Age and malignant melanoma: Comparison of variables in different age-groups

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Variables were compared in patients with clinical stage I superficial spreading melanoma who had been divided into three age-groups. The study included 736 consecutive patients who were prospectively entered into the data base of the Melanoma Cooperative Group of New York University Medical Center. Compared with the younger patients (<40 years), older patients (≥60 years) had superficial spreading melanomas that were, on average, of greater thickness, level, and diameter. Younger patients were more likely than older patients to show evidence that their melanomas arose from preexisting nevocytic nevi. There was no difference in the 10-year survival between groups when melanomas were matched by thickness. Thus it is as important to perform periodic total cutaneous examinations in the elderly as it is in younger persons, and age alone should not determine management strategies. (J AM ACAD DERMATOL 1989;21:717-22.)

The annual incidence rate of cutaneous melanoma has been increasing dramatically in the United States,[1] especially in the elderly population, a population that is continually expanding.[2-4] The long-term increase in the resultant mortality rate has been more rapid than that caused by any other malignant neoplasm, with the possible exception of cancer of the lung in women.[5-7]

The purpose of our study was to determine which factors in younger patients differ from those in older patients with superficial spreading melanomas. These differences may provide insight into the influence of age on the biology of cutaneous melanoma and might suggest age-dependent differences in management.

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MATERIAL AND METHODS

This study was restricted to superficial spreading melanomas because there are differences in anatomic distribution, pathogenesis, biologic behavior, and age at onset of lentigo maligna melanoma and acral-lentiginous melanoma.[8-11] Nodular melanomas were excluded because some authors[12] have found that a nodular growth pattern significantly alters prognosis even after adjusting for lesion thickness.

Relevant factors were retrieved from the prospective computerized data base of the Melanoma Cooperative Group of New York University Medical Center. From a total of 1153 patients registered between 1972 and 1982, there were 736 with histologically diagnosed superficial spreading melanomas selected for study. In a case with multiple primary lesions, only information concerning the lesion that first brought the patient into the data base was used. All superficial spreading melanomas included in this study had the following characteristics: (1) they were stage I primary lesions (with no clinical evidence of satellite, in-transit, regional-node, or distant metastases) on entry into the data base; (2) they had a Clark level of II to V[13]; (3) they had a measurable tumor thickness (Breslow)[14]; (4) they occurred in white persons; and (5) they had a recorded age.

A CDC 6600 computer, located at the Courant Mathematics and Computing Laboratory of New York University, was used. Analyses were performed by means of version No. 8.0 of the Statistical Package for the Social Sciences.[15,16] When a particular computer analysis was

Table I. Tendency to sunburn (by history)

Burn	Age-group (yr)		
	<40 (%)	40-59 (%)	≥60 (%)
Practically none	5.9	8.2	9.9
Mildly red	17.3	24.5	29.7
Moderate burn	30.8	32.9	31.2
Painful burn	45.9	34.4	29.2
Total No.*	185	331	202

*$p = 0.01$.

Table II. Total number of nevocytic nevi (on physical examination)

Moles	Age-group (yr)		
	<40 (%)	40-59 (%)	≥60 (%)
None	1.6	2.4	2.0
1-25	60.3	69.1	83.7
26-100	28.0	22.2	12.3
>100	10.1	6.3	2.0
Total No.*	189	333	203

*$p < 0.001$.

performed, any case that lacked a value for the relevant variable was excluded from that analysis.

For all analyses, patients were grouped according to age: group I (<40 years); group II (40 to 59 years); and group III (≥60 years). The distributions of different variables were compared across age-groups by chi-square analysis, and a finding was considered statistically significant if $p \leq 0.05$.

RESULTS

Those variables for which there was a significant difference in distribution by age-group are shown in Tables I to VI. As ascertained by history, painful sunburns seemed to develop more readily in group I patients at some time in their lives than in older persons (Table I).

In Table II the data show that there were fewer nevocytic nevi, as estimated by an examining physician, for group III patients.

Group I patients were more likely to give a history of a preexisting nevocytic nevus at the site of the superficial spreading melanoma compared with persons in the other age-groups ($p < 0.001$). On the other hand, histologic evidence (Table III) suggests that young patients may overstate the incidence of preexisting nevocytic nevi. Finally, the melanomas seen in group III patients were of greater diameter,

Table III. Nevocytic nevus associated with cutaneous melanoma (on microscopic examination)

Lesion	Age-group (yr)		
	<40 (%)	40-59 (%)	≥60 (%)
Present	29.3	20.8	14.9
Absent	70.7	79.2	85.1
Total No.*	181	312	194

*$p = 0.01$.

Table IV. Largest diameter of cutaneous melanoma

Largest diameter (mm)	Age-group (yr)		
	<40 (%)	40-50 (%)	≥60 (%)
0-15	69.0	55.9	51.3
16-50	31.0	44.1	48.7
Total No.*	174	322	187

*$p = 0.002$.

tumor thickness, and level than those recorded from younger patients (Tables IV to VI).

