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Seasonal Variations of Pigmented Naevi

Intercorrelations of Clinical and Histological Variables with Special Reference to Seasonal Variation

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During 1984, junctional and compound naevi were registered significantly more often during the summer half-year (May–October) than the total number of naevi, which showed no seasonal variation. A series of 342 of these junctional and compound naevi have been the subject of a blind histological classification. Clinical information was obtained by a questionnaire mailed to the patients. The intercorrelations of 19 histological and 10 clinical variables were studied by χ^2-test. The seasonal variation of these variables was further studied by χ^2-test and by Hewitt's test. Patient's hair colour, eye colour and sex as well as mitoses and localization showed a significant correlation to season of the year. The trends of these findings, compared with the information about tumour duration, indicate a short-term latency effect of UV light on naevi which are excised during the summer half-year.

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Seasonal variation in the incidence of malignant melanomas (MM) due to a tumour-inducing and/or promoting effect of UV light has been observed all over the world (1, 2, 3). One might expect a similar trend in Norway, as the seasonal variation of sunshine duration here is highly significant (Table I), (4). The incidence of registered MM during the period 1973–82 in Norway is somewhat increased in June and September–October for women and in May–June and November for men (5). The latter trend during this period is not significant, however. The risk of melanoma is related to the number of naevi (6, 7) and seasonal variation in the occurrence of naevi has been reported (8, 9).

This subject has not been studied in Norway previously. The present paper concerns seasonal variations in part of a series of pigmented naevi which was published earlier. These previous publications discussed the histological and clinical correlations generally as well as regarding possible melanoma risk groups of patients particularly (10 and 11, respectively). The results concerning the clinical correlations of the irregular and atypical types of naevi indicate that these tumours may be melanoma precursors. The sunburners with a delicate skin type were found to be especially correlated to these lesions.

MATERIALS AND METHODS

Selection of the series

During 1984 altogether 1694 pigmented naevi were diagnosed at the Department of Pathology, Ullevaal Hospital, Oslo, including 716 dermal naevi and 978 junctional or compound naevi. Originally, the following lesions were excluded from the latter group (10): lesions from patients with non-European names, halo naevi and juvenile melanomas (65 cases) as well as lesions lacking an indisputable and complete epidermal component histologically (174 cases) and a further 5 cases which were reclassified as juvenile melanomas or superficial spreading melanomas *in situ*. Finally, 157 lesions were excluded representing 120 patients who have undergone more than one tumour excision each. Hence the original series presented 577 naevi from an equal number of patients, including the most irregular/atypical lesion from the 120 patients mentioned above. The procedure of selection was so far made without access to any clinical information. The present series represents part of these original cases by including only 342 naevi from patients answering "No" to questions concerning use of solarium and time spent on sun vacation in Southern climates after September 1st, 1983. Accordingly, tumours excised in January 1984 have been under no such influence for at least 4 months.

Clinical information

A standardized questionnaire was originally sent to each patient (10). Completed questionnaires were returned by 84% of the patients. The answers were supplemented when necessary, with information from the original biopsy requisition. The clinical variables which have been registered and graded are the following: sex, age, hair and eye colour, freckles, suntan ability, tendency to sunburn, use of solarium, sun vacation in Southern sunny climates, reason for tumour excision, tumour duration and tumour localization. The tendency and the ability of the patient to sunburn or suntan, respectively, have been registered separately and not in combinations as in the clinical skin typing system (12). This system

Table I. *Number of sunshine hours in each 'season', referring to 1984 (4)*

The various seasonal models have been used for χ^2-tests

Models of season		Summer half-year		Winter half-year		Total no. of hours
		A	B	C	D	
Ia	Months	March–Aug.		Sept.–Febr.		
	Sun h.	1 166		355		1 521
Ib[a]	Months	March–May	June–Aug.	Sept.–Nov.	Dec.–Febr.	
	Sun h.	521	645	249	106	1 521
IIa	Months	April–Sept.		Oct.–March		
	Sun h.	1 119		402		1 521
IIb	Months	April–June	July–Sept.	Oct.–Dec.	Jan.–March	
	Sun h.	548	571	165	237	1 521
IIIa	Months	May–Oct.		Nov.–April		
	Sun h.	1 064		457		1 521
IIIb	Months	May–July	Aug.–Oct.	Nov.–Jan.	Febr.–April	
	Sun h.	633	431	108	349	1 521

[a] This model corresponds to the four natural seasons of the year (spring, summer, autumn and winter) in Norway.

was considered too complicated for the patient to handle without any personal instruction and too difficult to reconstruct from the completed questionnaires.

