Actas Dermosifiliogr. 2009;100:205-11

ORIGINAL ARTICLE

Clinical and Epidemiologic Profile of Melanoma Patients According to Sun Exposure of the Tumor Site

E. Nagore, R. Botella-Estrada, C. Requena, C. Serra-Guillén, A. Martorell, L. Hueso, B. Llombart, O. Sanmartín, and C. Guillén

Servicio de Dermatología, Fundación Instituto Valenciano de Oncología, Valencia, Spain

Abstract. *Introduction.* Melanomas arising in areas with comparable levels of sun exposure have been shown to have similar genetic profiles. The aim of this study was to characterize the clinical features of melanoma patients according to the pattern of sun exposure: chronic, intermittent, or none.

Material and methods. From our melanoma database, we selected 789 consecutive patients with melanoma diagnosed in our center since January 2000. Epidemiologic data, phenotype, and personal and family history of cancer were retrieved. The observed frequency of each variable was compared.

Results. Most melanoma patients presented tumors on areas exposed intermittently to sunlight. In addition, these patients presented higher numbers of common and atypical melanocytic *nevi* and the melanoma very frequently arose in a pre-existing *nevus*. The second largest group was formed by patients with tumors on areas chronically exposed to sun and that had all the clinical lesions (solar lentigines and actinic keratoses) and epidemiologic characteristics typical of these areas. Finally, patients with melanomas on areas not exposed to sun were older, as occurred in the group with chronic exposure, and the diagnosis was made at more advanced stages of the disease.

Conclusions. There are many patients who did not fit these patterns of melanoma development. Clinical and biological characterization is therefore necessary to determine alternative pathways of development in order to establish specific preventive measures.

Key words: melanoma, sun exposure, epidemiology.

PERFIL CLÍNICO Y EPIDEMIOLÓGICO DE LOS PACIENTES CON MELANOMA CUTÁNEO SEGÚN EL GRADO DE EXPOSICIÓN SOLAR DE LA LOCALIZACIÓN DEL MELANOMA

Resumen. *Introducción.* Se ha observado que los melanomas tienen un perfil genético similar según el patrón de exposición al sol del área cutánea donde asientan. El objetivo de este estudio ha sido caracterizar desde el punto de vista clínico los pacientes con melanoma según su patrón de exposición al sol: crónico, intermitente y ausencia de exposición.

Material y métodos. Se seleccionaron 789 pacientes con melanoma diagnosticados en nuestro centro de forma consecutiva desde enero del año 2000 a partir de la base de datos de melanoma. Se obtuvieron los datos referentes a las características epidemiológicas, fenotípicas y los antecedentes personales y familiares de cáncer. Se compararon las frecuencias observadas de cada una de las variables estudiadas.

Resultados. Se observó que la mayoría de los pacientes tienen los melanomas en localizaciones expuestas al sol de forma intermitente. Además, estos pacientes tienen más nevus melanocíticos tanto comunes como atípicos y su melanoma se asocia con una elevada frecuencia a un nevus preexistente. Por otra parte, el segundo grupo en número está constituido por el grupo de pacientes con melanomas en áreas cutáneas expuestas al sol de forma crónica que presentaron todas las lesiones (lentigos solares y queratosis actínicas) y antecedentes típicos de esta localización. Finalmente, el grupo de melanomas que se presenta en áreas de piel no expuestas al sol tiene, al igual que el anterior, una edad de diagnóstico mayor y se diagnostican en fases avanzadas de la enfermedad.

Conclusiones. La presencia de un elevado número de pacientes que no sigue ninguno de los patrones mencionados suscita la necesidad de caracterizarlos clínica y biológicamente para conocer vías alternativas de desarrollo de un melanoma, y así poder establecer medidas preventivas adecuadas.

Palabras clave: melanoma, exposición solar, epidemiología.

Correspondence:
Eduardo Nagore
Servicio de Dermatología
Fundación Instituto Valenciano de Oncología
C/ Profesor Beltrán Báguena 8
46009 Valencia, Spain
eduyame@meditex.es

This research received the Juan de Azúa Award 2008 of the Spanish Academy of Dermatology and Venereology.

