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ORIGINAL ARTICLE

Risk factors for the development of a second melanoma in patients with cutaneous melanoma

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Abstract

Background Cutaneous melanoma patients have an increased risk of developing other neoplasms, especially cutaneous neoplasms and other melanomas. Identifying factors associated with an increased risk might be useful in the development of melanoma guidelines.

Objectives To identify risk factors related to the development of a second primary melanoma in a series of patients diagnosed with sporadic melanoma and to establish the estimated incidence rate.

Methods A longitudinal study based on prospective follow-up information of patients diagnosed with sporadic cutaneous melanoma at our centre from 2000 to 2015 was performed. Cumulative incidence was estimated based on competing risk models, and the association of characteristics with the risk of a second melanoma was performed by Cox proportional hazard models.

Results Out of 1447 patients included in the study, after a median follow-up of 61 months, 55 patients (3.8%) developed a second melanoma. Fair hair colour, more than 100 common melanocytic nevi and the presence of more than 50 cherry angiomas were independently associated with the development of a second melanoma. The site and the histological subtype of the first and second melanomas were not consistent. The second melanomas were thinner than the first ones.

Conclusions Fair-haired and multiple-nevi patients might benefit from more intensive prevention measures. The finding of cherry angiomas as a risk factor suggests that these lesions could be markers of skin sun damage in the setting of certain degree of genetic susceptibility.

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Conflicts of interest

None declared. The authors did the work without receiving any financial support from any third party. The authors have not got any financial relationships with entities in the bio-medical arena related to diagnosis and treatment of melanoma over the 36 months prior to the submission of this work. The authors have not got patents planned, pending or issued, broadly relevant to the work. The authors have not got other relationships or activities that readers could perceive to have influenced or that give the appearance of potencially influencing.

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Introduction

Melanoma is the major cause of death due to cutaneous cancer.[1] Nonetheless, its survival rate has increased in recent years thanks to campaigns of health education, prevention and early detection[2] and the development of new drugs in the treatment of metastatic melanoma.[3,4] This improvement in survival implies that a higher number of patients live longer after diagnosis and, therefore, the probability of developing other cancers increases. It is well known that patients with melanoma have an increased risk of having other neoplasms, and particularly of other melanomas and of non-melanoma skin cancers.[5–11] The incidence of new melanomas in patients with a previous melanoma varies widely in the literature and ranges from <1% to over 10% at 5 years.[12]

Susceptibility to the development of melanoma is very variable and depends on various factors. These include phenotypic factors such as fair skin, low phototype (I/II), blond or red hair colour and the number of common and atypical moles, and environmental factors such as severe sunburn, chronic sun exposure and the use of tanning beds.[13–16] In addition, a melanoma is a polygenic disease. The genomic alterations underlying the development of melanoma can be of low or high penetrance, the latter being responsible for a significant number of cases of familial melanoma. Patients belonging to families with mutations in these genes have an increased risk of melanoma.[17] This explains the need for an increased attention to secondary prevention measures in these patients as compared to patients with sporadic melanoma.[18,19]

The population with sporadic melanoma is very heterogeneous and has an increased risk of developing new melanomas. In this study, we aimed to identify characteristics that allow identifying high-risk groups of patients who might benefit from specific prevention programs.

Patients and methods

Design and study subjects

A longitudinal case–case study was designed based on the information prospectively collected in the melanoma database of the Department of Dermatology of the Instituto Valenciano de Oncología (IVO) in València (Spain). In this database, all patients treated at the centre since January 2000 are included and include a large number of clinical, histological and epidemiological variables. The characteristics of the database are described in detail in previous works.[11,20] In this study, we selected patients with melanoma, aged over 18 years old, diagnosed from 1 January 2000 to 31 October 2015. We excluded patients with familial melanoma and those with extracutaneous melanomas or melanomas of unknown origin. We included synchronous melanomas defined as those diagnosed simultaneously or within the first 3 months after the diagnosis of the first melanoma.

All these patients were followed up in accordance with the current local protocols, which include whole skin examination by a dermatologist. Visits were scheduled every 6 months for the first 3 years after diagnosis and then yearly from the fourth on. The study was approved by the IVO ethics committee and conducted in accordance with the Declaration of Helsinki principles.

