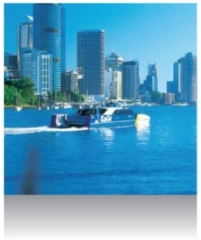
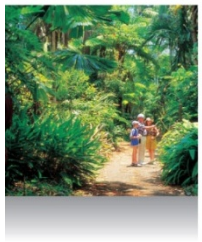





Darwin
Great
Barrier Reef
Queensland
Brisbane
Perth
Adelaide
Sydney
Melbourne
Canberra
Hobart


Hen's


HYPO GROUP


IRONMAN
TRIATHLON
austria
ALGE-TIMING
16.35.38
KÄRNTEN IRONMAN austria
KLAGENFURT
KLEINE ZEITUNG
PUMA
Hypo Group
Hervis
2136
H.-PETER


SSANGYONG
2136 Soyer H.-Peter, Dr. AUT M-50 66
PUMA
KLEINE ZEITUNG

NZ – World Capital of Melanoma

What's New in Melanoma Morphology?

p.soyer@uq.edu.au

telederm@uq.edu.au

THE NEW ZEALAND MEDICAL JOURNAL
Journal of the New Zealand Medical Association

The incidence and thickness of cutaneous malignant melanoma in New Zealand 1994–2004

Ann Richardson, Lynn Fletcher, Mary Jane Sneyd, Brian Cox, Anthony I Reeder

Abstract

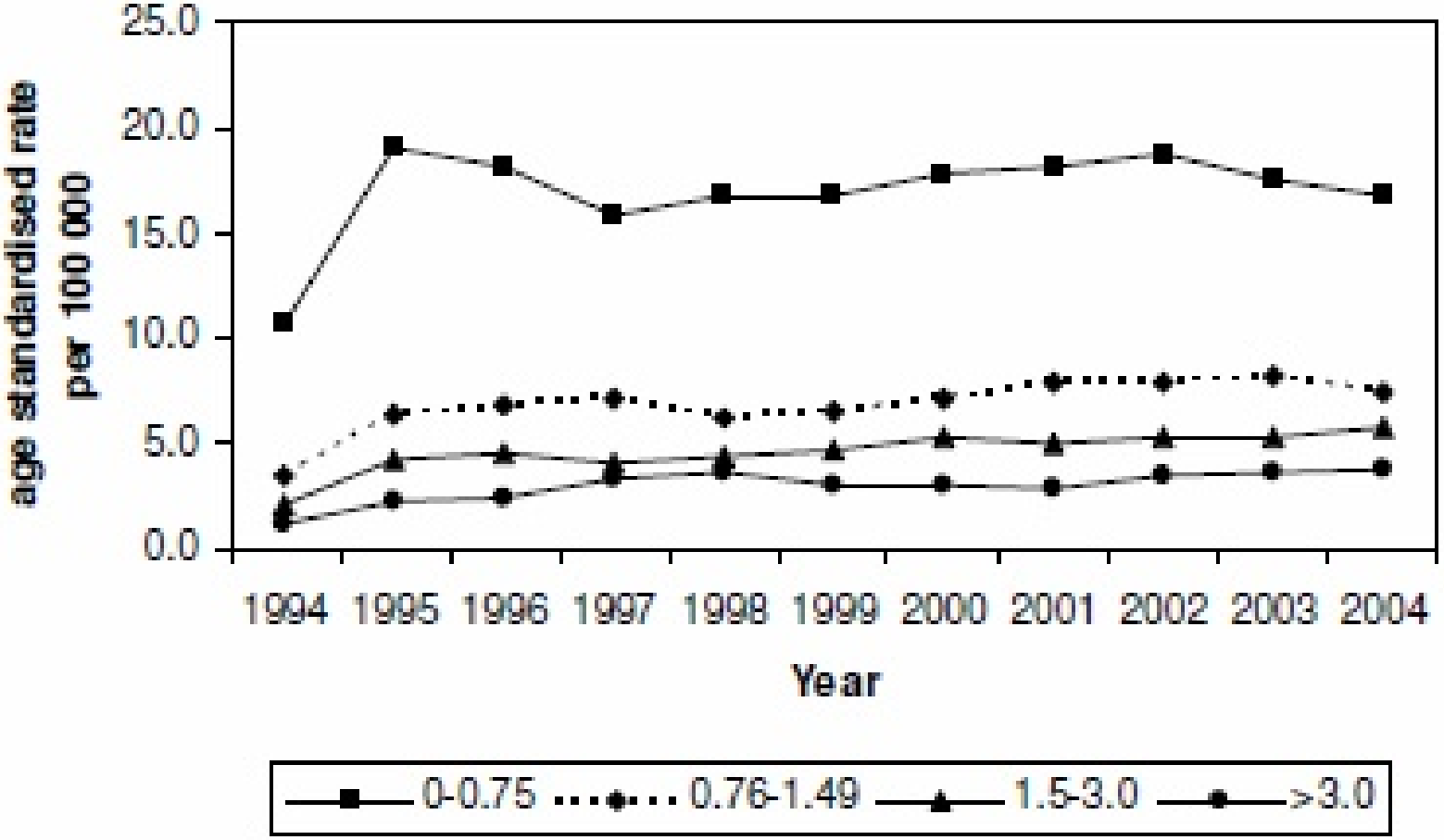
Aim To examine the incidence of thick melanoma in New Zealand from 1994–2004 and investigate associations with melanoma thickness.