Introduction

Melanoma is a highly aggressive cancer, and its incidence worldwide has increased more than for any other kind of cancer. Although melanoma was originally considered to be a homogeneous entity with a uniformly poor prognosis, the gradual development of pigmented-lesion research groups and multidisciplinary melanoma study teams has resulted in the description of a number of melanoma subtypes with relatively well-differentiated clinical and pathological features. Melanoma subtyping has traditionally been based on primary tumor site, degree of exposure to the sun, and the duration of intraepidermal growth. To date, 4 subtypes have been described that account for the majority of melanomas: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma.[1] This classification is further underpinned by recent descriptions of molecular differences between these subtypes. Thus, for example, gene amplifications for acral melanomas tend to occur in a number of distinct loci, and these alterations can even be detected in histologically normal melanocytes in the skin surrounding a lesion.[2] Furthermore, the frequency of somatic mutations in the *BRAF* and *N-RAS* genes varies according to melanoma subtype.[3-5] Nonetheless, a recently published study by Curtin et al[5] has demonstrated that molecular alterations are not so much associated with the cutaneous melanoma subtype as with the type and degree of sun-induced damage to the skin where the melanoma is located.

Given the conclusions of the study by Curtin et al,[5] there is an evident need to clinically characterize patients with cutaneous melanomas according to type and degree of sun-induced damage to the site where the melanoma develops.

The aim of this study was to describe and compare the clinical and epidemiologic characteristics of patients with cutaneous melanomas according to patterns of sun exposure of the tumor site.

Patients and Methods

A retrospective observational study was designed on the basis of data included in a cutaneous and mucosal melanoma database maintained by the dermatology department of the Instituto Valenciano de Oncología, Valencia, Spain.

The database, launched in 2000, has been regularly added to with data from patients diagnosed with melanoma (incident cases) and from follow-up patients with melanoma. Clinical, epidemiologic, and histologic data to be entered into the database is collected prospectively from the medical history and physical examination of patients, performed by dermatologists with experience in the follow-up of patients with melanoma. The database currently contains data on a total of 1265 patients.

For the purposes of this study, only patients diagnosed with cutaneous or mucosal melanoma from January 1, 2000 (when the database was launched) were included. In other words, the study only included incident cases for which data were introduced prospectively from January 1, 2000. Excluded from the study were patients with melanomas that had metastasized from an unidentified primary tumor, and also patients with multiple melanomas whose first melanoma had been diagnosed prior to January 1, 2000.

The independent variable was defined as the degree of sun exposure of the primary melanoma site (the site of the first diagnosed melanoma for cases of multiple melanomas). Degree of exposure to the sun was defined as follows: no exposure, intermittent (summertime) exposure, and continuous (year-round) exposure. Categories were assigned on the basis of data obtained from medical histories, physical examinations, and patient-reported data. It was preferred not to arrive at assumptions about exposure based solely on the melanoma site, given that people dress differently, and given the differences between the sexes.

The following 5 variables were considered in the comparative analysis of patient characteristics according to sun-exposure patterns:

1. Epidemiologic variables: age at diagnosis, sex, reason for the consultation that led to diagnosis (finding on self-examination, finding in a general medical examination, sign/symptom, nevus follow-up, or another person's observation), clinical staging, and tumor site (head/neck, upper limb, trunk, lower limb, hand/foot, or mucosa).
2. Phenotype: skin phototype, hair color, eye color, number of nevi (up to 20, 20-50, 51-100, or more than 100 nevi), presence of clinically atypical nevi,[6] presence of solar lentigines, presence of actinic keratosis, and presence of solar lentigines at the melanoma site.
3. Environmental factors: chronic work-related sun exposure (10 years or more), intermittent intensive sun exposure, number of severe sunburn episodes resulting in blistering or tenderness lasting for at least 48 hours (0, 1-5, 6-10, or more than 10 episodes), and previous sunburn of the melanoma site (no sunburn, mild sunburn, or at least 1 case of severe sunburn).
4. Personal or family history of cancer: a personal history of epithelial (basal or squamous cell) skin cancer or of other nonskin neoplasms, and/or a history of melanoma or other neoplasms among first-degree relatives.
5. Histologic data: histologic type (superficial spreading melanoma, nodular melanoma, lentigo maligna

melanoma, acral lentiginous melanoma, or other), Breslow tumor thickness, ulceration, and remains of a preexisting melanocytic nevus lesion in the tumor specimen.

Differences between the distributions of the variables in each category were evaluated using the Pearson $\chi 2$ test for qualitative variables, and the Kruskal-Wallis test for quantitative variables. Statistical significance was defined as $P<.05$. Statistical analyses were performed using SPSS version 12 (SPSS, Chicago, Illinois, USA).