Study variables

The dependent variable of this study was the development of a second melanoma. The development of this second neoplasm was evaluated as a time-dependent variable. We selected the following phenotypic, epidemiological and histological characteristics as independent variables: Age (≤45 years, >45 years), sex, phototype (I–II vs. III–V), hair colour (black/brown, blond and red), eye colour (dark, light), number of severe sunburns (≤5, >5), chronic sun exposure (no, ≤10, >10 years), presence of any clinically atypical nevus (yes, no), presence of common melanocytic nevi of at least 2 mm in diameter (<20, 20–50, 51–100, >100), seborrhoeic keratoses and cherry angiomas [no, <10, 10–20, 21–50, 51–100, >100; subsequently recoded for cherry angiomas, as it was significant in the univariate exploratory study by Classification and Regression Tree (CART) analysis, in ≤50 and >50]; personal history of basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) (yes, no), site of melanoma (head and neck, trunk, upper limbs, lower limbs and acral), histological subtypes of melanoma [superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), nodular melanoma (NM), acral lentiginous melanoma (ALM) and other/unspecified], melanoma stage (*in situ*, localized, locoregional, disseminated melanoma) and the presence of neval remnants contiguous to the melanoma (yes, no).

Severe sunburns were defined as those causing blisters or skin pain for at least 48 h. A nevus was deemed atypical when having a macular component and meeting at least three of the following five criteria: size ≥5 mm, asymmetry, irregular pigmentation, irregular borders and erythema.[21] Seborrhoeic keratosis and cherry angiomas should be clinically palpable and should have a 2-mm size at least. The background of basal cell and squamous cell carcinomas was confirmed through pathology reports.

We also evaluated the existence of non-synonymous melanocortin 1 receptor (*MC1R*) gene variants (yes, no) depending on the presence of any of the following variants: p.V60L, pD84E, p.V92M, p.R142H, p.R151C, p.I155T, p.V156L, p.R160W, p.R163Q and p.D294H.

The genetic study of *MC1R* gene variants was carried out through direct DNA sequencing according to previously described methods.[22]

Statistical analysis

Associations of patient characteristics and melanoma features with subsequent primary melanoma were assessed using chi-

squared and Fisher's exact tests. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) as measures of association between risk factors and incidence of second melanoma. Follow-up time started at time of primary melanoma diagnosis and ended at the time of diagnosis of the second melanoma or censoring, which ever occurred first. Censoring events were death or end of follow-up. All models were adjusted for age at diagnosis (≤45, >45 years). The ordinal variables were dichotomized through the CART analysis. We computed 5-year cumulative incidence based on competing risk models of second melanoma endpoint using multivariable subdistribution hazard models. Time since melanoma diagnosis was used as the time scale for this analysis. Kaplan–Meier method was used to calculate the estimated cumulative incidence and obtain the curves on the different characteristics studied and significance in the study with the chi-squared method. The differences between them were evaluated by means of the log-rank test. In all cases, a level of statistical significance was established for a value of $P < 0.05$.

The statistical analysis was performed with the IBM SPSS Statistics software for Windows (version 20.0; IBM Corp, Armonk, NY, USA) except for the analysis of competitive risks carried out with RStudio v0.99.902, using gam 1.12, survival v2.39-2, prodlim v1.5.7 and cmprsk v2.2-7, crrstep 2015-2.1.

Results

According to the selection criteria, 1447 patients were included in the study, with a median of 57 years of age at diagnosis of the first melanoma (interquartile range: 43–69). The characteristics of the population are displayed in Table 1.

After a median follow-up of 61 months, 55 patients (3.8%) developed a second melanoma, representing a ratio of 1 in 26 patients. The estimated cumulative incidence of second melanomas in the overall population was 1.6%, 2.3%, 3.3% and 6.7% at years 1, 2, 5 and 10. Table 2 shows the cumulative incidence differences of second melanomas at years 1, 2 and 5 for each significant variable in the contingency tables.

When comparing patients with a single melanoma versus those with at least two, it was observed that in the latter group, there was a higher number of patients with blond and red hair ($P = 0.001$), with a history of severe sunburn ($P = 0.049$), with common melanocytic nevi ($P < 0.001$) and atypical moles ($P < 0.001$) and multiple cherry angiomas ($P = 0.004$). The presence of at least one *MC1R* gene variant was also more frequent in patients with second melanomas ($P = 0.028$).

After the multivariate study, only the colour of light hair (blond and red hair), the presence of more than 100 common melanocytic nevi and the presence of more than 50 cherry angiomas maintained their statistical significance (Table 3, Fig. 1).

We studied the concordance between the site of the first and second melanomas (Table 4). The site of a second melanoma was reported in 46 patients. Only in 15 of them (32.6%), the site coincided with the first melanoma, a fact that occurred more frequently in melanomas occurring in the trunk (42.9%), followed by those in head and neck (33.3%).

Similarly, we studied the concordance between the histological type of first and second melanomas (Table 5). These data were known in 54 patients. In 28 patients of them (51.9%), the histological variant of the first melanoma was the same as in the second melanoma. In 24 of these 28 patients (85.7%), the type was SSM.

The tumour thickness of second melanomas was also compared to the first ones (Table 6). In general, the second melanomas were thinner than the first ones. Most of the second melanomas (48.1%) were *in situ* melanomas, followed by melanomas with a Breslow thickness ≤1 mm (33.3%). No second melanoma was diagnosed with a thickness above 4 mm.