Method The New Zealand Health Information Service provided information on all registrations for malignant melanoma from 1994–2004. Age-standardised registration rates were calculated. Logistic regression analysis was undertaken to identify factors associated with melanoma thickness.

Results The incidence of thick melanoma did not decrease during 1994–2004. There were statistically significant associations for age, gender, ethnic group, and type of melanoma with melanoma thickness. Of those diagnosed with melanoma, the proportion with thick melanoma was greater for older than younger people, for males compared with females, for Māori compared with non-Māori (despite the lower incidence in Māori), and for those diagnosed with nodular melanoma compared with other types of melanoma.

Conclusion Strategies to encourage the early detection of melanoma in New Zealand have not yet reduced the incidence of thick melanomas. This may be because it is too soon to see the impact of early detection, or because early detection strategies predominantly identify melanomas that are unlikely to progress, but miss thicker nodular melanomas.

NZMJ 8 August 2008, Vol 121 No 1279


25.0
20.0
15.0
10.0
5.0
0.0
age standardised rate per 100 000
1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004
Year
0-0.75
0.76-1.49
1.5-3.0
>3.0

What's New in Melanoma?

- Dermoscopy
- Clinicopathologic Correlation
- Melanoma Clasification
- Field Cells

Morphologic Dimension

What is your diagnosis?

International Dermoscopy Diploma

Medical University Graz

- Start
- Why dermoscopy?
- Approaches
- Recognition process
- What is your diagnosis?

WHAT IS YOUR DIAGNOSIS?

Click on the correct answer?

- Melanoma
- Benign Nevus
- I don't know!

Morphologic Dimension

What is your diagnosis?

International Dermoscopy Diploma

Medical University Graz

- Start
- Why dermoscopy?
- Approaches
- Recognition process
- What is your diagnosis?

WHAT IS YOUR DIAGNOSIS?

[Hover over the cities to explore Austria]

This is the AUSTRIAN NEVUS ...

EPIDEMIOLOGY AND HEALTH SERVICES RESEARCH

BJD British Journal of Dermatology

Systematic review of dermoscopy and digital dermoscopy/ artificial intelligence for the diagnosis of melanoma

S.M. Rajpara,* A.P. Botello,† J. Townend† and A.D. Ormerod*‡

*Department of Dermatology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, U.K.
†Department of Public Health, University of Aberdeen, Aberdeen, U.K.
‡Department of Medicine and Therapeutics, University of Aberdeen, Aberdeen, U.K.

Correspondence
Sanjay Rajpara.
E-mail: sanjay.rajpara@nhs.net

Accepted for publication
18 September 2008

Key words
artificial intelligence, dermoscopy, digital dermoscopy, melanoma, systematic review

Conflicts of interest
None declared.