Histological evaluation

The histological examination was made without access to any clinical information (10). The variables which have been registered and graded are the following: tumour type (regular, irregular or atypical), growth pattern (junctional or compound), lentiginous melanocytic growth at the epidermal basal layer, number of involved epidermal rete ridges, tumour diameter, upward intra-epidermal growth of melanocytes, hypertrophic single melanocytes at the epidermal basal layer, nuclear atypia, mitoses, epidermal pigmentation, dermal melanophages, subepidermal fibrosis, lymphocyte reaction, tumour cells in the dermal papillae, tumour regression, 'shoulder' phenomenon and surface protrusion. The regular tumour type shows well demarcated nests of regular nevus cells and no stromal reaction. The irregular tumour type shows confluent nests of nevus cells and/or a linear lentiginous growth of irregular or slightly atypical nevus cells along the epidermal basal layer as well as dermal fibrosis and lymphocyte reaction. The atypical tumour type includes in addition nevus cells with a more pronounced (moderate) nuclear atypia, but no Pagetoid intra-epidermal growth.

Statistical methods

The latency period from the tumour-releasing/promoting solar exposition to the excision of the lesion is not known. Therefore, various models of 'seasons' (Table I) have been used regarding the seasonal relationship of the clinical and histological variables as studied by χ^2-tests. In addition, Hewitt's non-parametric test for seasonality (13) has been used by ranking the monthly prevalence of the target subgroup of each variable (e.g. hair colour red/fair). The months of May–October have been chosen as the pre-assigned segment of 6 months according to the seasonal trend of the total number of junctional and compound naevi as shown in Table IV. In this paper the terms 'correlated' and 'correlation' indicate a significant relationship. 'Slight', 'moderate' and 'strong' correlation indicate the p-values <0.05, <0.01 and <0.001, respectively. Only significant relationships are illustrated. Regarding the statistical analysis, the problem with testing a vast number of hypotheses has not been subjected to any kind of adjustment for multiple comparisons. The analysis of the results is thus of an explorative nature and the p-values should be interpreted with care.

RESULTS

The selected series included 342 naevi from an equal number of patients aged 4–83 years with a total *mean age* of 29.5 years. There were 229 (67%) women and 113 (33%) men with a mean age of 28.6 and 32 years, respectively. The women were significantly younger than the men. There were 22 (6.4%) intra-epidermal and 320 (93.6%) compound naevi. *Tumour type* is classified as regular in 230 (67.3%) cases, as irregular in 106 (31%) cases and as atypical in 6 (1.8%) cases. The latter group was too small to show any conclusive trends. The *localization* and *duration* of the various tumour types are shown in Table II. Information about tumour duration is missing in 64 (19%) cases. The series included 37 (13.3%) patients with a tumour duration of <3 years and 15 cases (5.4%) with a tumour duration <1 year. Relatively many lesions in

Table II. *Localization and duration of tumour according to tumour type*

	Tumour type			Total	
	Regular (%)	Irregular (%)	Atypical (%)	No.	%
Localization					
Head/neck	76.3	21.1	2.6	38	100.0
Upper extr.	81.8	18.2		22	100.0
Lower extr.	36.1	58.3	5.6	36	100.0
Back	69.9	27.6	2.4	123	100.0
Rest of trunk	71.3	28.7		115	100.0
Total %	68.3	29.9	1.8		100.0
Total no.	228	100	6	334[a]	
Duration					
From birth	75.0	25.0		92	100.0
>3 years	70.5	26.8	2.7	149	100.0
1–3 years	54.5	45.5		22	100.0
1/2–1 year	50.0	40.0	10.0	10	100.0
3–6 months	33.3	66.7		3	100.0
1–3 months		100.0		2	100.0
Total %	69.1	29.1	1.8		100.0
Total No.	192	81	5	278[b]	

[a] In 8 cases the tumour localization is unknown.
[b] In 64 cases the tumour duration is unknown.

both groups were irregular naevi. As many as 92 lesions were claimed to be present from birth. Localization on the lower leg was significantly correlated to the irregular (and atypical) tumour types.

