene is responsible for a proportion (but not all) of the phenotypic variability in total naevus density.

The current picture concerning the combined inheritance of melanoma and naevi or dysplastic naevi is therefore far from clear and it is of considerable interest that in this overview the familial risk of melanoma appeared to be essentially independent of the total naevus count. This would suggest that the gene (or genes) determining susceptibility to melanoma increase melanoma risk without increasing the density of naevi. It is, however, important to note that in the 6 studies in which we were able to look at numbers of affected relatives, only 15 cases and 3 controls reported 2 or more affected first-degree relatives. Thus it is possible that some or most of the familial effect we have observed is due to more low penetrant genes than those segregating in the families used in the analyses described above or that some of the observed familial effect is environmental. The known genetically determined risk factors such as hair and eye colour are too weak to explain the observed familial risk, as is confirmed by the fact that adjustment for these risk factors does not alter the familial relative risk. In any event the small numbers of multiple case families observed in this overview does indicate that the proportion of melanoma in the general population due to high risk genes (like *MLM*) will be low. The cumulative risk of melanoma in *MLM* carriers has been estimated as 65% by age 80 (Cannon-Albright *et al.,* 1994). If *MLM* were to account for the entire familial excess risk of melanoma as determined by this overview, *MLM* would cause only 4% of all melanoma cases.

In conclusion, we estimate that the risk of melanoma in an individual with an affected first-degree relative is just over twice the population risk and that this risk factor is indepen-

dent of the naevus phenotype. In the absence of other major risk factors, in particular large numbers of naevi and/or dysplastic naevi, it is debatable whether such individuals should be specifically targeted for intervention. However, an individual with an affected first-degree relative and an abnormal naevus phenotype or with more than one affected first-degree relative clearly has a risk substantially higher than that of the general population and may need to be managed differently.

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APPENDIX

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REFERENCES

ANDERSON, D.E., SMITH, J.L., JR. and MCBRIDE, C.M., Hereditary aspects of malignant melanoma. *J. Amer. Med. Ass.,* **200,** 81–86 (1967).

BALE, S.J., DRACOPOLI, N.C., TUCKER, M.A., CLARK, W.H., FRASER, M.C., STRANGER, B.Z., GREEN, P., DONISKELLER, H., HOUSMAN, D.E. and GREENE, M.H., Mapping the gene for hereditary cutaneous malignant melanoma-dysplastic nevus to chromosome 1p. *N. Engl. J. Med.,* **320,** 1367–1372 (1989).

BLISS, J.M. and 13 OTHERS, Risk of cutaneous melanoma associated with pigmentation characteristics and freckling: systematic overview of 10 case-control studies. *Int. J. Cancer,* **62,** 367–376 (1995).

BRESLOW, N.E. and DAY, N.E., *Statistical methods in cancer research.* Vol. 1—*The analysis of case-control studies,* International Agency for Research on Cancer, Lyon, IARC Scientific Publication **32** (1980).

CANNON-ALBRIGHT, L.A., GOLDGAR, D.E., WRIGHT, E.C., TURCO, A., JOST, M., MEYER, L.J., PIEPKORN, M., ZONE, J.J. and SKOLNICK, M.H., Evidence against the reported linkage of cutaneous melanoma-dysplastic nevus syndrome locus to chromosome 1p36. *Amer. J. hum. Genet.,* **46,** 912–918 (1990).

CANNON-ALBRIGHT, L.A. and 15 OTHERS, Assignment of a locus for familial melanoma, MLM, to chromosome 9p13-p22. *Science,* **258,** 1148–1152 (1992).

CANNON-ALBRIGHT, L.A., MEYER, L.J., GOLDGAR, D.E., LEWIS, C.M., MCWHORTER, W.P., JOST, M., HARRISON, D., ANDERSON, D.E., ZONE, J.J. and SKOLNICK, M.H., Penetrance and expressivity of the chromosome 9p melanoma susceptibility locus (*MLM*). *Cancer Res.,* **54,** 6041–6044 (1994).

CAWLEY, E.P., Genetic aspects of malignant melanomas. *Arch. Dermatol.,* **65,** 440–450 (1952).

CLARK, W.H., JR., REIMER, R., GREENE, M.H., AINSWORTH, A. and MASTRANGELO, M., Origin of familial malignant melanoma from heritable melanocytic lesions. *Arch. Dermatol.,* **114,** 732–738 (1978).

CRISTOFOLINI, M., FRANCESCHI, S., TASIN, I., ZUMIANI, G., PISCIOLI, F., TALAMINI, R. and LA VECCHIA, C., Risk factors for cutaneous malignant melanoma in a Northern Italian population. *Int. J. Cancer,* **39,** 150–154 (1987).

GOLDGAR, D.E., CANNON-ALBRIGHT, L.A., MEYER, L.J., PIEPKORN, M.W., ZONE, J.J. and SKOLNICK, M.H., Inheritance of nevus number and size in melanoma and dysplastic nevus syndrome kindreds. *J. nat. Cancer Inst.,* **83,** 1726–1733 (1991).

GOLDSTEIN, A.M., DRACOPOLI, N.C., ENGELSTEIN, M., FRASER, M.C., CLARK, W.H., JR. and TUCKER, M.A., Linkage of cutaneous malignant melanoma/dysplastic nevus to chromosome 9p, and evidence for genetic heterogeneity. *Amer. J. hum. Genet.,* **54,** 489–496 (1994).

GREEN, A., MACLENNAN, R. and SISKIND, V., Common acquired naevi and the risk of malignant melanoma. *Int. J. Cancer,* **35,** 297–300 (1985).