Discussion

In our study of a series of 1447 patients with melanoma, 3.8% developed a second melanoma after a median follow-up of 5 years, an incidence similar to that reported in previous series[23–25] although in the literature, the incidence of multiple melanoma varies from 1% to 10%.[12,26–36] The cumulative incidence of a second melanoma in the total population of our study was 1.6% at year 1 and 3.3% at year 5, values also comparable to those previously reported.[37] However, considerable risk variations have also been reported, ranging from 1.5% to 11.4% at year 5.[24,31,33,38,39] This variability in the figures can be due to the lack of homogeneity in the studies.

In our series of patients, red and blond hair, having more than 100 common melanocytic nevi and more than 50 cherry angiomas were the features that significantly increased the risk of developing a second melanoma. The association with light hair colour and the presence of multiple melanocytic nevi was not surprising since both features are well-known risk factors for developing melanoma.[21,40] In addition, positive associations between both features and the development of multiple melanoma have also been reported.[25,41–43] An unexpected finding was the association between the occurrence of multiple cherry angiomas and an increased risk of a second melanoma. This association has not been reported in the literature. Cherry or senile angiomas are the most frequent cutaneous vascular tumours. Despite its frequency, its etiopathogenesis has not been studied thoroughly. They increase in number with age and have a familial component.[44,45] The development of cherry angiomas has been described as a consequence of severe skin damage after exposure to alkylating agents (nitrogen and sulphur mustards)[46–48] and other toxic agents (2-butoxyethanol and bromides),[49,50] associated with immunosuppression with cyclosporine,[51] with herpes virus 8,[52] to graft-versus-host disease[53,54] and to lymphoproliferative disorders such as Castleman disease.[55] The occurrence of cherry angiomas has been associated with the process of angiogenesis, arising from the increased

Table 1 Characteristics of the study population ($N = 1447$)

Characteristics	Second melanoma						*P*
	No		Yes		Total		
	N	%	*N*	%	*N*	%	
Age							ns
≤45 years	406	29.2	14	25.5	420	29.0	(0.552)
>45 years	986	70.8	41	74.5	1027	71.0	
Gender							ns
Male	689	49.5	32	58.2	721	49.8	(0.206)
Female	703	50.5	23	41.8	726	50.2	
Eye colour							ns
Black/brown	816	59.9	32	58.2	848	59.8	(0.797)
Blue/green	546	40.1	23	41.8	569	40.2	
Hair colour							0.001
Black/brown	1074	79.1	33	60.0	1107	78.4	
Blond	234	17.2	16	29.1	250	17.7	
Red	49	3.6	6	10.9	55	3.9	
Phototype							ns
I–II	479	35.2	22	40.7	501	35.5	(0.408)
III–V	880	64.8	32	59.3	912	64.5	
Lifetime severe sunburns							0.049
≤5	1099	81.5	39	70.9	1138	81.1	
>5	249	18.5	16	29.1	265	18.9	
Chronic sun exposure							ns
No	969	73.8	39	70.9	1008	73.7	(0.840)
≤10 years	74	5.6	4	7.3	78	5.7	
>10 years	270	20.6	12	21.8	282	20.6	
Common nevi							<0.001
<20	907	71.9	28	52.8	935	71.1	
20–50	188	14.9	10	18.9	198	15.1	
51–100	115	9.1	5	9.4	120	9.1	
>100	52	4.1	10	18.9	62	4.7	
Atypical nevus							<0.001
No	1098	82.2	25	46.3	1123	80.8	
Yes	238	17.8	29	53.7	267	19.2	
Seborrhoeic keratosis							ns
No	401	54.2	17	51.5	418	54.1	(0.122)
<10	182	24.6	7	21.2	189	24.5	
10–20	47	6.4	2	6.1	49	6.3	
21–50	60	8.1	7	21.2	67	8.7	
51–100	25	3.4	0	0.0	25	3.2	
>100	25	3.4	0	0.0	25	3.2	
Senile/cherry angiomas							0.004
No	340	45.8	9	27.3	349	45.0	
<10	200	27.0	11	33.3	211	27.2	
10–20	65	8.8	2	6.1	67	8.6	
21–50	98	13.2	4	12.1	102	13.2	
51–100	25	3.4	4	12.1	29	3.7	
>100	14	1.9	3	9.1	17	2.2	
Personal history of BCC							ns
No	1296	93.1	50	90.9	1346	93.0	(0.531)
Yes	96	6.9	5	9.1	101	7.0	
Personal history of SCC							ns
No	1370	98.4	55	100	1425	98.5	(0.347)
Yes	22	1.6	0	0	22	1.5	
Melanoma site							ns (0.535)
Head/neck	305	21.9	10	18.2	315	21.8	
Upper extremities	194	13.9	9	16.4	203	14.0	
Trunk	504	36.2	25	45.5	529	36.6	
Lower extremities	271	19.5	7	12.7	278	19.2	
Acral	118	8.5	4	7.3	122	8.4	
Histological subtype							ns
LMM	172	12.4	4	7.3	176	12.2	(0.603)
SSM	808	58.0	36	65.5	844	58.3	
NM	264	19.0	11	20.0	275	19.0	
ALM	69	5.0	1	1.8	70	4.8	
Other	79	5.7	3	5.5	82	5.7	
MC1R variants							0.028
No	425	36.7	11	21.6	436	36.0	
Yes	734	63.3	40	78.4	774	64.0	
Stage of melanoma							ns
In situ	226	16.5	9	16.4	235	16.5	(0.751)
Localized	920	67.2	35	63.6	955	67.0	
Locoregional	213	15.5	11	20.0	224	15.7	
Disseminated	11	0.8	0	0.0	11	0.8	
Nevus-associated melanoma							ns
No	941	74.6	37	72.5	978	74.5	(0.739)
Yes	320	25.4	14	27.5	334	25.5	