Those variables that proved to be statistically insignificant among the three age-groups are outlined in Table VII. It is important to note that, thickness for thickness, 10-year survival did not vary significantly according to increasing age ($p = 0.2$). As calculated by cumulative life-table analysis, their values were 90%, 85%, and 83%, respectively.

DISCUSSION

Painful sunburns seemed to develop more readily in group I patients than in older persons. Although one cannot be certain of the accuracy of such historical data, they are consistent with the report of Beitner et al.[17] that the mean age for cutaneous melanoma diagnosis increased with a tendency to tan without burning, as measured by minimal erythema dose (MED). They also found that in 73 control subjects, age was not correlated with MED, whereas Gilchrest et al.[18] suggested that with advancing age the inflammatory response to ultraviolet irradiation (the "sunburn reaction") is reduced. This may contribute to a decreased tendency toward painful sunburns in elderly persons.

On physical examination, group III patients had fewer nevocytic nevi. This is in agreement with the decreased prevalence of such nevi seen in the general

Table V. Thickness (Breslow)

Thickness (mm)	Age group (yr)		
	<40 (%)	40-59 (%)	≥60 (%)
0.00-0.75	37.2	31.3	29.1
0.76-1.49	36.2	32.4	24.8
1.50-2.99	16.0	23.2	32.0
>3.00	10.6	13.1	14.1
Total No.*	188	336	206

*$p = 0.006$.

Table VI. Level (Clark)

Level	Age-group (yr)		
	<40 (%)	40-59 (%)	≥60 (%)
II	38.4	27.4	26.1
III	30.0	35.1	21.7
IV	30.0	34.2	50.7
V	1.6	3.2	1.4
Total No.*	190	339	207

*$p < 0.0001$.

white population.[19-22] MacKie et al.[20] observed that nevocytic nevi were absent were 5.8% (6/103) of normal healthy white subjects between the ages of 40 and 59 years and were lacking in 31.1% (32/103) of subjects older than 60 years. By comparison, only 2.4% and 2.0% of our patients with the same age-distributions had no nevocytic nevi. This finding can be explained by the fact that compared with an age- and sex-matched control group, patients with melanoma have a significantly increased mole count.[23]

The origin of most cutaneous melanomas is believed to be intraepidermal melanocytes, either de novo or in association with a preexisting nevocytic nevus.[24-26] Superficial spreading melanomas that arise de novo may differ in their pathogenesis from those that arise in association with nevocytic nevi. Perhaps in younger persons the latter pathway is more prevalent. In support of this theory, on histologic examination a greater proportion of group I patients had evidence of nevocytic nevi contiguous to their superficial spreading melanomas (Table III).

De novo superficial spreading melanomas may arise primarily because of sun exposure of nonnevoid melanocytes in the epidermis. These melanocytes may need to be repeatedly irradiated by sunlight over a period of years for the consecutive steps of initiation, promotion, and malignant transformation

Table VII. Statistically nonsignificant variables

1. History
   - Sun exposure
   - Tendency to tan
2. Physical examination
   - Sex
   - Eye color
   - Hair color
   - Skin color
   - Freckles
3. History of primary lesion
   - Sun exposure to lesion site
   - Change in lesion
   - Change in size
   - Change in elevation
   - Change in color
   - Bleeding
   - Ulceration
4. Physical examination of the primary lesion
   - Location of lesion
5. Microscopic pathology
   - Number of positive regional lymph nodes
   - Host cellular response to radial growth phase of primary lesion
   - Host cellular response to vertical growth phase of primary lesion
6. Therapy
   - Elective regional lymph node dissection
7. Outcome
   - Survival

to occur, whereas melanocytic nevus cells may be intrinsically prone to malignant transformation[27-29] and thus require less sun exposure and perhaps a shorter lag time for superficial spreading melanoma to develop.

This proposal of dual pathways for the development of superficial spreading melanomas might serve to explain the somewhat paradoxic relationship that was observed between the prevalence of nevocytic nevi in the various age-groups and the age-specific incidence of cutaneous melanoma. The paradox arises because the risk for developing cutaneous melanoma increases directly with the absolute number of nevocytic nevi.[23,30-35] Although the number of nevocytic nevi per person decreases with advancing age, the age-specific incidence rate for cutaneous melanoma increases throughout life.[36] If the pathway for development of a superficial spreading melanoma from a precursor nevocytic nevus is distinct from that of one that arises de novo, it could be postulated that the number of nevocytic nevi may increase one's risk only for those superficial spreading melanomas that arise from nevocytic nevi. It

may be that as one ages, the incidence of cutaneous melanoma increases because the risk factors for de novo superficial spreading melanomas that are age associated, such as cumulative sun exposure, become more important.

Patients in the younger age-groups were more likely to give a history of a preexisting nevocytic nevus at the site of the superficial spreading melanoma, even though the visibility (i.e., anatomic distribution) of these melanomas did not change with age. Reports indicate that a clinical history of a preexisting pigmented lesion at the site of a cutaneous melanoma may be elicited from as few as 18% to as many as 85% of patients.[26] Because so many pigmented lesions often develop in older persons (including solar lentigines and seborrheic keratoses), they may be less able to associate their superficial spreading melanomas with preexisting nevocytic nevi.

