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Common and Dysplastic Naevi as Risk Factors for Cutaneous Malignant Melanoma in a Swedish Population.

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Common naevi, dysplastic naevi (DN) and other phenotypic features were evaluated as melanoma risk factors in a Swedish case-control study. One-hundred and twenty-one prevalent melanoma cases and 378 randomly selected controls participated. The mean total body naevus count was 115 in the cases and 67 in the controls. Fifty-six per cent of the cases and 18% of the controls had clinical DN. The corresponding figures for histologically diagnosed DN were 40% and 8% respectively. Clinical DN was as good as histologically diagnosed DN in identifying individuals at risk for melanoma. Subjects with sun-sensitive skin, ≥ 150 naevi and presence of DN have 50 times higher melanoma risk than those without these characteristics.

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Sweden is a country with a high incidence of cutaneous malignant melanoma (CMM). Since 1960 the incidence rate has increased by on average 5% per year, accompanied by an annual 3% increase in the mortality rate (1). In general, this has been attributed to a change in sunbathing habits to more intermittent and intense UV exposure in combination with our fair complexion. The steady increase has led to discussions about various preventive steps such as public education programmes and regular skin examinations of high-risk individuals. Since we lack a curative treatment for advanced melanoma and the prognosis is correlated to the thickness of the tumour, secondary prevention such as skin examination could be helpful in reducing the mortality rate. Such surveillance programmes already exist for patients with xeroderma pigmentosum and dysplastic naevus syndrome. However, these two high-risk groups constitute only a minor proportion of the melanoma patients.

In recent years, a number of case-control studies from other countries have pointed at the presence of atypical (dysplastic) naevi and many common naevi as two major risk factors for CMM (2–10) and as such can be used as potential tools for selecting individuals at risk of developing CMM. We had the clinical impression, however, that Swedes have more common naevi and a higher prevalence of dysplastic naevi than what has been reported from other populations. For that reason, we performed a case-control study of a Swedish population in which we evaluated the importance of various pigmentary phenotypic features focusing in particular on the number of common naevi (CN) and the presence of dysplastic naevi (DN) as melanoma risk factors.

METHODS

Cases

All patients, 30–50 years of age, with the diagnosis of CMM between 1964 and 1986 and living in Göteborg were selected from the Regional Cancer Register, n = 197. Of these, 78% (n = 154) were still alive. In all but two cases permission to contact the patient was obtained from his or her physician. A letter was sent to each patient offering a free skin examination by a dermatologist (A.A.) and an oncologist (U.S.). Ten patients declined participation and an additional 5 could not be reached. The remaining 137/152 (90%) were examined. Of these, 16 patients were excluded from analysis, 6 because tumour material could not be found for histological re-evaluation and 10 because of an incorrect diagnosis. On re-evaluation these 10 lesions were judged to be 6 dysplastic naevi, 2 juvenile melanomas, one blue naevus and one pigmented spindle cell naevus. Two patients were retained in the study although material from their primary melanoma could not be traced. In these cases the diagnosis was verified by histological examination of metastases. In 12 cases the tumour was judged to be a malignant melanoma in situ. The histological re-examination was performed by one pathologist (M.S.). Altogether 121 patients (52 men, 69 women, mean age 43.5 years) were included for analysis.

Controls

Five-hundred subjects within the same age-span (30–50 years) were randomly selected from the census file in Göteborg. Like the melanoma patients, they were offered a free skin examination. Thirty one (6%) had moved from the area, lacked a permanent address, were severely ill or were deceased. Three hundred and eighty-three of the remaining 469 (82%) were examined. Five of the subjects examined were excluded from analysis, four due to a non-Caucasian

origin and one because a malignant melanoma in situ was diagnosed in this study. Of the 18% drop-outs, one-third were interviewed by telephone. Their main reason for declining participation was lack of time. Thus, a total of 378 controls (182 men, 196 women, mean age 42.5 years) were included in the analysis. This equals 76% of the original 500 subjects. The study was performed during the winter seasons 1986–88 and began with the oldest individuals. The control subjects are described in detail in a previous paper (11).