ALM, acral lentiginous melanoma; BCC, basal cell carcinoma; LMM, lentigo maligna melanoma; *MC1R*, melanocortin 1 receptor gen; NM, nodular melanoma; SCC, squamous cell carcinoma; SSM, superficial spreading melanoma.

number of proangiogenic molecules such as vascular endothelial growth factor and other cytokines.[46,52,55] The pathogenesis of cherry angiomas is not clearly known currently and its association with other skin tumours and, in particular, with melanoma, cannot be explained based on the current literature. Borghi et al.[56] conducted a cross-sectional study to identify potential predisposing factors associated with the development of multiple cherry angiomas. That study included 1302 patients and found that advanced age, chronic immunosuppressive therapy, skin cancers (melanoma and non-melanoma skin cancer) and extracutaneous cancers were significantly associated with the existence of multiple angiomas in these patients. The second phase of this study analysed the association between cherry angiomas and skin cancer.[57] Multiple angiomas were significantly more frequent in patients with melanoma under 70 years old. Recently, one study has identified somatic activating mutations

Table 2 Cumulative incidence of second melanoma at 1, 2 and 5 years by significant variables

Characteristics	1 year	2 years	5 years
Hair colour			
Dark	1.3	1.8	2.8
Blond	2.0	3.4	4.6
Red	6.1	8.3	8.3
Severe sunburns			
≤5	1.5	2.1	3.0
>5	2.4	4.2	4.8
Atypical nevi			
No	0.9	1.8	2.0
Yes	4.8	5.7	8.1
Common nevi			
≤100	1.7	2.4	3.2
>100	1.7	1.7	4.3
Senile/cherry angiomas			
≤50	1.4	1.9	2.8
>50	4.6	7.1	11.2
MC1R variants			
No	1.2	1.4	2.2
Yes	2.0	3.2	4.4

Table 3 Univariate and multivariate Cox regression models for variables associated with the development of a second melanoma in melanoma patients

Characteristics	Univariate analysis			Multivariate analysis		
	HR	CI 95% HR	*P*	HR	CI 95% HR	*P*
Hair colour			0.002			0.025
Dark	Ref.	Ref.		Ref.	Ref.	
Blond	2.3	1.1–3.6	0.026	2.2	1.0–4.7	0.048
Red	3.4	1.7–9.7	0.002	3.5	1.2–10.4	0.022
Common nevi >100	4.9	2.5–9.8	<0.001	5.6	2.5–12.5	<0.001
Some atypical nevus	4.5	2.7–7.7	<0.001	NS	NS	NS
Senile/cherry angiomas >50	3.3	1.4–8.0	0.010	3.9	1.7–9.1	0.001
Any *MC1R* variant	2.1	1.1–4.1	0.031	NS	NS	NS
Severe sunburns >5	1.7	1.0–3.1	0.071	NS	NS	NS

CI, Confidence interval; HR, Hazard ratio; NS, not significant; Ref., reference category.

in *GNAQ* and *GNA11* in a sample of cherry angiomas that also share uveal melanoma, blue nevus and melanoma associated with blue nevus.[58] In our study, the finding of cherry angiomas as a risk factor suggests that these lesions might be markers of actinic skin damage in patients with some degree of genetic susceptibility. If this finding is an independent risk factor for the development of a second melanoma, it needs to be elucidated in further studies. This might provide a chance finding or it might be a confounding factor associated with other variables not analysed in our study.

Most second melanomas did not occur in the same site as the first melanomas. Only in 32.6% of cases, the sites of the first and second melanomas were the same, with the trunk being the site with the highest correlation (9 cases). This finding is comparable to that reported in other series[28,32,41,59] and emphasizes the importance of full skin examination during the follow-up of patients with melanoma.