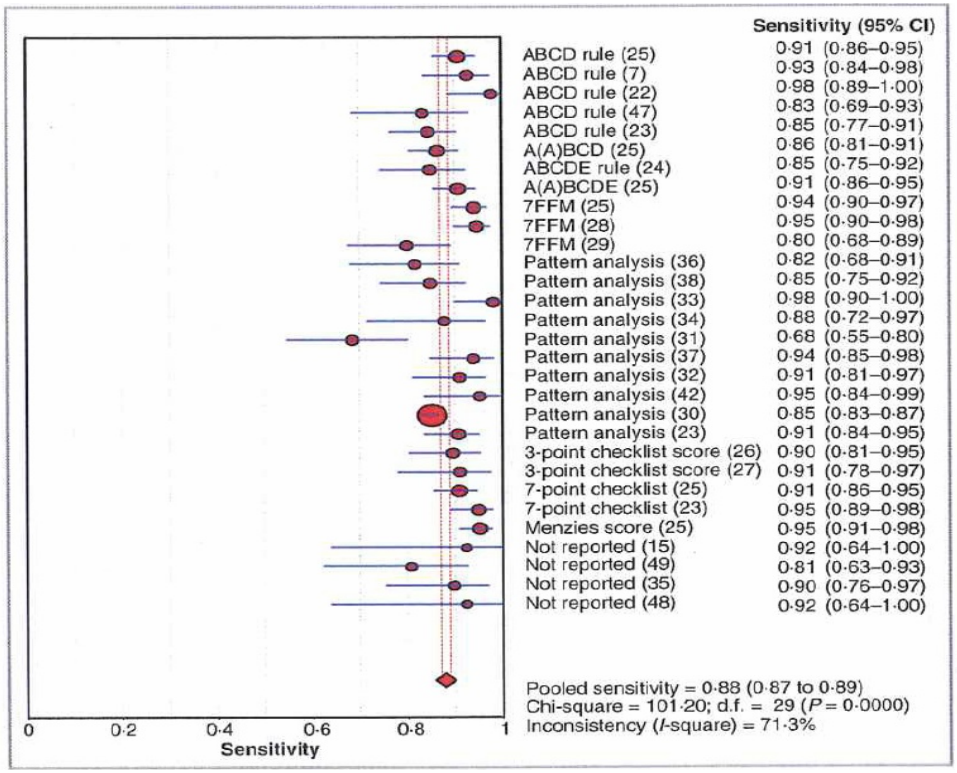
DOI 10.1111/j.1365-2133.2009.09093.x

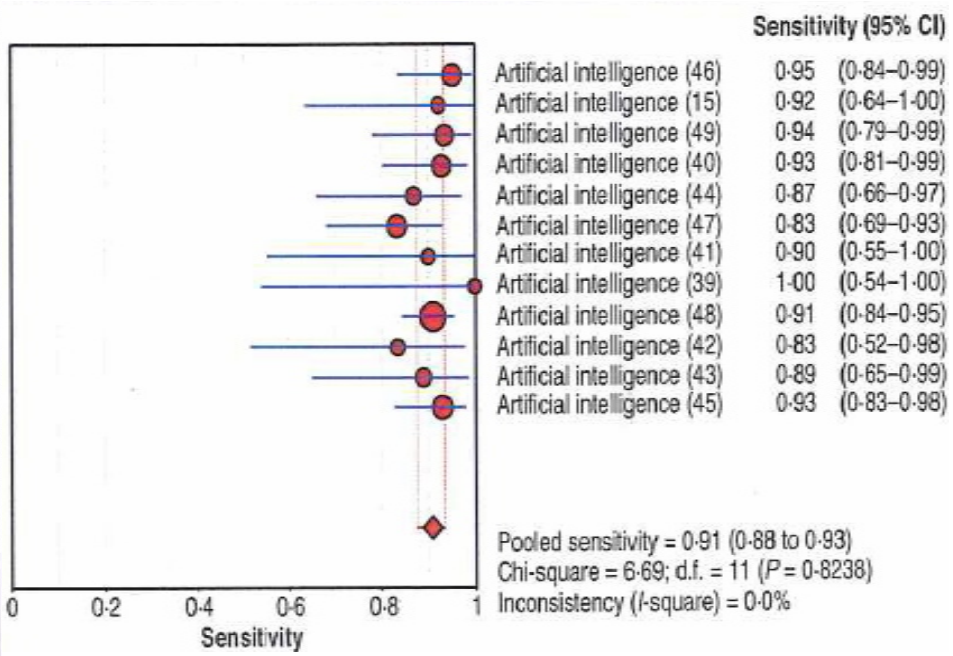
Summary

Background Dermoscopy improves diagnostic accuracy of the unaided eye for melanoma, and digital dermoscopy with artificial intelligence or computer diagnosis has also been shown useful for the diagnosis of melanoma. At present there is no clear evidence regarding the diagnostic accuracy of dermoscopy compared with artificial intelligence.

Objectives To evaluate the diagnostic accuracy of dermoscopy and digital dermoscopy/artificial intelligence for melanoma diagnosis and to compare the diagnostic accuracy of the different dermoscopic algorithms with each other and with digital dermoscopy/artificial intelligence for the detection of melanoma.