In all three age-groups a *history* of a pigmented melanocytic nevus at the superficial spreading melanoma site was obtained far more frequently than that determined *histopathologically*. This discrepancy was largest in the youngest age-group and decreased with age. The error may arise from the younger patients mistaking the radial growth phase of superficial spreading melanoma for a mole. In all groups the history obtained with regard to the presence of a preexisting "mole" at the site of a superficial spreading melanoma seems unreliable.

A residual component of a nevocytic nevus has been noted in contiguity with a cutaneous melanoma in 18% to 72% of cases.[26] Because the growth of cutaneous melanoma may obliterate all or part of a precursor lesion, the actual frequency of precursor lesions in association with cutaneous melanoma is likely to be underestimated, especially in those of larger tumor volume.[25] The superficial spreading melanomas of the older patients were, on average, larger and thicker (Tables IV to VI), and it is therefore theoretically possible that they may have arisen in association with nevocytic nevi in an equal or greater percentage of cases than the superficial spreading melanomas of the younger patients.

The observation that group III patients were more likely to have superficial spreading melanomas with larger diameters than the younger patients is consistent with the data of Cohen et al.[37] Lentigo maligna melanomas, however, which tend to have larger diameters and to be found in older persons, were included in their study population. This may explain why the increase in tumor diameter in that study was most prominent in patients older than 60 years of age compared with those younger than 60 years. Our data showed the same pattern of larger lesions in the elderly, although lentigo maligna melanoma was excluded from our study. Lesion diameter of superficial spreading melanoma is directly related to lesion thickness.[38] The direct relationship of age to thickness (Table V) is in accordance with this finding.

There are several possible explanations for a positive correlation between age and superficial spreading melanomas of larger dimensions. It may be that delayed detection of these melanomas in the elderly is a factor. Their duration, as stated by patients, did not vary according to age, although histories obtained regarding this point are not a reliable indicator. Delayed detection in the elderly might be explained in several ways: (1) obscuration of superficial spreading melanomas by the numerous benign pigmented lesions that frequently develop with aging,[39] (2) less observation or lessened ability to see pigmented skin lesions, (3) less concern with physical appearance, and (4) medical care that is inferior to that received by younger persons.[40]

The positive correlation between Clark's levels of invasion and age may be related to differences in skin thickness. Black[41] reported that the skins of persons older than 65 years of age are thinner than those of younger patients. If skin thickness diminishes with age, then lesions of the same thickness would be expected to penetrate to deeper levels in the old than in the young.[39]

Another explanation for the greater size of the superficial spreading melanomas in group III patients in this study is that cutaneous melanomas that arise de novo may grow more rapidly than those that arise in association with nevocytic nevi.[42,43] Indeed, our results show that a greater proportion of superficial spreading melanomas in the elderly arise without a preceding nevocytic nevus.

Local detrimental effects of long-term sun exposure on cell-mediated immunity[44] may play a role in the more rapid growth of superficial spreading melanoma in skin that has had more cumulative sun exposure. If general diminished responsiveness of the immune system with aging was the main cause of increased liability to malignancy and to more rapid tumor growth,[45] one would expect an increased rate of metastases, which was not found. The percentage of nodal metastases in group III patients in this study was similar to that in the young despite the tendency toward thicker superficial spreading melanomas in

the older age-group. This finding is in agreement with the data of Cohen et al.[37] who suggested that in the older patient cutaneous melanomas penetrate to a greater extent locally in both depth and width before dissemination occurs. This may suggest that a local sun-induced decrease in immunity is relatively more important in the greater size of superficial spreading melanomas in the elderly than a general decrease in immune responsiveness.

In further support of a local decrease in immune surveillance, our results suggest that superficial spreading melanomas in the elderly, thickness for thickness, are not associated with a poorer prognosis. Others,[46] too, have found that age per se is not an independent prognostic variable but draws its prognostic significance largely from its close relation with tumor thickness. Cohen et al.,[37] however, reported that age was highly significant as a prognostic factor for poor survival. Although the adverse relation of advancing age with survival in that analysis was partially explained by predominance of other unfavorable factors, such as primary sites, depth of lesions, or histologic types, age remained an independent prognostic factor for increased mortality rate because of cutaneous melanoma. Our data indicate that there may be justification to avoid elective regional lymph node dissection in elderly patients, especially because its value has been questioned.[47-50]

The 1981 report for Surveillance, Epidemiology and End Results (SEER) for the years 1973 to 1977 indicates that for each 5-year increase in age, the incidence rate of cutaneous melanoma per 100,000 increases.[36] Beginning with approximately 0.1 per 100,000 for the 5 to 9 year age-group, it increases to 21.8 per 100,000 for the 85+ year age-group. Because the cutaneous melanoma incidence increases with each decade of life, cutaneous examinations of elderly patients should be performed at least as often as for younger patients. If complete physical examination of the entire cutaneous surface is accomplished for *all* patients, cure rates for cutaneous melanoma should improve and mortality rates should decrease.

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