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Is the prognosis and course of acral melanoma related to site-specific clinicopathological features?

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Abstract. – OBJECTIVE: Acral melanoma is an uncommon type of melanoma in Caucasian patients. However, acral melanoma is the most common type of melanoma in African and Asian patients. Comparison analyses between hand-acral melanoma and foot-acral melanoma have been rarely reported in the literature. Acral melanoma is an uncommon melanocytic tumor characterized by an intrinsic aggressiveness, with specific histological and clinicopathological features. Acral melanoma involves the palms, soles and sub-ungueal sites.

PATIENTS AND METHODS: A total of 244 patients with acral melanoma were included in our analysis. The current study was performed in three different medical centers: Sapienza University of Rome, San Gallicano Institute of Rome and University of Magna Graecia (Italy). The Kaplan-Meier product was used to estimate survival curves for disease-free survival and overall survival. The log-rank test was used to evaluate differences between the survival curves. Assuming that the effects of the predictor variables are constant over time, the independent predictive factors were assessed by Spearman's test and subsequently data were analyzed performing Cox proportional-hazard regression.

RESULTS: In both univariate and multivariate analyses Breslow thickness ($p < 0.0001$) and ulceration ($p = 0.003$) remained the main predictors. General BRAF mutation was detected in 13.8% of cases. We found that median Breslow value and the percentage of recurrences were similar in hand-acral melanoma and foot-acral melanoma, as well as there were no differences in both short and long-term.

CONCLUSIONS: The absence of differences in survival between hand-acral melanoma and foot-acral melanoma shows that the aggressiveness of the disease is related to distinct mutational rate, as well as to anatomical site-specific features, rather than to the visibility of the primary lesion.

Key Words:
Melanoma, Multivariate analysis, Survival rate, Vitamin D.

Introduction

Acral melanoma (AM) is an uncommon skin malignancy, affecting the palms, soles and nails[1]. It represents about 2%-10% of all melanoma cases[2]. Furthermore, AM is the most common type of melanoma in African and Asian patients, with a lower incidence in white patients[2]. In African and Asian patients AM reaches high Breslow values, while in Caucasian patients often it shows lower Breslow values, ranging between 0 and 1.0 mm[3].

Several factors have been identified as possible inducers of the malignancy in Caucasian patients, including ultraviolet rays, chemical exposure and traumatic risk factors. However, up to date the pathogenesis of AM remains unknown[2,4]. Surely, the natural course of AM differs from the other types of melanoma. This could be also explained by the BRAF-/c-KIT+ profile often showed by AM, highlighting underlying biological differences between the melanocytes of acral sites and the ones of other anatomical areas. Recently, these features have been also related with lower serological levels of vitamin D observed in AM patients[5].

It is known that AM has a worse prognosis and several authors postulate that this could be related to a delay of diagnosis, as well as to an intrinsic more aggressiveness of the tumor[6]. In this regard, studying AM according to the anatomic localization (hand or foot) could give further informations about the behavior of the malignancy.

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Comparison analyses between hand-AM (H-AM) and foot-AM (F-AM) have been rarely reported in the literature[7], also for the general low incidence of H-AM.

The aim of the current study was to evaluate the general clinicopathological features of AM and, subsequently, any survival and prognostic differences, in F-AM and H-AM.

Patients and Methods

We computer-searched the clinical records of all our patients registered into a melanoma database from June 1998 to April 2015, to identify patients with a primary AM. The current study was performed in three different medical centers: Sapienza University of Rome, San Gallicano Institute of Rome and University of Magna Graecia (Italy). The study was approved by the respective Ethical Comittee of the Departments.

AM was defined as a melanoma localized on palmar, plantar and sub-ungual sites. Patients with a positive history of a previous melanoma located in non-acral sites were excluded. To avoid clinical biases, we included in the study only patients treated in our Institutes within 5 months from the excision of the primary tumor.

Clinical and pathological data were obtained from our electronic databases. The following parameters were collected and analyzed: sex (female or male), age (≤ 60 or ≥ 61 years), Breslow thickness (≤ 1.0 mm or ≥ 1.01 mm), ulceration (presence or absence), mitotic rate (if ≥ 1 mm^2), histotype (if acral lentiginous or other histotypes, as superficial spreading and/or nodular melanoma), presence and localization of the first metastasis and BRAF mutation. Regarding the mitotic rate and BRAF mutation, we must highlight that we have found data of only 115 patients (47.7%) and 65 patients (30%) respectively.