Methods A literature search on dermoscopy and digital dermoscopy/artificial intelligence for melanoma diagnosis was performed using several databases. Titles and abstracts of the retrieved articles were screened using a literature evaluation form. A quality assessment form was developed to assess the quality of the included studies. Heterogeneity among the studies was assessed. Pooled data were analysed using meta-analytical methods and comparisons between different algorithms


Sensitivity (95% CI)
ABCD rule (25) 0·91 (0·86–0·95)
ABCD rule (7) 0·93 (0·84–0·98)
ABCD rule (22) 0·98 (0·89–1·00)
ABCD rule (47) 0·83 (0·69–0·93)
ABCD rule (23) 0·85 (0·77–0·91)
A(A)BCD (25) 0·86 (0·81–0·91)
ABCDE rule (24) 0·85 (0·75–0·92)
A(A)BCDE (25) 0·91 (0·86–0·95)
7FFM (25) 0·94 (0·90–0·97)
7FFM (28) 0·95 (0·90–0·98)
7FFM (29) 0·80 (0·68–0·89)
Pattern analysis (36) 0·82 (0·68–0·91)
Pattern analysis (38) 0·85 (0·75–0·92)
Pattern analysis (33) 0·98 (0·90–1·00)
Pattern analysis (34) 0·88 (0·72–0·97)
Pattern analysis (31) 0·68 (0·55–0·80)
Pattern analysis (37) 0·94 (0·85–0·98)
Pattern analysis (32) 0·91 (0·81–0·97)
Pattern analysis (42) 0·95 (0·84–0·99)
Pattern analysis (30) 0·85 (0·83–0·87)
Pattern analysis (23) 0·91 (0·84–0·95)
3-point checklist score (26) 0·90 (0·81–0·95)
3-point checklist score (27) 0·91 (0·78–0·97)
7-point checklist (25) 0·91 (0·86–0·95)
7-point checklist (23) 0·95 (0·89–0·98)
Menzies score (25) 0·95 (0·91–0·98)
Not reported (15) 0·92 (0·64–1·00)
Not reported (49) 0·81 (0·63–0·93)
Not reported (35) 0·90 (0·76–0·97)
Not reported (48) 0·92 (0·64–1·00)
Pooled sensitivity = 0·88 (0·87 to 0·89)
Chi-square = 101·20; d.f. = 29 (P = 0·0000)
Inconsistency (I-square) = 71·3%
0
0·2
0·4
0·6
0·8
1
Sensitivity


Sensitivity (95% CI)
Artificial intelligence (46) 0·95 (0·84–0·99)
Artificial intelligence (15) 0·92 (0·64–1·00)
Artificial intelligence (49) 0·94 (0·79–0·99)
Artificial intelligence (40) 0·93 (0·81–0·99)
Artificial intelligence (44) 0·87 (0·66–0·97)
Artificial intelligence (47) 0·83 (0·69–0·93)
Artificial intelligence (41) 0·90 (0·55–1·00)
Artificial intelligence (39) 1·00 (0·54–1·00)
Artificial intelligence (48) 0·91 (0·84–0·95)
Artificial intelligence (42) 0·83 (0·52–0·98)
Artificial intelligence (43) 0·89 (0·65–0·99)
Artificial intelligence (45) 0·93 (0·83–0·98)
Pooled sensitivity = 0·91 (0·88 to 0·93)
Chi-square = 6·69; d.f. = 11 (P = 0·8238)
Inconsistency (I-square) = 0·0%
0
0·2
0·4
0·6
0·8
1
Sensitivity

420 Dermatologists
for 21 Mill inhabitants
in Australia

850 Dermatologists
for 8 Mill inhabitants
in Austria

Dermoscopic features of melanomas associated with *MC1R* variants in Spanish *CDKN2A* mutation carriers

F. Cuéllar,*† S. Puig,*‡ I. Kolm,* J. Puig-Butille,‡§ P. Zaballos,¶ R. Martí-Laborda,** C. Badenas‡§ and J. Malvehy*‡

*Melanoma Unit, Department of Dermatology and §Department of Molecular Genetics, IDIBAPS, Hospital Clínic Barcelona, 08036 Barcelona, Spain
†CONACYT, Mexico
‡U726 CIBERER, ISCIII, Barcelona, Spain
¶Department of Dermatology, Hospital Santa Tecla, Tarragona, Spain
**Department of Dermatology, Hospital Universitari Arnau de Vilanova, Universitat de Lleida, Lleida, Spain

Correspondence
Susana Puig.
E-mail: spuig@clinic.ub.es

Accepted for publication
7 July 2008

Key words
CDKN2A, dermoscopy, MC1R, melanoma, red hair, total dermoscopy score

Conflicts of interest
None declared.

F.C., S.P. and I.K. contributed equally to the development of the manuscript.