Results

Of a total of 826 eligible patients (defined as patients attending a first in-hospital melanoma consultation in the specified study period), 37 patients were excluded: 19 (2.3%) patients with melanomas that had metastasized from an unidentified primary tumor; 15 (1.8%) patients for whom no information was available on the kind of sun exposure of the melanoma site; and 3 patients with ocular melanomas. The final sample used for the study was thus composed of 789 patients with skin or mucosal melanomas (representing 95.5% of the total of eligible patients). The group included 408 women (51.7%) and 381 men (48.3%), and mean age at diagnosis was 56 years (interquartile range, 42-68 years). Most patients had localized disease at diagnosis, as follows: 84 (10.6%) patients with melanoma in situ; 586 (74.3%) patients with stage I or II melanomas; 96 (12.2%) patients with locoregional disease; and 7 (0.9%) patients with distant metastasis. The most frequent tumor sites were as follows: the trunk in 299 patients (37.9%); the head and neck in 156 patients (19.8%); the lower limbs in 149 patients (18.9%); acral areas in 69 patients (8.7%); and the mucosa in 10 patients (1.3%). In regard to the degree of exposure of the skin where the melanoma had developed, continuous exposure was reported (or was patently evident) in 172 cases (21.8%), intermittent exposure in 533 cases (67.6%), and no exposure in 84 cases (10.6%).

The differences encountered between the 3 sun-exposure groups are summarized in Tables 1, 2 and 3.

Statistically significant—and obvious—differences were encountered in terms of melanoma distribution by site: head and neck for continuous exposure, trunk for intermittent exposure, and acral parts for nonexposure. The same occurred with histologic type: the proportion of lentigo maligna melanomas was much higher on continuously exposed skin, 75% of the tumors on intermittently exposed skin were superficial spreading melanomas, and the highest proportion of acral lentiginous melanomas was found on nonexposed skin (Table 1). Melanomas in nonexposed skin occurred to a noticeably high degree in women (64%); the equivalent percentages for intermittently and continuously exposed skin were 54% and 38%, respectively. Melanomas in nonexposed and continuously exposed skin presented mainly in older patients (58% and 63% of patients aged over 60 years, respectively), whereas just 30% of this age group—compared to 41% of patients aged between 40 and 60 years—had melanomas in intermittently exposed skin. There were no differences between the 3 sun-exposure categories in regard to the reason for the consultation leading to the diagnosis (typically a sign or symptom of the lesion).

As for melanoma characteristics, tumors were significantly thicker in nonexposed skin (mean, 4 mm) and, to a lesser extent, in continuously exposed skin (mean, 2.6 mm), compared to intermittently exposed skin (mean, 1.9 mm). As would be expected, ulceration was more common in sites with thicker tumors, with a frequency of 53% in nonexposed skin, 37% in continuously exposed skin, and 19% in intermittently exposed skin. Clinical stage was most advanced in nonexposed skin, with almost 20% of patients having locoregional disease and 4% having metastatic disease at diagnosis. Melanomas in continuously exposed skin were staged as carcinoma in situ in 19% of the cases. A pre-existing melanocytic nevus was encountered in 39% of the melanomas in intermittently exposed skin, compared to 25% and 22% in continuously exposed and nonexposed skin, respectively. All these differences were statistically significant.

As for patient phenotypes (Table 2), no statistically significant differences were found in relation to phototype, hair color, or eye color. The total number of melanocytic nevi was significantly greater in patients with melanomas occurring in intermittently exposed skin, and likewise for the presence of at least 1 clinically atypical nevus. Solar lentigines occurred more frequently in continuously exposed skin (93%), compared to intermittently (86%) and non-exposed (77%) skin, and actinic keratoses were also more frequent in continuously exposed skin. Lentigines at the melanoma site were particularly common in continuously exposed skin (75%) and, to a lesser degree, in intermittently exposed skin (53%). In regard to the melanomas that developed in intermittently exposed skin, the absence of lentigines, which are clinical indicators of sun-induced damage, correlated to a statistically significant degree with lower numbers of melanocytic nevi (Table 4).