We followed all patients from the date of the first visit to date of death or last follow-up. Patients underwent regular follow-up with periodical exams, and instrumental assessment through radiography, sonography, computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy and positron emission tomography (PET).

At first, we examined the total number of patients included in the analysis. Subsequently patients have been divided in 2 sub-groups and analyzed separately in patients with F-AM and patients with H-AM.

Statistical Analysis

Disease free survival (DFS) was calculated from diagnosis of the primary tumor to the date of the first recurrence. Overall survival (OS) was calculated from the diagnosis of the primary tumor to date of death and/or last follow-up. The Kaplan-Meier product was used to estimate survival curves for DFS and OS. The log-rank test was used to evaluate differences between the survival curves. Patients who were lost at follow-up or who were alive at the time of the last follow-up were censored at the date of their last follow-up. Assuming that the effects of the predictor variables are constant over time, the independent predictive factors were assessed by Spearman's test and subsequently data were analyzed performing Cox proportional-hazard regression. In all statistical methods a p-value < 0.05 was considered statistically significant.

Results

A total of 244 patients with AM were included in our analysis. Among them 200 patients were classified as F-AM, while 44 as H-AM.

Acral Melanoma Patients

The characteristics of patients are summarized in Table I. General median age at time of the di-

Table I. Baseline characteristics of patients.

	N	Median
Gender		
Male	113	NP
Female	131	
Age		
≥ 61	129	62
≤ 60	115	
Ulceration		
Presence	25	NP
Absence	219	
Breslow		
≤ 1.0 mm	137	
≥ 1.01 mm	107	
Mitotic rate		
< 1.0/mm^2	84	NP
≥ 1.0/mm^2	31	
Histotype		
ALM	131	NP
NOT-ALM	113	

N means number; NP means not provided; ALM means acral lentiginous melanoma; NOT-ALM means not acral lentiginous melanoma.

agnosis was 62 years (ranging between 18 years and 89 years). One-hundred thirteen patients were male, while 131 were female. Median Breslow thickness was 0.8 mm (ranging between 0 and 10 mm) and the ulceration was present in 25 patients, respectively 16 in F-AM and 9 in H-AM (Table I). Performing Kaplan-Meier product and log-rank test, median disease DFS was 33.5 for H-AM and 45 months for F-AM ($p = 0.1$). Regarding OS also a better behavior was observed for F-AM (48 months versus 35 months), although without reaching the statistical significance ($p = 0.1$) (Figure 1).

Patients with an age ≤ 60 years showed a better DFS than the ones ≥ 61 years (46 versus 35; $p < 0.0005$). Female patients showed a DFS of 45 months versus 40 months of male patients ($p = 0.04$). Patients with a Breslow ≤ 1.01 mm showed a DFS of 47 months, while the ones with a thickness ≥ 1.01 mm of 35 ($p < 0.001$). Patients without ulceration showed a DFS of 52 months, while the ones with ulceration of 43 months ($p = 0.003$). Patients with a mitotic rate < 1.0 mm^2 showed a DFS of 46 months versus 43 months of the ones with a mitotic rate ≥ 1.01 mm^2. Finally, the acral lentiginous histotype did not show a different DFS, when compared to other histological subtypes ($p = 0.1$). At Cox proportional-hazard regression, only the variable Breslow reached the statistical significance ($p < 0.0001$) (Table II).

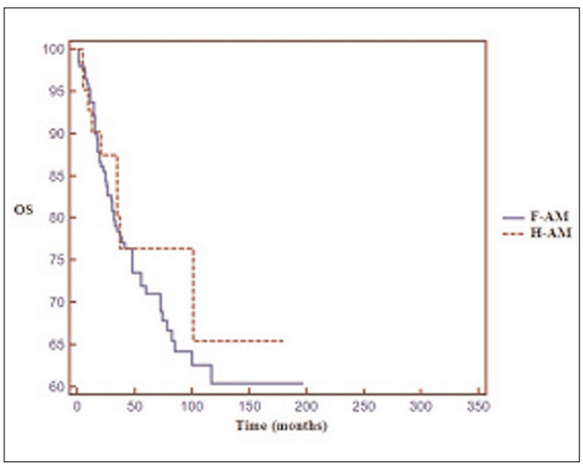

Figure 1. Kaplan-Meier curves and log-rank test of overall survival (OS), according to acral melanoma of the foot (F-AM) and of the hand (H-AM).