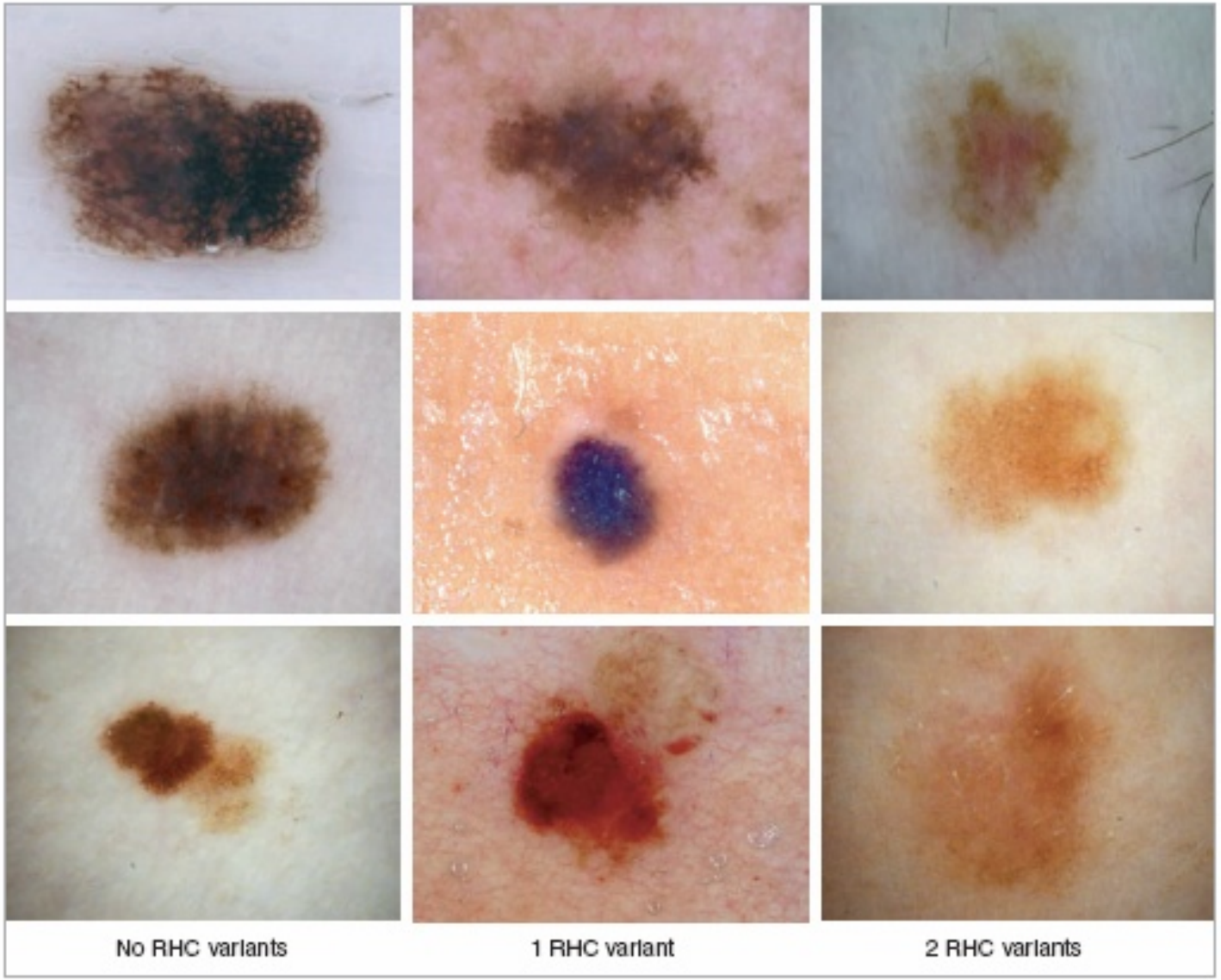
DOI 10.1111/j.1365-2133.2008.08826.x

Summary

Background The presence of at least one MC1R gene variant is associated with a reduction in age at melanoma diagnosis in families with *CDKN2A* mutations.
Objectives To describe dermoscopic features of early melanoma in *CDKN2A* gene mutation-positive Spanish individuals and to evaluate the possibility of a correlation between particular dermatoscopic pattern and MC1R gene variants.
Methods Patients in whom a melanoma was diagnosed during specific follow up of high-risk individuals carrying *CDKN2A* mutations (with familial or personal history of previous melanoma) were included in this study. The decision to remove such melanomas was taken on the basis of history, clinical and dermoscopic evaluations including total body photography and digital dermoscopy.
Results Of the nine patients included in this study, three were noncarriers of the red hair MC1R polymorphism, three patients had one red hair MC1R polymorphism and three patients had two red hair MC1R polymorphisms. On dermoscopic analysis of suspect melanocytic lesions we found that the mean ± SD ABCD total dermoscopy score (TDS) was significantly higher in noncarriers of red hair MC1R polymorphisms than in carriers of two MC1R gene red hair variants (6·8 ± 0·4 vs. 4·4 ± 0·9; P = 0·014).