We also did not find a clear correlation between the histological subtype of the first and second melanomas. Only in slightly over half of the patients, the histological type of the first melanoma coincided with the second, with SSM being the variant with the highest agreement and the most frequent in total terms in the two groups of patients.

61% of the first melanomas had a Breslow thickness ≤1 mm (16.6% of *in situ* melanomas) while this percentage increased to 81.4% in the second melanomas (48.1% of *in situ* melanomas). This trend towards thickness reduction in the second melanomas has been reported in most studies.[7,12,23,26,28,32–34,36,38,60–62] One study published just like the opposite, the mean tumour thickness of the second melanomas was slightly higher than the mean tumour thickness of the first ones.[27] In this study, patients undergoing rigorous controls had thinner second melanomas than the rest suggesting that medical surveillance, self-examination and/or preventive measures taken by increasingly more aware patients are responsible for this tendency to less invasive second melanomas. Currently, the role of potential biological differences between the first and second melanomas cannot be ruled out either.

Another issue worth highlighting is the diagnosis of second melanomas beyond 5 years after first diagnosis. The median follow-up in our study was 5 years, and therefore, the data related to this fact lack sufficient statistical power. However, 16 of the 55 second melanomas (29%) were detected during the follow-up after the 5th year of diagnosis, which is consistent with those reported in other studies.[25,38,61] Although the risk of developing a second melanoma is higher in the first 5 years,[28,34] cases have been reported up to 2–3 decades after the first melanoma.[23,38] Some studies have shown that the risk of a second melanoma remains stable and does not diminish with time.[12,31,63] All these data underscore the need to monitor patients throughout their lives to detect melanomas early, the importance of self-examination and preventive behaviours.

The main strength of our study is having been based on the information collected meticulously, homogeneously and prospectively in a single institution, including a large number of variables.

Our work also has some limitations. During the follow-up period (a median of 5 years), only 55 patients developed a second melanoma (3.8%). This fact may have conditioned that some variables did not reach statistical significance when they

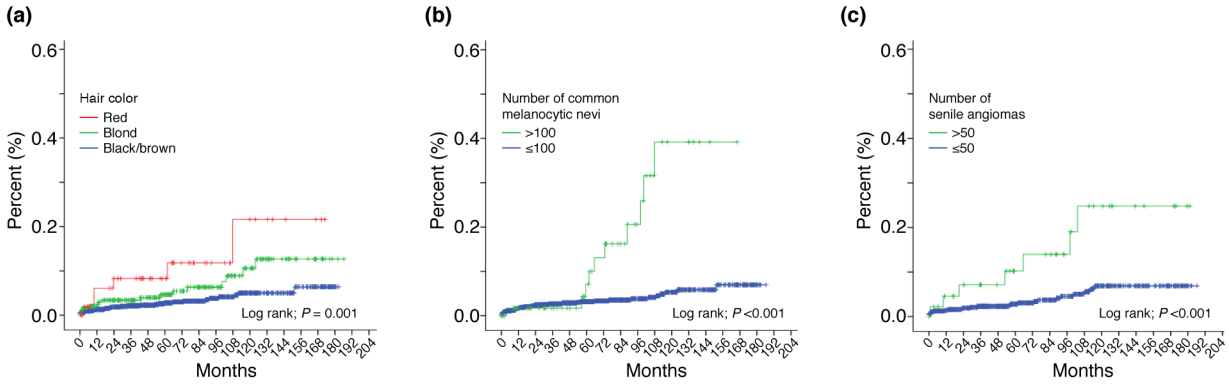

Figure 1 Cumulative incidence curves for variables with statistical significance in the multivariate analysis: (a) hair colour, (b) number of common melanocytic nevi and (c) number or senile angiomas.

Table 4 Site of first and second melanomas

Site	First melanoma					
Second melanoma	**Head/neck**	**Upper extremity**	**Trunk**	**Lower extremity**	**Acral**	**Total**
Head/neck	3 (33.3%)	1 (12.5%)	3 (14.3%)	0 (0%)	1 (33.3%)	8 (17.4%)
Upper extremity	0 (0%)	1 (12.5%)	7 (33.3%)	1 (20%)	0 (0%)	9 (19.6%)
Trunk	2 (22.2%)	5 (62.5%)	9 (42.9%)	1 (20%)	2 (66.7%)	19 (41.3%)
Lower estremity	2 (22.2%)	0 (0%)	2 (9.5%)	2 (40%)	0 (0%)	6 (13%)
Acral	2 (22.2%)	1 (12.5%)	0 (0%)	1 (20%)	0 (0%)	4 (8.7%)
Total	9 (100%)	8 (100%)	21 (100%)	5 (100%)	3 (100%)	46 (100%)

Color shade enhance diagonal cells which refer to concordant cases.