Regarding OS, we observed a better survival for patients with a Breslow ≤1.01 mm (52 months versus 48 months; $p < 0.0001$) and for patients without ulceration (59.5 versus 48

Table II. Disease free survival (DFS), overall survival (OS) and clinicopathological features in patients with acral melanoma.

	DFS (median months)	p^a	p^b	OS (median months)	p^c
Gender					
Male	40	< 0.0005	NS	48	NS
Female	45			48	
Age					
≥ 61	35	0.04	NS	42	NS
≤ 60	46			52	
Ulceration					
Presence	43	0.003	NS	48	0.05
Absence	52			59.5	
Breslow					
≥ 1.01 mm	35	< 0.001	< 0.0001	48	< 0.0001
≤ 1.00 mm	47			52	
Anatomical site					
Foot	45	NS	NS	48	NS
Hand	33.5			35	
Mitotic Rate					
< 1/mm^2	46	NS	NS	50	NS
≥ 1/mm^2	43			48	
Histotype					
ALM	43	NS	NS	51	NS
NOT-ALM	43			46	

ALM means acral lentiginous melanoma; NOT-AM means other melanoma histotypes. p^a Kaplan-Meier product and log-rank test between DFS curves; p^b Cox proportional hazards-regression between DFS and predictive factors analyzed; p^c Kaplan-Meier product and log-rank test between OS curves.

months; $p = 0.05$). We found no significant statistical differences regarding age (52 months for patients ≤ 60 years versus and 42 months for the ones ≥61 years; $p = 0.08$), sex (48 months for male and 48 months for female patients; = 0.8), histotype (46 months for superficial spreading and 51 months for acral lentiginous; $p = 0.4$) and mitotic rate (50 for mitotic rate ≥ 1/mm^2 and 48 for mitotic rate < 1/mm^2). Although we did not find a statistical significance, patients with H-AM showed worse prognosis than patients with F-AM (35 versus 48; $p = 0.1$) (Table II).

Finally, regarding BRAF mutation, we were able to collect data for only 65 patients and the mutation was detected in the 13.8% of cases (8 F-AM and 1 H-AM).

Acral Melanoma of the Foot

Regarding F-AM, median age of the patients at time of diagnosis was 60 years (ranging between 18 and 89 years), 103 patients were female (51.5%), 16 patients showed an ulceration in the primary tumor and median Breslow thickness was 0.8 mm (ranging between 0 and 10 mm). The first site of recurrence was local/in transit dermal metastases (n=15), followed by local lymph-nodal metastases (n=12). Distant metastases, as first recurrence, have been found in 17 patients (lung [n=7], liver [n=5], brain [n=2], bone [n=1], adrenal glands [n=1] and peritoneum [n=1]) (Table III). Using nonparametric Spearman's coefficient test between DFS and the single variables, we found an association between DFS and the variable age ($p < 0.0001$; Spearman's coefficient: 0.27), Breslow ($p < 0.001$; Spearman's coefficient: 0.42) and ulceration ($p = 0.0005$; Spearman's coefficient: 0.24). While the statistical significance was not reached for the variable sex ($p = 0.10$; Spearman's coefficient: 0.11) and histological type ($p = 0.15$; Spearman's coefficient: -0.10). However, in the multivariate analysis, Breslow thickness remained the only independent risk factor ($p = 0.01$) (Table IVa).

Acral Melanoma of the Hand

Regarding H-AM, median age was 65.5 years (ranging between 37 and 84 years), 27 patients were female (61%). Ulceration was observed only in two patients and median Breslow thickness was 0.5 mm (ranging between 0 and 5.5 mm) (Table IVb). Recurrences involved local/in transit skin (n = 4), peripheral lymph nodes (n=3) and distant metastasis in two cases (in both cases was the liver). Performing non-parametric Spearman's coefficient test between DFS and the single variables, we found an association only with Breslow thickness ($p = 0.01$; Spearman's coefficient: 0.370). Also in the multivariate analysis, the variable Breslow remained the main predictor ($p = 0.01$) (Table IVb).