Questionnaire

The patient and the doctor together filled in the questionnaire. Ethnic origin and heredity for CMM were registered. An assessment of skin type according to Melski was made (12). Hair colour at the age of twenty was estimated and rated according to a three-point scale as dark brown, light brown or red/blond. Eye colour was registered as brown/mixed, blue/grey or green. The use of oral contraceptives was noted.

Skin examination

The total body skin examination included skinfolds, palms, soles, scalp and genital area. All brown macular or raised lesions $\geq$ 2 mm considered to be pigmented melanocytic naevi were counted. It was sometimes difficult to discriminate between naevi, freckles and lentigines. When in doubt, the lesion was not counted. The major clinical criterion used to identify a dysplastic naevus was a diameter $\geq$ 5 mm. In addition, at least two of the following criteria were required: an ill-defined or irregular border, speckled pigmentation, erythema or a pebbled surface (13). A pigmented naevus $\geq$ 10 mm and anamnestically apparent during the first year of life was considered to be a congenital melanocytic naevus.

All subjects with clinical DN, except melanoma patients with advanced disease, were offered the opportunity to have the lesions excised for histological examination. The pathologist examined all biopsies without knowing if the patient was a control subject or a melanoma patient. To further avoid bias in the histological diagnosis, some flat common naevi were excised and the slides were added to those from clinical DN.

Pathology

The histological diagnosis of DN was based on the following criteria.

1. Irregular melanocytic hyperplasia (random single cells, forming streaks or interretal bridges) in the basal layer of the epidermis.
2. Little or no nesting of the proliferated melanocytes.
3. Lentiginous acanthosis of the epidermis.
4. Stromal changes: subepidermal fibrosis, nonspecific inflammatory infiltrate and occurrence of melanophages.
5. Additional possible features in the dermal component of a compound DN: the component is thin, inconspicuous and less horizontally extended than the epidermal component. The constituent cells have an immature »lymphoid« appearance.
6. Cellular atypia of significant degree (i.e. exceeding what is generally seen in a lentigo maligna) was usually not seen.

The first two features listed were considered obligatory. Furthermore, the lesions had to demonstrate enough cellular epidermal components to be properly judged according to the above criteria (14,15).

Statistical methods

Spearman's rank test was used for the correlation analyses. For comparisons between groups, Wilcoxon's two-sample test was used. For comparisons of proportions between groups, Fisher's exact test was used. Trends in contingency tables were analysed using the Mantel-Haenzel chi-square test (16). The relative risk of melanoma, with confidence limits, was calculated. A stepwise logistic regression analysis was applied in order to assess the risk factors that contribute independently of each other to the risk of melanoma. The relative risk with confidence limits adjusted for important confounding variables was calculated. To estimate the probability of having a clinical DN as a function of number of common naevi, a maximum-likelihood estimation under order restrictions was used (17). Two-sided tests were used.

RESULTS

A total of 121 melanoma patients and 378 control subjects were examined. The age at diagnosis of the patients with melanoma ranged between 19 and 50 years, median 36 years, and the time from diagnosis to interview ranged from 1 to 24 years, median 7 years. Of the 119 melanomas re-evaluated, 55 were classified as superficially spreading melanoma, 16 as nodular melanoma, 9 as lentigo maligna melanoma, and 8 as spindle cell melanoma. As many as 31 of the melanomas could not be classified at re-evaluation partly due to the minimal amount of melanoma tissue remaining in the paraffin blocks. Six subjects had a history of 2 primary melanomas and 8 patients had been or were under treatment for recurrent disease. Subjects who had their melanoma diagnosed 5 years or less before the investigation ($n = 58$) did not differ from patients who had the lesion diagnosed earlier ($n = 63$) regarding all phenotypic variables, including the mean total body naevus count. Nor did the histological classification of the melanoma correlate to any of the phenotypic variables studied, and the 12 patients with melanoma in situ did not differ from those with invasive melanoma. All patients were therefore analysed regardless of when the melanoma was diagnosed, the histological classification or the level of invasion.