Table 5 Histological subtype of first and second melanomas

Second melanoma	First melanoma					
	LMM	**SSM**	**NM**	**ALM**	**Other**	**Total**
LMM	3 (75%)	5 (14.3%)	2 (18.2%)	1 (100%)	0 (0%)	11 (20.4%)
SSM	1 (25%)	24 (68.6%)	8 (72.7%)	0 (0%)	3 (100%)	36 (66.7%)
NM	0 (0%)	5 (14.3%)	1 (9.1%)	0 (0%)	0 (0%)	6 (11.1%)
ALM	0 (0%)	1 (2.9%)	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)
Total	4 (100%)	35 (100%)	11 (100%)	1 (100%)	3 (100%)	54 (100%)

Color shade enhance diagonal cells which refer to concordant cases.
ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.

Table 6 Breslow of first and second melanomas

Tumour thickness	First melanoma		Second melanoma	
	N	**%**	***N***	**%**
In situ	9	16.6	26	48.1
≤1.00 mm	24	44.4	18	33.3
1.01–2.00 mm	5	9.3	5	9.3
2.01–4.00 mm	11	20.4	5	9.3
>4 mm	5	9.3	0	0

actually have a risk value. In addition, no reliable estimates of long-term risk can be obtained in this monitoring period. The data come from a referral centre in the treatment of cancer. Therefore, we cannot rule out a possible selection bias and we cannot ignore a possible memory bias when collecting variables related to sun exposure.

In conclusion, being red haired or blond haired, having more than 100 common melanocytic nevi and more than 50 cherry angiomas were significantly associated with the risk of developing a second primary melanoma in patients with a first

melanoma. Further studies should corroborate the association with cherry angiomas. Our findings can help identify a subgroup of high-risk patients who might benefit from preventive measures, particularly education programs on self-examination and photoprotection. They can also contribute to the implementation of specific monitoring protocols in this population.

References

1 Hollestein LM, van den Akker SAW, Nijsten T, Karim-Kos HE, Coebergh JW, de Vries E. Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. *Ann Oncol* 2012; **23**: 524–530.

2 Tripp MK, Watson M, Balk SJ, Swetter SM, Gershenwald JE. State of the science on prevention and screening to reduce melanoma incidence and mortality: the time is now. *CA Cancer J Clin* 2016; **66**: 460–480.

3 Ribas A, Hamid O, Daud A *et al*. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. *JAMA* 2016; **315**: 1600–1609.

4 Long GV, Stroyakovskiy D, Gogas H *et al*. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet* 2015; **386**: 444–451.

5 van der Leest RJT, Flohil SC, Arends LR, de Vries E, Nijsten T. Risk of subsequent cutaneous malignancy in patients with prior melanoma: a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2015; **29**: 1053–1062.

6 Caini S, Boniol M, Botteri E *et al*. The risk of developing a second primary cancer in melanoma patients: a comprehensive review of the literature and meta-analysis. *J Dermatol Sci* 2014; **75**: 3–9.

7 Bradford PT, Freedman DM, Goldstein AM, Tucker MA. Increased risk of second primary cancers after a diagnosis of melanoma. *Arch Dermatol* 2010; **146**: 265–272.

8 Spanogle JP, Clarke CA, Aroner S, Swetter SM. Risk of second primary malignancies following cutaneous melanoma diagnosis: a population-based study. *J Am Acad Dermatol* 2010; **62**: 757–767.

9 Crocetti E, Guzzinati S, Paci E *et al*. The risk of developing a second, different, cancer among 14560 survivors of malignant cutaneous melanoma: a study by AIRTUM (the Italian Network of Cancer Registries). *Melanoma Res* 2008; **18**: 230–234.

10 Bhatia S, Estrada-Batres L, Maryon T, Bogue M, Chu D. Second primary tumors in patients with cutaneous malignant melanoma. *Cancer* 1999; **86**: 2014–2020.

11 Espinosa P, Pfeiffer RM, García-Casado Z *et al*. Risk factors for keratinocyte skin cancer in patients diagnosed with melanoma, a large retrospective study. *Eur J Cancer* 2016; **53**: 115–124.

12 Moore MM, Geller AC, Warton EM, Schwalbe J, Asgari MM. Multiple primary melanomas among 16,570 patients with melanoma diagnosed at Kaiser Permanente Northern California, 1996 to 2011. *J Am Acad Dermatol* 2015; **73**: 630–636.

13 Berking C, Takemoto R, Satyamoorthy K, Elenitsas R, Herlyn M. Basic fibroblast growth factor and ultraviolet B transform melanocytes in human skin. *Am J Pathol* 2001; **158**: 943–953.

14 Wang SQ, Setlow R, Berwick M *et al*. Ultraviolet A and melanoma: a review. *J Am Acad Dermatol* 2001; **44**: 837–846.