Discussion

AM is considered a sub-group of melanoma with an intrinsic high aggressiveness[7-9], specific histological and clinicopathological features, compared with other types of melanoma[7]. Up to date, most published studies about AM, considered only the acral site, regardless the histotype (if acral lentiginous or not) and the specific anatomical areas (hand or foot). However, we performed the current report extending the analysis also to these clinicopathological features.

Compared with other reports[2,6,10-12], our general median Breslow value was lower (median 0.8 mm)[2]. Our population consisted of only Caucasian patients, with a slight majority of female patients (54.3%). In this regard, these aspects may have had an influence on the relatively low median Breslow, above all if we compare the current report with another large study where the median Breslow value was 2.1 mm and the African-Americans population of patients reached the 11%[3]. Indeed, according to the recent literature, non-Hispanic whites patients (especially female) usually show the highest percentage of thin AM (with 43% diagnosed at 0.01-

Table III. First site of recurrence and percentage of recurrence in acral melanoma of the hand (H-AM) and acral melanoma of the foot (F-AM).

	%	Dermal	Nodal	Liver	Lung	Brain	Other
Foot	21	15	12	5	7	2	3
Hand	20.5	4	3	2	–	–	–

Table IVa. Univariate and multivariate analysis regarding each predictive factor in acral melanoma of the foot (F-AM).

	p^a	p^b
Gender	NS	NS
Age	< 0.0001	NS
Ulceration	0.0005	NS
Breslow	< 0.001	0.01
Mitosis	NS	NS
Histotype	NS	NS

NS means not significant. p^a No parametric Spearman's Coefficient test; p^b Cox proportional hazards-regression between disease free survival and predictive factors analyzed.

1.00 mm), contrarily to Asian and African patients[3,13]. In any case, Breslow thickness and the ulceration remained the main prognostic factors, regardless gender, age, mitotic rate and histotype, as reported also in two previous studies[2,7].

The hypothesis that mitotic rate was the main predictive factor for AM aggressiveness was not confirmed in our report. Indeed, mitotic rate was not related to a difference in the prognosis, as also reported by several authors[2,6,8]. By contrast, ulceration showed a statistical significant value in both DFS and OS, even though its incidence was relatively low (10.3%), with a greater involvement of F-AM. Most likely, the low median Breslow thickness explains also how the ulceration was present in a low percentage of patients.

In addition, according to the histotype, we did not find substantial differences in both short and long-term, similarly to what reported in the literature[3,7].

However, the aim of the current report was also to evaluate differences in term of DFS and OS between F-AM and H-AM.

Table IVb. Univariate and multivariate analysis regarding each predictive factor in acral melanoma of the hand (H-AM).

	p^a	p^b
Gender	NS	NS
Age	NS	NS
Ulceration	NS	NS
Breslow	0.01	0.01
Mitosis	NS	NS
Histotype	NS	NS

NS means not significant. p^a No parametric Spearman's Coefficient test; p^b Cox proportional hazards-regression between disease free survival and predictive factors analyzed.

It is reported that higher aggressiveness of AM is proper to later diagnoses and more advanced thickness[7]. However, in a sample of 244 patients we did not find significant differences in DFS and OS between F-AM and the H-AM. Furthermore, we found a worse prognosis for H-AM (although without reaching the statistical significance) which is considered an anatomical site more easily diagnosable (Table II). We observed also that the two samples were highly comparable according to the Breslow, as also confirmed by sample *t*-test ($p = 0.2$; standard error: 0.2). In this regard, the aggressiveness of AM could be explained only partially by the theory that AM is often related to a delay in the diagnosis, with a consequent higher Breslow value[2,3,7,10,11]. In addition, a further confirmation of the absence of difference between F-AM and H-AM was also the fact that the percentage of metastases was the same between F-AM and H-AM, with a 21% in F-AM and 20.5% in H-AM (Table III).