The *intercorrelations of the clinical variables* as well as their correlation to tumour type are shown in Table III. Red/fair hair colour and blue/grey eye colour are strongly correlated with a freckled skin type which sunburns easily and has a poor ability to suntan. Additionally, red/fair hair colour correlates to tumour duration <6 months. Furthermore, the irregular tumour type is correlated to male patients >30 years and to the tendency to sunburn.

Table IV illustrates the *monthly prevalence* regarding the total input of specimens as well as the total number of pigmented naevi registered at the Department in 1984. The monthly prevalence of the latter is insignificantly low in July and December. The only significant trend concerns the 978 lesions registered as junctional or compound naevi which are found especially often during the months of May–October, i.e. during late spring, summer and early autumn. The selected naevi of the present series have lost this significant trend. The *seasonal correlations* of some clinical and histological variables are shown in Table V. Among the various models of seasons which have been studied (Table I) only model III shows a significant trend: The naevi which are excised during the summer half-year (May–October) represent significantly often patients with red/fair hair colour and/or blue/grey eyes. These lesions are significantly often located on the head/neck region and/or show mitoses. Conversely, the naevi excised during the winter half-year (November–April) are often from men and/or patients with dark hair and/or dark eye colour. These tumours are significantly often located on the back.

DISCUSSION

As shown in Table IV the *total input of specimens* generally and of pigmented naevi particularly to the Department show no seasonal variation which might have explained the slightly significant variation of the total number of junctional and compound naevi regardless of tumour type. This latter seasonal variation may, therefore, indicate a tumour inducing/promoting effect of UV light on the junctional melanocytes correspondingly to previous reports from other study groups (8, 9). The lack of this trend of growth pattern in the present study may be due to the procedure of selection. The exclusion of travellers and solarium users from this study is, however, presumed not to have led to any significant exclusion of potential melanoma precursor lesions, as such categories do not correlate to any special tumour type (11).

Table III. *Intercorrelations of the clinical variables and their correlations to tumour type*

The significant *p*-values of χ^2-tests are shown. *P*-values of <0.05, <0.01 and <0.001 correspond to a slight, a moderate, and a strong correlation, respectively

Clinical variable	Sex	Hair colour	Eye colour	Tumour type
Age	0.012			0.033
Sex	×			0.011
Localization	0.033			0.002
Duration		0.002	<0.001	0.05
Reason for excis.		0.025		
Hair colour		×	<0.001	
Freckled skin		0.002	0.042	
Ability to suntan		<0.001		
Tend. to sunburn		<0.001	0.022	0.028

Table IV. *Seasonal variation of prevalence according to Hewitt's test for seasonality (13) regarding*

A. Total number of biopsy specimens registered in 1984 (not significant)
B. Total number of pigmented naevi registered in 1984 (not significant)
C. All junctional and compound naevi registered in 1984 ($p=0.05$)
D. Junctional and compound naevi in the present series (not significant)

Month	A.	B.		C.		D.		
	Total no.	No.	% of A.	No.	% of B.	No.	% of B.	% of C.
January	1 766	154	8.72	79	51.3	31	20.1	39.2
February	1 682	125	7.43	65	52.0	31	24.8	47.7
March	1 619	122	7.54	56	54.1	21	17.2	37.5
April	1 320	126	9.55	61	48.4	25	19.8	41.0
May	1 773	190	10.72	123	64.7	41	21.6	33.3
June	1 557	127	8.16	82	64.6	35	27.6	42.7
July	1 086	74	6.81	44	59.5	11	14.9	25.0
August	1 493	144	9.65	92	63.9	26	18.1	28.3
September	1 696	164	9.67	108	65.9	35	21.3	32.4
October	1 941	190	9.79	107	56.3	29	15.3	27.1
November	1 885	188	9.97	106	56.3	40	21.3	37.3
December	1 451	90	6.20	55	61.1	17	18.9	30.9
Total	19 269	1 694		978		342		

Regarding *tumour duration*, the need for a personal interview with the patient is obvious. For instance, 92 lesions were claimed to be present at birth. This does not necessarily mean that they were all congenital, only that they had been present for as long as the patients could remember. Conversely, the description of short tumour duration probably often reflects recent changes in the lesion. Still, these may well be sun-induced. Mitoses in melanocytes have been observed only a few days after UV light irradiation of animal skin (14). Further, sunburn episodes appear to be important to the development of MM (15, 16) and may also activate the junctional component of naevi.