15 Berwick M. Epidemiology: current trends, risk factors and environmental concerns. In Balch CM, AN Houghton, AJ Sober S-J Soon, eds. Cutaneous Melanoma, 3rd edn. St. Louis: Quality Medical Publishing, 1998: 551–571.

16 Burton RC. Malignant melanoma in the year 2000. *CA Cancer J Clin* 2000; **50**: 209–213.

17 Avilés JA, Lázaro P. Genetic predisposition in cutaneous melanoma. *Actas Dermosifiliogr* 2006; **97**: 229–240.

18 Platz A, Ringborg U, Hansson J. Hereditary cutaneous melanoma. *Semin Cancer Biol* 2000; **10**: 319–326.

19 Florell SR, Boucher KM, Garibotti G *et al*. Population-based analysis of prognostic factors and survival in familial melanoma. *J Clin Oncol* 2005; **23**: 7168–7177.

20 Nagore E, Botella-Estrada R, Requena C *et al*. Clinical and epidemiologic profile of melanoma patients according to sun exposure of the tumor site. *Actas Dermosifiliogr* 2009; **100**: 205–211.

21 Gandini S, Sera F, Cattaruzza MS *et al*. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer* 2005; **41**: 28–44.

22 García-Casado Z, Traves V, Bañuls J *et al*. BRAF, NRAS and MC1R status in a prospective series of primary cutaneous melanoma. *Br J Dermatol* 2015; **172**: 1128–1131.

23 Manganoni A, Farisoglio C, Tucci G, Facchetti F, Calzavara PP. The importance of self-examination in the earliest diagnosis of multiple primary cutaneous melanomas: a report of 47 cases. *J Eur Acad Dermatology Venereol* 2007; **21**: 1333–1336.

24 van der Leest RJT, Liu L, Coebergh JWW *et al*. Risk of second primary in situ and invasive melanoma in a Dutch population-based cohort: 1989–2008. *Br J Dermatol* 2012; **167**: 1321–1330.

25 Schuurman MS, de Waal AC, Thijs EJM, van Rossum MM, Kiemeney LALM, Aben KKH. Risk factors for second primary melanoma among Dutch patients with melanoma. *Br J Dermatol* 2017; **176**: 971–978.

26 Bower MR, Scoggins CR, Martin RCG *et al*. Second primary melanomas: incidence and outcome. *Am Surg* 2010; **76**: 675–681.

27 De Giorgi V, Rossari S, Papi F *et al*. Multiple primary melanoma: the impact of atypical naevi and follow up. *Br J Dermatol* 2010; **163**: 1319–1322.

28 Stam-Posthuma JJ, van Duinen C, Scheffer E, Vink J, Bergman W. Multiple primary melanomas. *J Am Acad Dermatol* 2001; **44**: 22–27.

29 Hwa C, Price LS, Belitskaya-Levy I *et al*. Single versus multiple primary melanomas: old questions and new answers. *Cancer* 2012; **118**: 4184–4192.

30 Jones MS, Torisu-Itakura H, Flaherty DC *et al*. Second primary melanoma: risk factors, histopathologic features, survival, and implications for follow-up. *Am Surg* 2016; **82**: 1009–1013.

31 Levi F, Randimbison L, Te V-C, La Vecchia C. High constant incidence rates of second cutaneous melanomas. *Int J Cancer* 2005; **117**: 877–879.

32 Titus-Ernstoff L, Perry AE, Spencer SK *et al*. Multiple primary melanoma. *Arch Dermatol* 2006; **142**: 433–438.

33 Ferrone CR, Ben Porat L, Panageas KS *et al*. Clinicopathological features of and risk factors for multiple primary melanomas. *JAMA* 2005; **294**: 1647–1654.

34 Buljan M, Situm M, Bolanca Z, Zivković MV, Mihić LL. Multiple primary melanoma: epidemiological and prognostic implications; analysis of 36 cases. *Coll Antropol* 2010; **34**(Suppl 2): 131–134.

35 Youlden DR, Youl PH, Soyer HP, Aitken JF, Baade PD. Distribution of subsequent primary invasive melanomas following a first primary invasive or in situ melanoma Queensland, Australia, 1982–2010. *JAMA Dermatol* 2014; **150**: 526–534.

36 Krajewski AC, Hart DR, Hieken TJ. Multiple primary melanoma in the elderly. *Am J Surg* 2016; **211**: 84–88.

37 Slingluff CL, Vollmer RT, Seigler HF. Multiple primary melanoma: incidence and risk factors in 283 patients. *Surgery* 1993; **113**: 330–339.

38 Kang S, Barnhill RL, Mihm MC, Sober AJ. Multiple primary cutaneous melanomas. *Cancer* 1992; **70**: 1911–1916.

39 Goggins WB, Tsao H. A population-based analysis of risk factors for a second primary cutaneous melanoma among melanoma survivors. *Cancer* 2003; **97**: 639–643.