Patient	Sex	Age (years)	Familial MM	Skin colour	Hair colour	Eye colour	MM localization	Histology	Breslow thickness (mm)	Clark level	*CDKN2A* mutation	RHC variants
1	F	47	Yes	Very fair	Red	Green/hazel	Extremities (lower limb)	*In situ*	–	I	G101W	R151C, D294H
2	F	27	Yes	Fair	Blond	Green/hazel	Trunk (back)	Malignant blue naevus	–	–	358delG	R160W
3	M	39	No	Fair	Brown	Green/hazel	Trunk (back)	SSMM	0·5	II	G101W	R151C
4	F	35	Yes	Olive	Brown	Brown	Extremities (lower limb)	SSMM	0·5	II	L65P	–
5	F	53	Yes	Olive	Brown	Green/hazel	Extremities (lower limb)	*In situ*	–	I	G101W	–
6	M	46	Yes	Very fair	Red	Green/hazel	Extremities (lower limb)	SSMM	0·5	II	G101W	R151C (homozygous)
7	M	52	Yes	Fair	Brown	Brown	Trunk (back)	SSMM	0·5	II	R87W	–
8	F	23	Yes	Very fair	Red	Green/hazel	Extremities (lower limb)	*In situ*	–	I	G101W	R160W, R151C
9	M	35	Yes	Fair	Red	Green/hazel	Trunk (lateral thorax)	*In situ*	–	I	358delG	R160W

MM, malignant melanoma; SSMM, superficial spreading MM.


No RHC variants
1 RHC variant
2 RHC variants

CONCISE COMMUNICATION

BJD British Journal of Dermatology

Dermoscopic patterns and subclinical melanocytic nests in normal-appearing skin

A. Scope, A.A. Marghoob, C.S. Chen, J.A. Lieb, M.A. Weinstock* and A.C. Halpern for the SONIC Study Group

Dermatology Service, Memorial Sloan-Kettering Cancer Center, 160 East 53rd Street, 2nd Floor, New York, NY 10022, U.S.A.
*Dermatoepidemiology Unit, VA Medical Center and Department of Dermatology, Rhode Island Hospital and Brown University, Providence, RI, U.S.A.

Correspondence
Allan C. Halpern.
E-mail: halperna@mskcc.org

Accepted for publication
19 October 2008

Key words
children, dermoscopy, skin

Conflicts of interest
None declared.

Additional members of the SONIC Study Group are listed at the end of the article.