The melanoma patients had a more sun-sensitive skin type and a predominance for blond and red hair colour compared with controls, $p < 0.001$. Brown/

Table I. *Risk factors for CMM*

Variable	Category	Cases		Controls		Relative risk	Relative risk
		n=121		n=378		crude (95% CI)	adjusted (95% CI)*
		%	n	%	n		
Skin type	III and IV	69	(84)	92	(348)	1	
	I and II	31	(37)	8	(30)	5.1 (3.0–8.7)	3.6 (1.9–6.9)
Hair colour	dark brown	8	(10)	16	(59)	1	
	light brown	49	(59)	62	(235)	1.5 (0.7–3.1)	1.9 (0.8–4.8)
	red/blond	43	(28/24)	22	(17/67)	3.6 (1.7–7.7)	2.7 (0.0–7.1)
Eye colour	brown/mixed	11	(13)	20	(77)	1	
	blue/grey	63	(76)	65	(244)	1.8 (1.0–3.5)	1.4 (0.7–3.0)
	green	26	(32)	15	(57)	3.3 (1.6–6.9)	3.9 (1.5–10.3)
Total body	1–74	40	(48)	65	(247)	1	
naevus count	75–149	34	(41)	28	(105)	2.0 (1.2–3.2)	1.2 (0.7–2.2)
	≥150	26	(32)	7	(26)	6.3 (3.5–11.6)	2.6 (1.1–6.1)
Number of	0	44	(53)	82	(310)	1	
clinical DN	1–2	27	(33)	13	(51)	3.8 (2.2–6.4)	2.5 (1.3–4.5)
	≥3	29	(35)	5	(17)	12.0 (6.3–23.0)	5.6 (2.5–12.5)
Presence of	No	60	(72)	92	(348)	1	
histological DN	Yes	40	(49)	8	(30)	7.9 (4.7–13.3)	4.6 (2.5–8.4)**

* The stepwise logistic regression model included; skin type, hair colour, eye colour, total body naevus count, number of clinical DN, age and sex.

** Tested in a separate analysis excluding the variable "Number of clinical DN".

mixed eye colour was more common among controls, $p < 0.05$, and green eyes were more common among patients, $p < 0.01$. No difference was found in the frequency of blue/grey eye colour between the two groups (Table I). Eight per cent of the melanoma patients and 3% of the controls reported heredity for CMM. The patients also had a slight increase in the occurrence of congenital melanocytic naevi. These two differences were not statistically significant. To reach significance for these variables, a larger material is probably required. No difference was found between patients and controls regarding sex, age or the use of oral contraceptives.

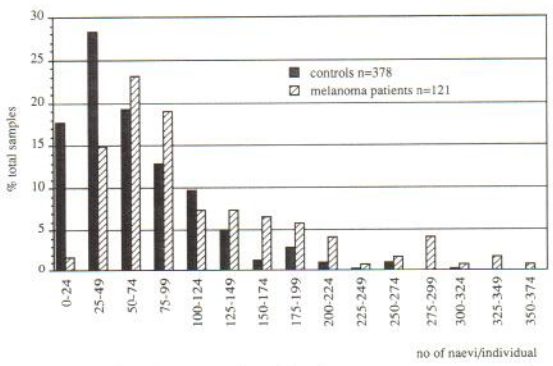

Fig. 1. The distribution of total body naevus counts in melanoma patients and controls.

Total body naevus count

The melanoma patients had almost twice as many naevi as the controls. The mean (SE) total body naevus count (common and dysplastic naevi) was 115 (7) (median 89) versus 67 (3) (median 54), $p < 0.001$. The number of naevi was not influenced by age, sex or skin type in either group. The numerical distribution of naevi within the melanoma and the control samples is shown in Fig. 1. As many as 26% of the melanoma patients had 150 naevi or more. The corresponding figure for the controls was 7%. Only 2% of the patients but 18% of the controls had less than 25 naevi.

Eighty patients (66%) had had 1–23 naevi excised before or after the diagnosis of melanoma. Altogether as many as 310 naevi had been removed and 286 of these were histologically re-evaluated. Those not re-examined had been excised from the face or neck region and were histologically diagnosed as intradermal naevi. These 310 naevi were included in the naevus counts. Some of the controls had a history of an occasional skin lesion which had been excised. With a few exceptions, these were not sent

Table II. *Total body naevus count*

Category	Cases			Controls			p-value*
	n	mean(SE)	median	n	mean(SE)	median	
All	121	115(7)	89	378	67(3)	54	p<0.001
Without DN	53	78(7)	59	310	58(3)	47	p<0.01
With clinical DN	68	144(10)	117	68	107(7)	102	p<0.05
With histological DN	49	146(12)	121	30	121(11)	117	N.S.