GREENE, M.H. and FRAUMENI, J.J., JR., The hereditary variant of malignant melanoma. *In:* W.H. Clark, L.I. Goldman and M.J. Mastrangelo (eds.), *Human malignant melanoma.* Grune & Stratton, New York (1979).

GREENE, M.H., CLARK, W.H., JR., TUCKER, M.A., KRAHMER, K.H., ELDER, D.E. and FRASER, M.C., The high risk of malignant melanoma in melanoma prone families with dysplastic naevi. *Ann. int. Med.,* **102,** 458–469 (1985).

GREENE, M.H., GOLDIN, L.R., CLARK, W.H., JR., LORRIEN, E., KRAEMER, K.H., TUCKER, M.A., ELDER, D.E., FRASER, M.C. and ROWE, S., Familial cutaneous malignant melanoma: autosomal dominant trait possibly linked to the Rh locus. *Proc. nat. Acad. Sci. (Wash.),* **80,** 6071–6075 (1983).

HOLLY, E.A., KELLY, J.W., SHPALL, S.N. and CHIU, S.-H., Number of melanocytic nevi as a major risk factor for malignant melanoma. *J. Amer. Acad. Dermatol.,* **17,** 459–468 (1987).

HOLMAN, C.D.J. and ARMSTRONG, B.K., Pigmentary traits, ethnic origin, benign nevi and family history as risk factors for cutaneous malignant melanoma. *J. nat. Cancer Inst.,* **72,** 257–266 (1984).

HUSSUSSIAN, C.J., STREUWING, J.P., GOLDSTEIN, A.M., HIGGINS, P.A.T., ALLY, D.S., SHEAHAN, M.D., CLARK, W.H., JR., TUCKER, M.A. and DRACOPOLI, N.C., Germline p16 mutations in familial melanoma. *Nature (Lond.) Genet,* **8,** 15–21 (1994).

KAMB, A., GRUIS, N.A., WEAVER-FELDHAUS, J., LIU, Q., HARSHMAN, K., TAVTIGIAN, S.V., STOCKERT, E., DAY, R.S., III, JOHNSON, B.E. and SKOLNICK, M.H., A cell cycle regulator potentially involved in genesis of many tumour types. *Science,* **264,** 436–440 (1994*a*).

KAMB, A. and 23 OTHERS, Analysis of the p16 gene (*CDKN2*) as a candidate for the chromosome 9p melanoma susceptibility locus. *Nature (Lond.) Genet.,* **8,** 22–26 (1994*b*).

KEFFORD, R.F., SALMON, J., SHAW, H.M., DONALD, J.A. and MCCARTHY, W.H., Hereditary melanoma in Australia: variable association with dysplastic nevi and absence of genetic linkage to chromosome 1p. *Cancer Genet. Cytogenet.,* **51,** 45–55 (1991).

KOPF, A.W., HELLMAN, L.J., ROGERS, G.S., GROSS, D.F., RIEGEL, D.S., FRIEDMAN, R.J., LEVENSTEIN, M., BROWN, J., GOLOMB, F.M., ROSES, D.F., GUNPORT, S.L. and MINTZIS, M.M., Familial malignant melanoma. *J. Amer. Med. Ass.,* **256,** 1915–1919 (1986).

KRAEMER, K.H. and GREENE, M.H., Dysplastic nevus syndrome. Familial and sporadic precursors of cutaneous melanoma. *Dermatol. Clin.,* **3,** 225–237 (1985).

LYNCH, H.T., FRIOHOT, B.C. and LYNCH, J.F., Familial atypical multiple mole melanoma syndrome. *J. med. Genet.*, **15,** 352–356 (1978).

NANCARROW, D.J., PALMER, J.M., WALTERS, M.K., KERR, B.M., HAFNER, G.J., GARSKE, L., MCLEOD, G.R. and HAYWARD, N.K., Exclusion of the familial melanoma locus (*MLM*) from the PND/D1S47 regions of chromosome arm 1p in 7 Australian families. *Genomics,* **12,** 18–25 (1992).

NANCARROW, D.J. and 12 OTHERS, Confirmation of chromosome 9p linkage in familial melanoma. *Amer. J. hum. Genet.,* **53,** 936–942 (1993).

NORRIS, W., A case of fungoid disease. *Edinburgh surg. J.,* **16,** 562–565 (1820).

ØSTERLIND, A., TUCKER, M.A., HOU-JENSEN, K., STONE, B.J., ENGHOLM, G. and JENSEN, O.M., The Danish case-control study of cutaneous malignant melanoma. I. Importance of host factors. *Int. J. Cancer,* **42,** 200–206 (1988).

SWERDLOW, A.J., ENGLISH, J., MACKIE, R.M., O'DOHERTY, C.J., HUNTER, J.A.A., CLARK, J. and HOLE, D.J., Benign melanocytic naevi as a risk factor for malignant melanoma. *Brit. med. J.,* **292,** 1555–1559 (1986).

VAN HAERINGEN, A., BERGMAN, W., NELEN, M.R., VANDERKOOIJMEIJS, E., HENDRIKSE, I., WIJNEN, J.T., KHAN, P.M., KLASEN, E.C. and FRANTS, R.R., Exclusion of the dysplastic nevus syndrome (DNS) locus from the short arm of chromosome 1 by linkage studies in Dutch families. *Genomics,* **5,** 61–64 (1989).

WALLACE, C.D., BEARDMORE, G.L., LESLEY, A. and EXTON, B., Familial malignant melanoma. *Ann. Surg.,* **177,** 15–20 (1971).

WALTER, S.D., MARRETT, L.D., FROM, L., HERTZMAN, C., SHANNON, H.S. and ROY, P., The association of cutaneous malignant melanoma with the use of sunbeds and sunlamps. *Amer. J. Epidemiol.,* **131,** 232–243 (1990).