Finally, there were more patients with a history of smoking and of melanoma site sunburn in the groups with melanomas in continuously and intermittently exposed skin (Table 3). Patients whose exposure to the sun was work-related mostly had melanomas in continuously exposed skin, and, to a lesser degree, in nonexposed skin. Patients with melanomas in intermittently exposed skin had the highest rate of intermittent exposure to the sun, at 97%,

Table 1. Epidemiologic and Histologic Characteristics According to Skin Exposure to Sun

Characteristics	*Nonexposed Skin (n = 84)*		*Intermittently Exposed Skin (n = 533)*		*Continuously Exposed Skin (n = 172)*		*P*
	N	*%*	*N*	*%*	*N*	*%*	
Sex							
Male	30	35.7	245	46.0	106	61.6	< 0.001
Female	54	64.3	288	54.0	66	38.4	
Age, y							
< 40	9	10.7	152	28.5	18	10.5	< 0.001
40-60	26	31.0	220	41.3	46	26.7	
> 60	49	58.3	161	30.2	108	62.8	
Site							
Head/neck	15	17.9	2	0.4	139	80.8	< 0.001
Upper limbs	2	2.4	95	17.8	9	5.2	
Trunk	20	23.8	270	50.7	9	5.2	
Lower limbs	2	2.4	143	26.8	4	2.3	
Acral areas	35	41.7	23	4.3	11	6.4	
Mucosa	10	11.9	0	0.0	0	0.0	
Reason for consultation							
Self-examination finding	4	5.7	31	6.2	7	4.5	NS
Medical examination finding	8	11.4	65	13.0	20	13.0	
Sign/symptom	53	75.7	320	63.9	109	70.8	
Nevus follow-up	0	0	37	7.4	5	3.2	
Another person's observation	5	7.1	48	9.6	13	8.4	
Histologic type							
Lentigo malignant melanoma	2	2.6	13	2.5	48	29.6	< 0.001
Superficial spreading melanoma	30	38.5	395	75.2	67	41.4	
Nodular melanoma	19	24.4	96	18.3	32	19.8	
Acral lentiginous melanoma	21	26.9	9	1.7	7	4.3	
Others	6	7.7	12	3.3	8	4.9	
Breslow thickness							
Mean (SD)	4.0	3.8	1.9	2.7	2.6	2.8	< 0.001
Ulceration							
No	29	46.8	358	81.0	79	62.7	< 0.001
Yes	33	53.2	84	19.0	47	37.3	
Previous nevus							
No	42	77.8	223	61.3	64	75.3	0.006
Yes	12	22.2	141	38.7	21	24.7	
Clinical stage							
In situ	4	4.9	48	9.1	32	19.3	< 0.001
Localized	58	71.6	410	77.9	118	71.1	
Locoregional	16	19.8	65	12.4	15	9.0	
Distant metastases	3	3.7	3	0.6	1	0.6	

Abbreviation: NS, nonsignificant.

compared to 72% and 78% of the patients with melanomas in non-exposed and continuously exposed skin, respectively. All these differences were statistically significant.

No differences were observed in melanoma frequency in patients with a personal or family history of non-melanoma skin or other cancers.

Discussion

It should be noted that the results discussed below are based on unprocessed data, compiled prospectively, and reflecting just a single institution. Only patients diagnosed with melanoma at the time of the first consultation were included in the study. Biased recall in patients must be assumed in regard to details of past sunburn episodes, whether in a general sense or in regard to the site where the melanoma developed.

Our study reveals clinical and epidemiologic differences between patients when classified according to whether the site where their melanoma developed was unexposed to the sun or continuously or intermittently exposed, suggesting that there is no single route to developing a melanoma.

Table 2. Epidemiologic and Histologic Characteristics According to Skin Exposure to Sun

Characteristics	*Nonexposed Skin (n = 84)*		*Intermittently Exposed Skin (n = 533)*		*Continuously Exposed Skin (n = 172)*		*P*
	N	*%*	*N*	*%*	*N*	*%*	
Phototype							
I or II	29	38.2	179	34.6	68	42.5	NS
III or IV	47	61.8	339	65.4	92	57.5	
Hair color							
Dark	59	81.9	377	76.9	116	74.4	NS
Fair	12	16.7	93	19.0	32	20.5	
Red	1	1.4	20	4.1	8	5.1	
Eye color							
Brown/dark	48	64.0	316	63.2	91	57.6	NS
Blue/green	27	36.0	184	36.8	67	42.4	
Number of nevi							
< 20	45	77.6	274	62.6	97	81.5	0.004
20-50	6	10.3	67	15.3	12	10.1	
51-100	5	8.6	64	14.66	5.0		
> 100	2	2.4	33	7.5	4	3.4	
Atypical nevi							
No	60	87.0	399	78.5	133	90.5	0.002
Yes	9	13.0	109	21.5	14	9.5	
Solar lentigines							
No	14	23.3	68	13.8	11	7.3	0.006
Yes	46	76.7	423	86.2	140	92.7	
Actinic keratoses							
No	47	88.7	410	91.7	82	69.5	< 0.001
Yes	6	11.3	37	8.3	36	30.5	

Abbreviation: NS, nonsignificant.