Regarding the first site of recurrence, both H-AM and F-AM showed more tendency for cutaneous metastases. Indeed, Bastian et al[9] showed that specific genetic amplifications (as 11q13) in AM arise early in the progression of the disease, with malignant cells present beyond the histologically detectable margin (detected in the epidermis up to 3 mm beyond the histologically recognizable extent of the melanoma), thereby revealing a mechanism of local recurrence. This is also supported by the subsequent "field cell theory" of AM, where the acral and mucosal melanomas could originate from field melanocytes detected in normal skin extending over the obvious lesion[14,15]. All these features explain the greater tendency of AM to involve the skin as first site of metastatization.

Another pivotal point in AM is the molecular and genetic analysis[2]. Indeed, AM shows a lower mutational rates than non-AM, but a higher focal amplification[16,17]. BRAF kinase (a serine/threonine kinase of the RAS/RAF/MEK/ERK pathway) is mutated only in about 13% of AM cases, while c-KIT is mutated in about 20% of AM[2], showing a BRAF/c-KIT profile similar to the one of melanoma of chronic sun-exposed areas (as lentigo maligna melanoma), where c-KIT pathway plays a pivotal role[18,19]. In this regard, biological differences of the melanocyte of acral and non-acral sites (as the absence of stem cell niche in the buldge region of the hair follicle) may play a role in the pathogenesis and in the prognosis of AM as well[20].

Finally, recent studies on serological levels of vitamin D and on vitamin D receptor (VDR) have tried to give an explanation on the pathogenesis of shield sites melanoma (including AM), showing how patients with melanoma of shield sites have lower serological values of vitamin-D compared with patients with melanoma of non-shield sites, with also a relative worse prognosis[5,21-23]. Maybe UV radiations, through photosynthesis of vitamin D, have a protective effect in melanoma of sun-exposed sites, requiring cumulative UV doses to develop the malignancy, explaining also how melanoma of the face (as lentigo maligna melanoma) usually shows a better survival[13,22,23]. In this regard, increased exposure to UVA and UVB and a consequent increase in vitamin D might cause a redistribution of prognosis in sun-exposed and not-sun-exposed sites, as well as the onset of different types of melanoma.

A criticism to this study was that there were only a small part of patients with available mitotic rate and BRAF mutation.

Conclusions

To our knowledge, this is one of the largest study regarding AM, considering that it includes also 44 cases of H-AM, which rarely have been reported in literature, above all in Caucasian patients.

In AM the main predictors were Breslow thickness and ulceration. Age, sex, mitotic rate, histotype and anatomical site (H-AM or F-AM) were no prognostic indicators in our population. The percentage of recurrence was similar between H-AM and F-AM and there were no differences in both short and long-term, although a worse prognosis for H-AM was observed.

We can point out that the prognosis of AM is not related to the hidden localization of the lesion (with a delay in the diagnosis and relative higher Breslow value) but to site-specific clinicopathological features, as confirmed by the absence of differences in term of median Breslow thickness and DFS/OS between F-AM and H-AM. Finally, in 65 patients a BRAF mutation was detected in 13.8% of cases.