The latency time for the development of superficial spreading melanomas and nodular melanomas is considered to be less than 3 years (17, 18). As the irregular (dysplastic) naevi are believed to be potential precursors to superficial spreading melanomas (19, 20), they probably develop after an even shorter latency time. In the present study only 37 cases were registered with a duration <3 years including 15 lesions with a duration <1 year. These latter cases are, in fact, correlated to the irregular tumour type. We do not know, however, whether an episode of sunburn was actually the reason for patient referral and tumour excision in these cases. They are correlated to

Table V. *Seasonal correlations of various clinical and histological variables according to χ^2-tests and Hewitt's tests*

The significant *p*-values are illustrated

Variable	Trend			Test	*p*-value
Sex	Women	~ May–Oct.	Men ~ Nov.–April	χ^2	0.022
Localization	Head/neck	~ May–Oct.	Back ~ Nov.–April	Hewitt	0.020
Hair colour	Red/fair	~ May–Oct.	Dark ~ Nov.–April	χ^2	0.036
–	Red/fair	~ May–Oct.		Hewitt	0.030
Eye colour	Blue/grey	~ May–Oct.	Dark ~ Nov.–April	χ^2	0.008
–	Blue/grey	~ May–Oct.		Hewitt	0.020
–	(Blue/grey	~ May–July	Dark ~ Nov.–Jan.)	χ^2	0.006
Mitoses	Present	~ May–Oct.		Hewitt	0.030

the red/fair hair colour of the patient, but not to the tendency to sunburn, and they were not excised during any particular season of the year. These trends ought to be studied in a larger, prospective series.

Furthermore, concerning *delay in tumour excision*, we do not have any information in this study about the duration of the time lag from the patient's registration of warning signals from a naevus, up to its removal. It is our experience, however, that 'doctor's delay' is no longer than 1–2 months in Oslo. One may therefore expect that tumour change induced in the unaccustomed skin during the spring and summer ought to have led to tumour excision before November, i.e. within the summer half-year of May–October as defined in this study, given that the tumour is located in an averagely observable skin region. It is interesting, therefore, that localization on the back is seen to be significant, when the winter months of November–April are chosen as the pre-assigned half-year by Hewitt's test (Table V). This may be due to a delay in the patient's own reaction to tumour change in this poorly observable skin region.

Regarding *seasonal variations*, some other trends are remarkable. Skin type *per se* shows no seasonal variation. However, clinical variables correlated with the tendency to sunburn such as red/fair hair colour and blue/grey eye colour are both correlated to tumour excision during the summer half-year (Table V). In fact, blue/grey eye colour is correlated to tumour excision as early as during May–July. Concerning histological features, previous studies (7–8) have shown a correlation of mitoses, lymphocyte reaction and tumour regression to tumour excision during the summer months. These studies were not concerned with tumour type. In the present series, only mitoses have a similar seasonal correlation even when the χ^2-tests are made separately for each sex. The tumours showing mitoses include the six atypical naevi and 30 of the 106 irregular naevi. Regarding tumour type, the lesions classified as irregular are significantly often located on the lower extremity. They are, however, also correlated to the male sex of the patient, and male patients have their lesions significantly often on the dorsal region (Tables II, III) which is correlated to tumour excision during the winter half-year (Table V). A late reaction to sun-induced change in lesions on the back, especially among the male patients, may therefore explain why excision of the irregular tumour type is not significantly concentrated within the summer half-year. Comparatively, the head–neck region is correlated to tumour excision at this time of the year as well as to the regular tumour type. This may be due to a slightly significant trend among the female patients, i.e. excision between March and August of some large regular naevi ($p=0.021$), probably for cosmetic reasons.

The correlation of tumour excision during the summer half-year with certain clinical features typical of melanoma patients as well as with mitotic activity in potential melanoma precursor lesions is remarkable. The trends in the present study indicate some short-term latency effect of UV-light on pigmented naevi. There are, however, several weak points. Lack of precise information concerning skin type, total number of pigmented naevi and nature of previously excised lesions, preferably collected in personal interviews, is obvious. A multiple regression analysis is also needed. A larger prospective study is therefore planned.

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