Published studies indicate that, biologically speaking, melanomas have a number of genetic patterns,[5] and studies also provide evidence of at least 2 different routes of development for melanomas.[7] The first route is through ultraviolet-radiation stimulation of skins that are particularly sensitive to the sun (for example, fair- or red-haired people, and susceptible phototypes), with the skin eventually showing signs of chronic sun-induced damage and other skin tumors. The second route operates in nevus-prone individuals who may have a predisposition to melanocytic proliferation. In such patients, ultraviolet radiation is likely to play a less significant etiopathogenic role than in the first route (merely acting as an initiator).[7] Assumed—and widely accepted in regard to both routes—is that exposure to sun is a primary cause of melanoma.[8-11] Nonetheless, although these 2 routes explain the development of many melanomas, they fail to explain the development of melanomas in areas with little exposure (soles, anal region, or armpits) or no exposure (mucosa) to ultraviolet light, and which, moreover, show different genetic profiles.[5]

Using our series of patients, we present a clinical characterization of subtypes of melanoma studied from a genetic perspective[5] and classified according to degree of exposure to the sun.

Firstly, most melanomas develop in skin that is intermittently exposed to sun light (68% of cases). Recent meta-analyses have demonstrated intermittent sun exposure to be a risk factor in developing a melanoma,[11] especially in patients with multiple common and atypical nevi who recall having been sunburned at the site where the melanoma developed. The resulting tumors are mainly superficial spreading melanomas; they are slow growing, tend to be diagnosed reasonably early (as evidenced by the fact that they are less thick at diagnosis), and are likely to have developed from an existing nevus. Melanomas associated with a nevus have been shown to occur at different sites and to have different risk factors than de novo melanomas.[12,13] The possible link between nevi and melanomas may be explained by the fact that *BRAF* mutation patterns are similar for both lesions in melanomas that develop in intermittently sun-exposed skin.[14] Nonetheless, in our study, nearly half (47%) of the patients with melanoma had no solar lentigines; in other words, there was no evidence of sun-induced damage in the area of skin where the melanoma developed. This absence of

Table 3. Environmental and Individual Susceptibility Factors According to Skin Exposure to Sun Factors

Characteristics	*Nonexposed Skin (n = 84)*		*Intermittently Exposed Skin (n = 533)*		*Continuously Exposed Skin (n = 172)*		*P*
	N	*%*	*N*	*%*	*N*	*%*	
Severe sunburn							
No	41	56.9	211	42.8	76	50.3	NS
1-5	20	27.8	193	39.1	52	34.4	
6-10	7	9.7	62	12.6	14	9.3	
> 10	4	4	27	5.5	96.0		
Sunburn in melanoma site							
No	58	92.1	106	25.0	49	37.4	< 0.001
Mild	3	4.8	199	46.9	55	42.0	
Severe	2	3.2	119	28.1	27	20.6	
Work-related sun exposure							
No	44	72.1	368	84.4	75	56.0	< 0.001
Yes	17	27.9	68	15.6	59	44.0	
Intermittent sun exposure							
No	16	28.1	14	3.3	24	22.2	< 0.001
Yes	41	71.9	407	96.7	84	77.8	
Personal history of melanoma							
No	55	88.7	399	87.5	120	87.6	NS
Yes	7	11.3	57	12.5	17	12.4	
Personal history of other cancers							
No	77	92.8	493	92.7	155	91.7	NS
Yes	6	7.2	39	7.3	14	8.3	
Family history of melanoma							
No	76	96.2	494	95.6	160	98.2	NS
Yes	3	3.8	23	4.4	3	1.8	
Family history of other cancers							
No	45	57.7	305	60.3	96	60.0	NS
Yes	33	42.3	201	39.7	64	40.0	

Abbreviation: NS, nonsignificant.

sun-induced damage was associated particularly with melanomas that developed in areas of intermittent exposure with fewer nevi, suggesting the possibility of another development route for melanomas that is neither associated with nevi nor with a high degree of exposure to the sun.