*Wilcoxon's two-sample test.

for histological examination and therefore could not be included in our counts. It is obvious that this difference could not influence our counts significantly. Instead, the main reason for these re-evaluations was to find naevi fulfilling the criteria for DN excised before this entity was described.

Dysplastic naevi

One or more clinical DN were present in 56% (CI 47–65%) of the melanoma patients and in 18% (CI 14–22%) of the controls, $p < 0.001$. Twenty-nine per cent of the patients had ≥ 3DN, to be compared with 5% of the controls (Table I). The group of melanoma patients with clinical DN includes 10 subjects without clinical DN at the time of the examination but with an earlier diagnosis of histologically verified DN (cf. above). Of the 286 previously excised lesions 44 were histological DN at re-evaluation. In 48 of the 58 patients with clinical DN at the examination we excised 1–8 naevi and in 64 of 68 controls with DN we removed 1–5 naevi. Forty per cent (CI 31–49%) of all melanoma patients had histologically verified DN. The prevalence in the control group was 8% (CI 5–11%), $p < 0.001$ (Table I). Five out of 6 patients with two primary melanomas had histologically verified DN. DN were not more common in cases with the melanoma diagnosed within the last 5 years. When control subjects with and without DN were studied separately, there was a marked difference in mean total body naevus count. Those with clinical DN had a mean of 107 naevi (median 102) and those without a mean of 58 (median 47). A similar difference was seen for melanoma patients, where the corresponding figure for those with DN was 144 (median 117) and for those without 78 (median 59) (Table II). In controls, subjects with clinical DN had a more sun-sensitive skin than those without DN, $p < 0.001$. This correlation between DN and skin type was not seen in the melanoma group, possibly due to the larger proportion of subjects with a sun-sensitive skin in this group as a whole. As expected, melanoma patients without DN had a more sun-sensitive skin than controls without DN, $p < 0.001$. This difference between melanoma patients and controls disappeared when the subgroups with DN were compared. Sex had no influence on the presence of clinical DN in either of the groups. In the melanoma group, however, there was a significant male predominance of subjects with histologically verified DN (52% men and 32% women), $p < 0.05$. A similar sex difference could not be found in the control group. This finding is hard to explain and needs further penetration. Neither in the melanoma patients nor in the controls did age have any influence on the presence of clinically or histologically verified DN.

Relative risk (RR)

The crude relative risk for CMM was calculated for all variables studied. A significantly increased relative risk was found for: skin type, hair colour, eye colour, number of naevi, number of clinical DN and the presence of histologically verified DN (Table I). The cut points for the total body naevus counts were choosen in reference to the mean value of the controls. In a stepwise logistic regression procedure the adjusted RR was calculated for all these significant risk factors together with sex and age. In the model the number of clinical DN and the presence of histologically verified DN were tested separately. The risk of melanoma was most strongly correlated to the presence of 3 or more clinical DN, RR 12.0. It remains the strongest risk factor (RR 5.6) even after adjustment for the contribution of all other variables to the relative risk. The presence of histologically verified DN was also a strong risk factor both before (RR 7.9) and after adjustment (RR 4.6). In addition, we found an increasing melanoma risk with an

Table III. *Relative risk for CMM**

Skin type	I+II		III+IV	
Presence of clinical DN	No	Yes	No	Yes
Number of naevi				
1–74	4	14	1	3
75–149	8	26	2	6
≥150	16	50	4	11

*The table gives the relative risk for different groups defined by combining different variables compared to the group with the lowest risk (=1).

increasing total number of naevi, but after adjustment the relative risk decreased and was statistically significant only at the level ≥ 150 naevi. A sun-sensitive skin, red/blond hair and green eye colour constitute three other risk factors for melanoma. After correcting for the other variables, red/blond hair colour was no longer a significant risk factor. However, when analysing the trend from dark to red/blond hair a lighter hair colour remained a significant melanoma risk factor, $p < 0.001$ (Table I).