Statement of Interests

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Piliang MP. Acral lentiginous melanoma. Clin Lab Med 2011; 31: 281-288.
2) Bello DM, Chou JF, Panageas KS, Brady MS, Coit DG, Carvajal RD, Ariyan CE. Prognosis of acral melanoma: a series of 281 patients. Ann Surg Oncol 2013; 20: 3618-3625.
3) Bradford PT, Goldstein AM, McMaster ML, Tucker MA. Acral lentiginous melanoma: incidence and survival patterns in the United States, 1986-2005. Arch Dermatol 2009; 145: 427-434.
4) O'Leary JA, Berend KR, Johnson JL, Levin LS, Seigler HF. Subungual melanoma: a review of 93 cases with identification of prognostic variables. Clin Orthop Relat Res 2000; 378: 206-212.
5) Paolino G, Moliterni E, Didona D Garelli V, Corsetti P, Lopez T, Richetta AG, Cantisani C, Bottoni U, Calvieri S. Clinicopathological features, vitamin D serological levels and prognosis in cutaneous melanoma of shield-sites: an update. Med Oncol 2015; 32: 451.
6) Tan K-B, Moncrieff M, Thompson JF McCarthy SW, Shaw HM, Quinn MJ, Li LX, Crotty KA, Stretch JR, Scolyer RA. Subungual melanoma: a study of 124 cases highlighting features of early lesions, potential pitfalls in diagnosis, and guidelines for histologic reporting. Am J Surg Pathol 2007; 31: 1902-1912.
7) Boriani F, O'Leary F, Tohill M, Orlando A. Acral Lentiginous Melanoma--misdiagnosis, referral delay and 5 years specific survival according to site. Eur Rev Med Pharmacol Sci 2014; 18: 1990-1996.
8) Feibleman CE, Stoll H, Maize JC. Melanomas of the palm, sole, and nailbed: a clinicopathologic study. Cancer 1980; 46: 2492-2504.
9) Bastian BC, Kashani-Sabet M, Hamm H Godfrey T, Moore DH 2nd, Bröcker EB, LeBoit PE, Pinkel D. Gene amplifications characterize acral melanoma and permit the detection of occult tumor cells in the surrounding skin. Cancer Res 2000; 60: 1968-1973.
10) Phan A, Touzet S, Dalle S, Ronger-Savle' S, Balme B, Thomas L. Acral lentiginous melanoma: a clinicoprognostic study of 126 cases. Br J Dermatol 2006; 155: 561-569.
11) Kuchelmeister C, Schaumburg-Lever G, Garbe C. Acral cutaneous melanoma in Caucasians: clinical features, histopathology and prognosis in 112 Patients. Br J Dermatol 2000; 143: 275-280.
12) Slingluff CL, Vollmer R, Seigler HF. Acral melanoma: a review of 185 patients with identification of prognostic variables. J Surg Oncol 1990; 45: 91-98.

13) Kindem S, García-Ladaria J, Requena C, Guillén C, Oliver V, Nagore E. Survival advantage of women in localized melanoma mainly relies on clinical-pathological differences by sex. A retrospective study of 1,607 patients in Valencia, Spain. Eur J Dermatol 2015; 25: 247-254.

14) Takata M, Murata H, Saida T. Molecular pathogenesis of malignant melanoma: a different perspective from the studies of melanocytic nevus and acral melanoma. Pigment Cell Melanoma Res 2010; 23: 64-71.

15) Kim JY, Hwang EJ, Choi M, Jo SJ, Cho KH. Recurrent acral lentiginous melanoma in situ suggesting the field cell theory. Ann Dermatol 2014; 26: 779-781.

16) Krauthammer M, Kong Y, Ha BH Evans P, Bacchiocchi A, McCusker JP, Cheng E, Davis MJ, Goh G, Choi M, Ariyan S, Narayan D, Dutton-Regester K, Capatana A, Holman EC, Bosenberg M, Sznol M, Kluger HM, Brash DE, Stern DF, Materin MA, Lo RS, Mane S, Ma S, Kidd KK, Hayward NK, Lifton RP, Schlessinger J, Boggon TJ, Halaban R. Exome sequencing identifies recurrent somatic RAC1 mutations in melanoma. Nat Genet 2012; 44: 1006-1014.

17) Curtin JA, Fridlyand J, Kageshita T Patel HN, Busam KJ, Kutzner H, Cho KH, Aiba S, Bröcker EB, LeBoit PE, Pinkel D, Bastian BC. Distinct sets of genetic alterations in melanoma. N Engl J Med 2005; 353: 2135-2147.

18) Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol 2006; 24: 4340-4346.

19) Bauer J, Büttner P, Murali R, Okamoto I, Kolaitis NA, Landi MT, Scolyer RA, Bastian BC. BRAF mutations in cutaneous melanoma are independently associated with age, anatomic site of the primary tumor, and the degree of solar elastosis at the primary tumor site. Pigment Cell Melanoma Res 2011; 24: 345-351.

20) Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. J Natl Cancer Inst 2003; 95: 806-812.

21) Holick MF. Evolution and function of vitamin D. Recent Results Cancer Res 2003; 164: 3-28.

22) Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricker A, Eberle C, Barnhill R. Sun exposure and mortality from melanoma. J Natl Cancer Inst 2005; 97: 195-199.

23) Lee EY, Williamson R, Watt P, Hughes MC, Green AC, Whiteman DC. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. J Natl Cancer Inst 2003; 95: 806-812.