Table 4. Relationship Between Number of Nevi and Melanoma Site Lentigines in Patients With Melanoma on Intermittently Sun-Exposed Skin

Number of nevi	*Lentigines in Melanoma Site*			
	No		*Yes*	
	N	*%*	*N*	*%*
< 20	140	70.0	128	57.1
21-50	23	11.5	44	19.6
51-100	25	12.5	32	14.3
> 100	12	6.0	20	8.9

Secondly, some melanomas develop in parts of the skin that are chronically exposed to the sun. Signs of chronic sun-induced damage—such as lentigines and actinic keratosis—were observed in patients who were generally older when melanoma was diagnosed. These patients generally had few nevi, had a personal background of chronic occupational exposure, and had experienced sunburn episodes affecting the melanoma site. Although not statistically significant, there was a greater prevalence of low phototype skin and a noticeably low frequency of a family history of melanoma in these patients. This profile coincides with that described by Whiteman and coworkers as reflecting 1 of the 2 possible routes for the development of melanoma.[7,15]

Finally, we characterized patients with melanomas arising on areas of the body with very little or no exposure to the sun. A very high proportion of these patients (92%)

reported never having been sunburned in the melanoma site. These predominantly female patients aged over 60 years had few risk factors for developing cancer, and did not appear to be susceptible to sun exposure or to be nevus-prone, yet had a high proportion of acral lentiginous melanomas that were diagnosed late. Despite the fact that such patients may be viewed as having different kinds of melanomas (mucosa, soles, etc), the genetic profile for these melanomas has, in fact, been characterized as similar.[5]

In conclusion, although some development routes for melanomas have been well defined, there are other possible routes that require study and genetic and clinical characterization.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Crowson AN, Magro CM, Barnhill RL, Mihm MC Jr. Pathology. En: Balch CM, Houghton AN, Sober AJ, Soong SJ, editors. Cutaneous melanoma. 4th ed. St. Louis, Missouri: Quality Medical Publishing, Inc.; 2003. p. 171-208.
2. Bastian BC, Kashani-Sabet M, Hamm H, Godfrey T, Moore DH 2nd, Bröcker EB, et al. Gene amplifications characterize acral melanoma and permit the detection of occult tumor cells in the surrounding skin. Cancer Res. 2000;60:1968-73.
3. Maldonado JL, Fridlyand J, Patel H, Jain AN, Busam K, Kageshita T, et al. Determinants of BRAF mutations in primary melanomas. J Natl Cancer Inst. 2003;95:1878-90.
4. Cohen Y, Rosenbaum E, Begum S, Goldenberg D, Esche C, Lavie O, et al. Exon 15 BRAF mutations are uncommon in melanomas arising in non-sun-exposed sites. Clin CancerRes. 2004;10:3444-7.
5. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005;353:2135-47.
6. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Abeni D, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer.2005;41:28-44.
7. Whiteman DC,Watt P, Purdie DM, Hughes MC, HaywardNK, Green AC. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. J Natl Cancer Inst. 2003;95:806-12.
8. Marks R. Epidemiology of melanoma. Clin Exp Dermatol.2000;25:459-63.
9. Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control. 2001;12:69-82.
10. Rodenas JM, Delgado-Rodríguez M, Herranz MT, Tercedor J, Serrano S. Sun exposure, pigmentary traits, and risk of cutaneous malignant melanoma: a case-control study in a Mediterranean population. Cancer Causes Control. 1996;7:275-83.
11. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005;41:45-60.
12. Carli P, Massi D, Santucci M, Biggeri A, Giannotti B. Cutaneous melanoma histologically associated with a nevus and melanoma de novo have a different profile of risk: results from a case-control study. J Am Acad Dermatol. 1999;40: 549-57.
13. Marks R, Dorevitch AP, Mason G. Do all melanomas come from «moles»? A study of the histological association between melanocytic naevi and melanoma. Australas J Dermatol. 1990;31:77-80.
14. Pollock PM, Harper UL, Hansen KS, Yudt LM, Stark M, Robbins CM, et al. High frequency of BRAF mutations in nevi. Nat Genet. 2003;33:19-20.
15. Whiteman DC, Parsons PG, Green AC. p53 expression and risk factors for cutaneous melanoma: a case-control study. Int J Cancer. 1998;77:843-8.