DOI 10.1111/j.1365-2133.2009.09073.x

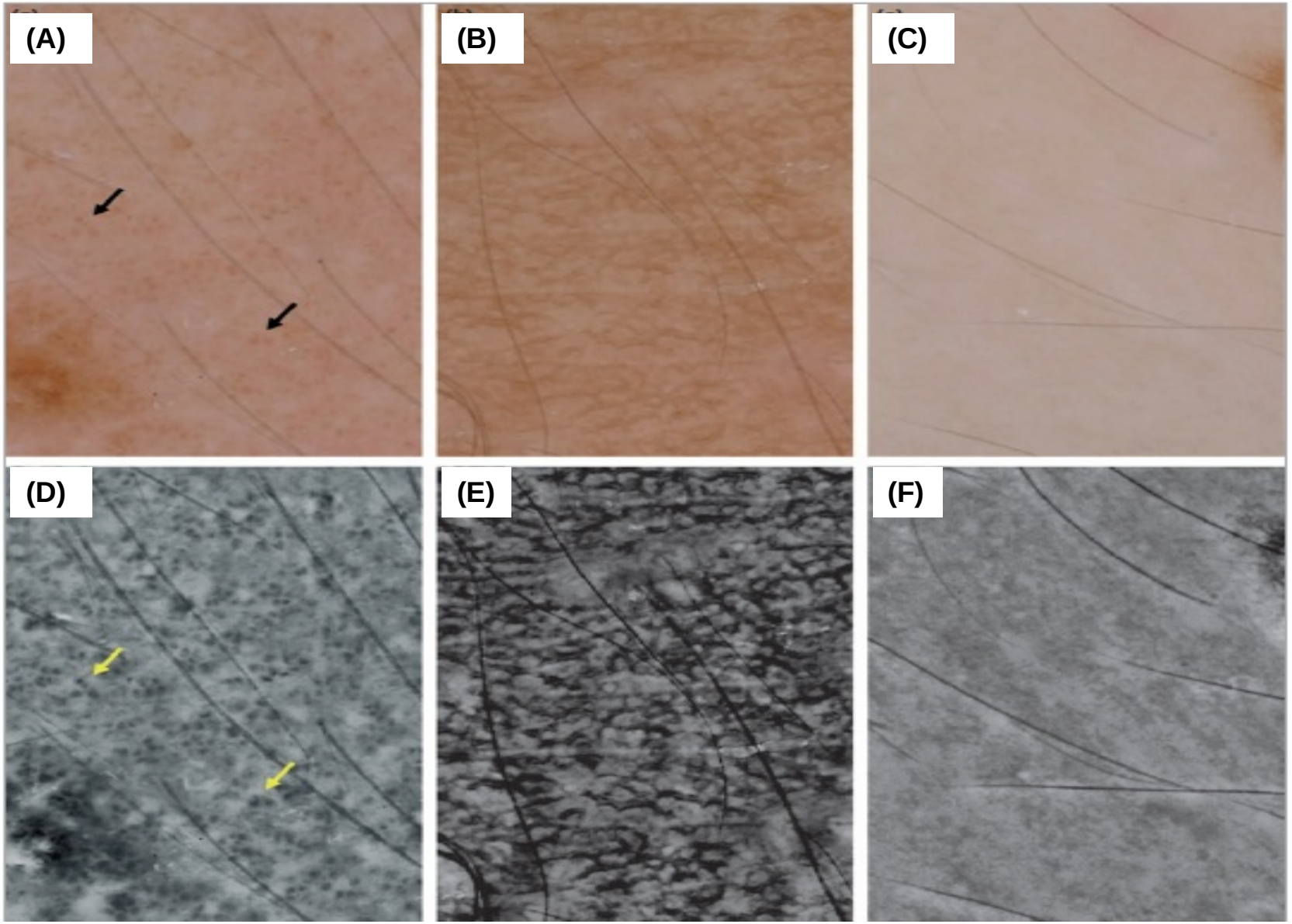
Summary

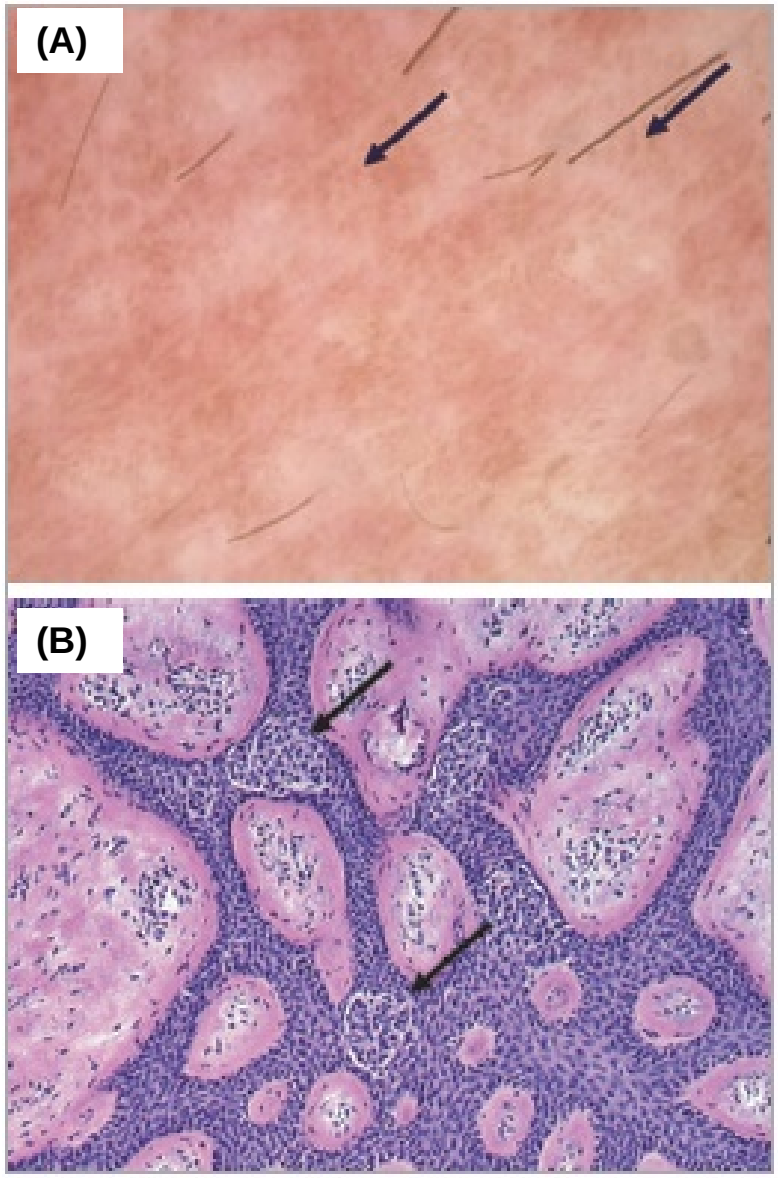
Background Dermoscopic patterns of normal-appearing skin have received little scrutiny. We have recently completed an analysis of dermoscopic patterns of naevi in children.