The relative risk for subjects regarding the three most important risk factors is shown in Table III. Subjects with clinical DN, more than 150 naevi and a sun-sensitive skin have 50 times higher melanoma risk than subjects without clinical DN, with few naevi and a good tanning ability. Due to small numbers, such a risk calculation was not made for the subjects with ≥ 3 dysplastic naevi. These data would not be reliable. We compared the probability (in per cent) of correctly classifying a person as a melanoma case or a control based on the presence of clinically versus histologically verified DN using a logistic regression model. For this analysis, we included subjects without DN and subjects with clinical DN excised and analysed histologically during this study only (melanoma patients n = 98, controls n = 374). Clinical DN turned out to be an as good as or even better prognostic tool than histologically verified DN (64% versus 61%). This analysis can be used only to compare these two variables with each other. Because of the larger number of exclusions among the melanoma patients, due to earlier excised DN, the numerical values as such are underestimated.

DISCUSSION

This is the first Swedish case-control study dealing with the risk factors for CMM, focusing especially on the number of common naevi and the prevalence of dysplastic naevi. We selected subjects between 30 and 50 years of age as most CN as well as DN have appeared by this time. Secondly, it is in this age-group that the incidence of melanoma begins to rise and preventive measures become important. The control group was randomly selected from a census file and since the participation rate was high, the control group is considered representative of the Swedish population in this age-group.

This is a study of prevalent melanoma patients. Of our cases 75% had their melanomas diagnosed less than 10 years and 95% less than 15 years before the investigation. The 10 and 15-year relative survival for patients in our sampling frame is 80% and 75% respectively. The melanoma patients whose tumours were diagnosed within the last 5 years did not differ from those with an earlier diagnosis in any of the variables studied. This led to the conclusion that our patients do not differ significantly from melanoma cases being diagnosed today.

We would like to stress that all patients included had their tumour sections re-evaluated and the diagnosis confirmed. In this study, 7.6% of the original melanoma cases were excluded because the diagnosis could not be verified on re-examination. In a previous study, randomly re-evaluating the diagnosis of malignant melanoma in the National Cancer Register, an incorrect diagnosis was found in 3.7% of the cases. Higher figures of misdiagnosis have been reported for melanoma survivors (18).

We have recently reported that Swedes have more than twice as many common naevi as other populations studied (11). Even so, the melanoma patients had almost twice as many naevi as the controls. This finding is in agreement with the results from other case-control studies, but our counts are again extremely high (5,8). This might partly be explained by the age-range studied, and the fact that in contrast to other studies our skin examination included skinfolds, palms, soles, scalp and genital area. Furthermore, our counts include most previously excised and histologically verified naevi. Even the possible recall bias among melanoma patients regarding the number of excised skin lesions was eliminated by registering all scars. The validity of the naevus counts is discussed in detail in a previous paper (11). With all the precautions taken, we are convinced that our counts are close to the true value. Swedes might have a large number of naevi due to genetic factors. If UV-light is of importance for the

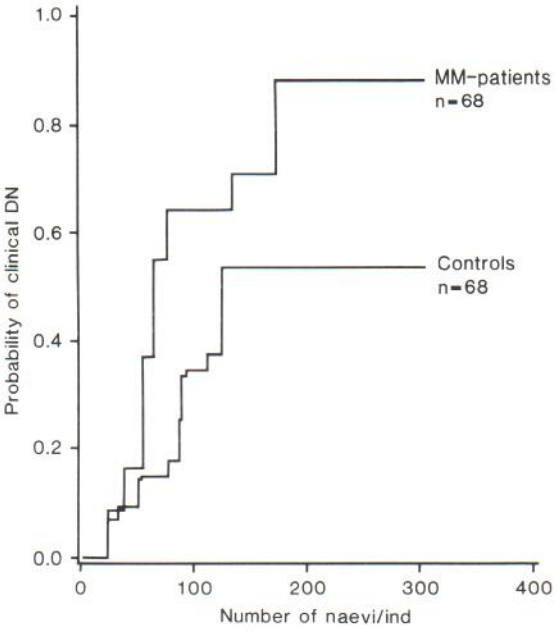

Fig. 2. The probability of having a clinical DN with increasing number of common naevi.

promotion of naevi, it is possible that the large number of naevi is due to our habits of intermittent and intense UV exposure in combination with our fair skin (19,20). As many of our melanoma patients had reduced their UV exposure after being diagnosed, it is possible that the difference in naevus counts between patients and controls might be even larger.