40 Gandini S, Sera F, Cattaruzza MS *et al*. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer* 2005; **41**:2040–2059.

41 Siskind V, Hughes MCB, Palmer JM *et al*. Nevi, family history, and fair skin increase the risk of second primary melanoma. *J Invest Dermatol* 2011; **131**: 461–467.

42 Burden AD, Newell J, Andrew N, Kavanagh G, Connor JM, MacKie RM. Genetic and environmental influences in the development of multiple primary melanoma. *Arch Dermatol* 1999; **135**: 261–265.
43 Begg CB, Hummer AJ, Mujumdar U *et al*. A design for cancer case–control studies using only incident cases: experience with the GEM study of melanoma. *Int J Epidemiol* 2006; **35**: 756–764.
44 Gao XH, Wang LL, Zhang L, Hong YX, Wei H, Chen HD. Familial nevus flammeus associated with early onset cherry angiomas. *Int J Dermatol* 2008; **47**: 1284–1286.
45 Clatterbuck RE, Rigamonti D. Cherry angiomas associated with familial cerebral cavernous malformations. *J Neurosurg* 2002; **96**: 964.
46 Ma HJ, Zhao G, Shi F, Wang YX. Eruptive cherry angiomas associated with vitiligo: provoked by topical nitrogen mustard? *J Dermatol* 2006; **33**: 877–879.
47 Askari N, Vaez-Mahdavi M-R, Moaiedmohseni S *et al*. Association of chemokines and prolactin with cherry angioma in a sulfur mustard exposed population – Sardasht-Iran cohort study. *Int Immunopharmacol* 2013; **17**: 991–995.
48 Zhu L, Zheng S, Wei H *et al*. Multiple cutaneous malignancies and cherry hemangiomas in a vitiligo patient treated with topical nitrogen mustard. *Dermatol Ther* 2014; **27**: 52–54.
49 Raymond LW, Williford LS, Burke WA. Eruptive cherry angiomas and irritant symptoms after one acute exposure to the glycol ether solvent 2-butoxyethanol. *J Occup Environ Med* 1998; **40**: 1059–1064.
50 Cohen AD, Cagnano E, Vardy DA. Cherry angiomas associated with exposure to bromides. *Dermatology* 2001; **202**: 52–53.
51 De Felipe I, Redondo P. Eruptive angiomas after treatment with cyclosporine in a patient with psoriasis. *Arch Dermatol* 1998; **134**: 1487–1488.
52 Borghi A, Benedetti S, Corazza M *et al*. Detection of human herpesvirus 8 sequences in cutaneous cherry angiomas. *Arch Dermatol Res* 2013; **305**: 659–664.
53 Garnis S, Billick RC, Srolovitz H. Eruptive vascular tumors associated with chronic graft-versus-host disease. *J Am Acad Dermatol* 1984; **10**(5 Pt 2): 918–921.
54 Adamski H, Le Gall F, Cartron L *et al*. Eruptive angiomatous lesions associated with graft-versus-host disease. *Br J Dermatol* 2003; **149**: 667–668.
55 Fajgenbaum DC, Rosenbach M, van Rhee F, Nasir A, Reutter J. Eruptive cherry hemangiomatosis associated with multicentric Castleman disease: a case report and diagnostic clue. *JAMA Dermatol* 2013; **149**: 204–208.
56 Borghi A, Minghetti S, Battaglia Y, Corazza M. Predisposing factors for eruptive cherry angiomas: new insights from an observational study. *Int J Dermatol* 2016; **55**: e598–e600.
57 Corazza M, Dika E, Maietti E, Musmeci D, Patrizi A, Borghi A. Eruptive cherry angiomas and skin melanoma: a fortuitous association? *Melanoma Res* 2019; **29**: 313–317.
58 Klebanov N, Lin WM, Artomov M *et al*. Use of targeted next-generation sequencing to identify activating hot spot mutations in cherry angiomas. *JAMA Dermatol* 2019; **155**: 211–215.
59 Johnson TM, Hamilton T, Lowe L. Multiple primary melanomas. *J Am Acad Dermatol* 1998; **39**: 422–427.
60 Giles G, Staples M, McCredie M, Coates M. Multiple primary melanomas: an analysis of cancer registry data from Victoria and New South Wales. *Melanoma Res* 1995; **5**: 433–438.
61 Savoia P, Quaglino P, Verrone A, Bernengo MG. Multiple primary melanomas: analysis of 49 cases. *Melanoma Res* 1998; **8**: 361–366.
62 Moseley HS, Giuliano AE, Storm FK, Clark WH, Robinson DS, Morton DL. Multiple primary melanoma. *Cancer* 1979; **43**: 939–944.
63 McCaul KA, Fritschi L, Baade P, Coory M. The incidence of second primary invasive melanoma in Queensland, 1982–2003. *Cancer Causes Control* 2008; **19**: 451–458.