The prevalence of clinical DN was 56% among the melanoma patients and 18% in the controls. The fact that DN is three times more common in melanoma cases supports the concept that DN is a marker of, and perhaps even a precursor to, CMM. Our prevalences of clinical DN are higher than what has been reported from Australia and Germany but similar to those reported from California (4,10,8). The prevalence of histological DN in the melanoma patients was 40%, compared to 8% in the controls. We have not found any case-control studies comparing the histological findings. In a French investigation of non-familial melanoma cases, 18% had histologically verified DN (21). In a non-melanoma population seen in a dermatology practice, a prevalence figure of 4.9% has been reported (22). It is, however, difficult to compare different studies. First, one has to bear in mind that histological prevalence figures depend on the number of lesions excised and this results in underestimation of the prevalence, especially in the control group. Another problem is the lack of concensus among pathologists regarding the histological criteria for DN. However, for identifying subjects at risk of developing CMM, our results indicate that the clinically diagnosed DN is as good a discriminator as the histologically diagnosed.

The presence of clinical DN was strongly associated with a large number of common naevi. The difference in likelihood of having a clinical DN between melanoma patients and controls for a given number of naevi indicates that it is not just a large number of naevi that increases the risk of a person's developing a DN or having a naevus diagnosed as dysplastic (Fig. 2). Instead, it points towards a true difference between melanoma patients and controls in the exposure or the response to an etiological factor. The differences between patients and controls diminish when subjects with and without DN are analysed separately. For example, controls with DN and melanoma patients had comparable numbers of naevi, and the controls with DN had, like the patients, a more sun-sensitive skin. This is in line with the view that DN is a strong independent risk factor for developing CMM.

Our finding of a more sun-sensitive skin in melanoma patients is consistent with a number of previous reports (23,24). Red/blond hair is another well-known risk factor, although it becomes less important when adjusted for other associated host factors. In other populations, blue eye colour is a well-documented risk factor. However, we found no association between blue/grey eye colour and melanoma, probably because blue eyes are such a common phenotypic feature in Sweden. Instead, green eye colour is a significant risk factor even after adjustment (Table I).

A sun-sensitive skin, a large number of naevi and the presence of DN, clinical or histological, contribute to a high risk in the present study. When combining the corresponding risk factors, a subgroup with 50 times higher melanoma risk than those without these characteristics can be identified (Table III). Using the Swedish incidence data for melanoma, this corresponds to a risk of having a melanoma diagnosed in 1 per 500 subjects per year. Considering a 10-year survival of at least 80 %, at the best one life per 2500 examined subjects per year could be saved by an earlier diagnosis. Taking only survival into account, these figures do not justify a regular screening programme, especially as it is well known that those ignoring early symtoms of disease are the same ones that avoid screening programmes. The benefits

of such preventive projects are therefore usually overestimated. It is more difficult to make a cost-benefit analysis considering the psychological gain of never having an invasive melanoma diagnosed versus the worries such a screening programme might induce. Nevertheless, this high-risk group is certainly an important target to reach for intensified education concerning early melanoma signs and sun awareness. If these subjects have difficulties in performing self-examination of their naevi they should be offered regular skin examinations.

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REFERENCES

1. Thörn M, Adami H-O, Bergström R, Ringborg U, Krusemo UB. Trends in survival from malignant melanoma: remarkable improvement in 23 years. J Natl Cancer Inst 1989; 81: 611–617.
2. Holman CD, Armstrong BK. Pigmentary traits, ethnic origin, benign nevi and family history as risk factors for cutaneous malignant melanoma. J Natl Cancer Inst 1984; 72: 257–266.
3. Green A, MacLennan R, Siskind V. Common acquired naevi and the risk of malignant melanoma. Int J Cancer 1985; 35: 297–300.
4. Nordlund JJ, Kirkwood J, Forget BM, Scheibner A, Albert DM, Lerner E, Milton GW. Demographic study of clinically atypical (dysplastic) nevi in patients with melanoma and comparison subjects. Cancer Res 1985; 45: 1855–1861.
5. Swerdlow AJ, English J, MacKie RM, O'Doherty CJ, Hunter JA, Clark J, Hole DJ. Benign melanocytic naevi as a risk factor for malignant melanoma. Br Med J 1986; 292: 1555–1559.
6. Dubin N, Moseson M, Pasternack BS. Epidemiology of malignant melanoma: pigmentary traits, ultraviolet radiation, and the identification of high-risk populations. Recent Results Cancer Res 1986; 102: 56–75.
7. Elwood JM, Williamson C, Stapleton PJ. Malignant melanoma in relation to moles, pigmentation, and exposure to fluorescent and other lighting sources. Br J Cancer 1986; 53: 65–74.
8. Holly EA, Kelly JW, Shpall SN, Chiu S-H. Number of melanocytic nevi as a major risk factor for malignant melanoma. J Am Acad Dermatol 1987; 17: 459–468.
9. Østerlind A, Tucker MA, Hou-Jensen K, Stone BJ, Engholm G, Jensen OM. The Danish case-control study of cutaneous malignant melanoma. I. Importance of host factors. Int J Cancer 1988; 42: 200–206.
10. Garbe C, Krüger S, Stadler R, Guggenmoos-Holzmann I, Orfanos CE. Markers and relative risk in a German population for developing malignant melanoma. Int J Dermatol 1989; 28: 517–523.
11. Augustsson A, Stierner U, Suurküla M, Rosdahl I. Prevalence of common and dysplastic nevi in a Swedish population. Br J Dermatol 1991; 124: 152–156.
12. Melski JW, Tanenbaum L, Parrish JA, Fitzpatrick TB, Bleich HL. Oral methoxalen photochemotherapy for the treatment of psoriasis: a cooperative clinical trial. J Invest Dermatol 1977; 68: 328–335.
13. Kelly JW, Crutcher WA, Sagebiel RW. Clinical diagnosis of dysplastic melanocytic nevi. J Am Acad Dermatol 1986; 14: 1044–1052.
14. Elder D. The dysplastic nevus. Pathology 1985; 17: 291–297.
15. Sagebiel RW, Banda PhW, Schneider JS, Crutcher WA. Age distribution and histologic patterns of dysplastic nevi. J Am Acad Dermatol 1985; 13: 975–982.
16. Landis RJ, Heyman ER, Koch GG. Average partial association in three way contingency tables: A review and discussion of alternative tests. Int Stat Rev 1978; 46: 237–254.
17. Barlow RE, Bartholomew DJ, Bremner JM, Brunk HD. Statistical inference under order restrictions. John Wiley & Sons, 1972.
18. Malec E, Eklund G, Lagerlöf B. Re-appraisal of malignant melanoma diagnosis in the Swedish Cancer Registry. Acta Path Microbiol Scand 1977; 85: 707–712.
19. Nicholls EM. Development and elimination of pigmented moles, and the anatomical distribution of primary malignant melanoma. Cancer 1973; 32: 191–195.
20. Kopf AW, Lazar M, Bart RS, Dubin N, Bromberg J. Prevalence of nevocytic nevi on lateral and medial aspects of arms. J Dermatol Surg Oncol 1978; 4: 153–158.
21. Grob JJ, Andrac L, Romano MH, Davin D, Collet-Villette AM, Munoz MH, Bonerandi JJ. Dysplastic naevus in non-familial melanoma. A clinicopathological study of 101 cases. Br J Dermatol 1988; 118: 745–752.
22. Crutcher WA, Sagebiel RW. Prevalence of dysplastic naevi in a community practice. Lancet 1984; i: 729.
23. Evans RD, Kopf AW, Lew RA, Rigel DS, Bart RS, Friedman RJ, Rivers JK. Risk factors for the development of malignant melanoma – I: Review of case-control studies. J Dermatol Surg Oncol 1988; 14: 393–408.
24. Beitner H, Ringborg U, Wennersten G, Lagerlöf B. Further evidence for increased light sensitivity in patients with malignant melanoma. Br J Dermatol 1981; 104: 289–294.