Objectives To describe dermoscopic patterns in the normal-appearing skin surrounding naevi and to explore histological features of patterned background skin.

Methods Dermoscopic images of back naevi were obtained from a population-based sample of fifth grade students. The dermoscopic pattern of the background skin around the naevi was analysed. We examined histopathological features of background skin patterns in a convenience sample of seven specimens from six adult patients.

Results We observed a dermoscopic pattern in the background of normal-appearing skin in 41% of 1192 dermoscopic images from the backs of the 443 children. The background skin pattern was less frequent in individuals with a fair skin ($P < 0{\cdot}001$). A globular pattern was observed in 201 images (17%) and a reticular pattern was seen in 287 images (24%), of which 112 images also showed globules. Inter-rater reliability between the two observers for a random


(A)
(B)
(C)
(D)
(E)
(F)


(A)
(B)

'On a clear day you can see forever.'

OPEN ACCESS Freely available online

PLoS one

The Influence of Clinical Information in the Histopathologic Diagnosis of Melanocytic Skin Neoplasms

Gerardo Ferrara[1], Zsolt Argenyi[2], Giuseppe Argenziano[3], Rino Cerio[4], Lorenzo Cerroni[5], Arturo Di Blasi[1], Elisa A. A. Feudale[6], Caterina M. Giorgio[3], Cesare Massone[5], Oscar Nappi[7], Carlo Tomasini[8], Carmelo Urso[9], Iris Zalaudek[5], Harald Kittler[10], H. Peter Soyer[11]*

1 Department of Pathology, Gaetano Rummo General Hospital, Benevento, Italy, **2** Department of Dermatology, University of Washington, Seattle, Washington, United States of America, **3** Department of Dermatology, Second University of Naples, Naples, Italy, **4** Department of Dermatology, University of London, London, United Kingdom, **5** Department of Dermatology, Medical University of Graz, Graz, Austria, **6** Department of Pathology, Basilicata Oncology Reference Centre, Rionero in Vulture, Italy, **7** Department of Pathology, Antonio Cardarelli General Hospital, Naples, Italy, **8** Department of Biomedical Sciences and Human Oncology, Second Dermatologic Division, University of Turin, Turin, Italy, **9** Department of Pathology, Dermatopathology Section, S.M. Annunziata Hospital, Florence, Italy, **10** Department of Dermatology, Division of General Dermatology, Medical University of Vienna, Vienna, Austria, **11** Dermatology Research Centre, The University of Queensland, School of Medicine, Princess Alexandra Hospital, Brisbane, Australia

Abstract

Background: We tested the relevance of clinical information in the histopathologic evaluation of melanocytic skin neoplasm (MSN).

- 99 equivocal melanocytic lesions

D1: Diagnosis with no information available

D2: Diagnosis with knowledge of age, sex and location

D3: Diagnosis with knowledge of the clinical diagnosis

D4: Diagnosis with clinical image

D5: Diagnosis with dermoscopic image

Table 1. Agreement (kappa) at every stage of diagnosis and number of "unknowns".

	Overall Agreement (Kappa)	95% CI	Agreement for category nevus (kappa)	95% CI	Agreement for category melanoma (kappa)	95%CI	Category "Unknown" (n)
D1	0,57	0,54–0,60	0,58	0,43–0,74	0,63	0,51–0,76	32
D2	0,64	0,61–0,66	0,64	0,48–0,79	0,66	0,53–0,78	9
D3	0,65	0,62–0,67	0,64	0,49–0,80	0,67	0,54–0,79	7
D4	0,66	0,64–0,69	0,67	0,51–0,82	0,67	0,54–0,80	3
D5	0,67	0,64–0,70	0,67	0,51–0,83	0,67	0,54–0,80	1

doi:10.1371/journal.pone.0005375.t001

Table 2. Change of diagnosis following provision of clinical information.

Diagnostic change		Diagnostic information				
		D2	D3	D4	D5	Total
Into benign	*Unknown to naevus*	14	1	3	2	20
	Melanoma to naevus	12	4	4	3	23
Into malignant	*Unknown to melanoma*	11	0	1	0	12
	Naevus to melanoma	11	3	11	6	31
Into unknown	*Nevus to unknown*	0	0	0	0	0
	Melanoma to unknown	1	0	0	0	1
	Total	49	8	19	11	87

doi:10.1371/journal.pone.0005375.t002

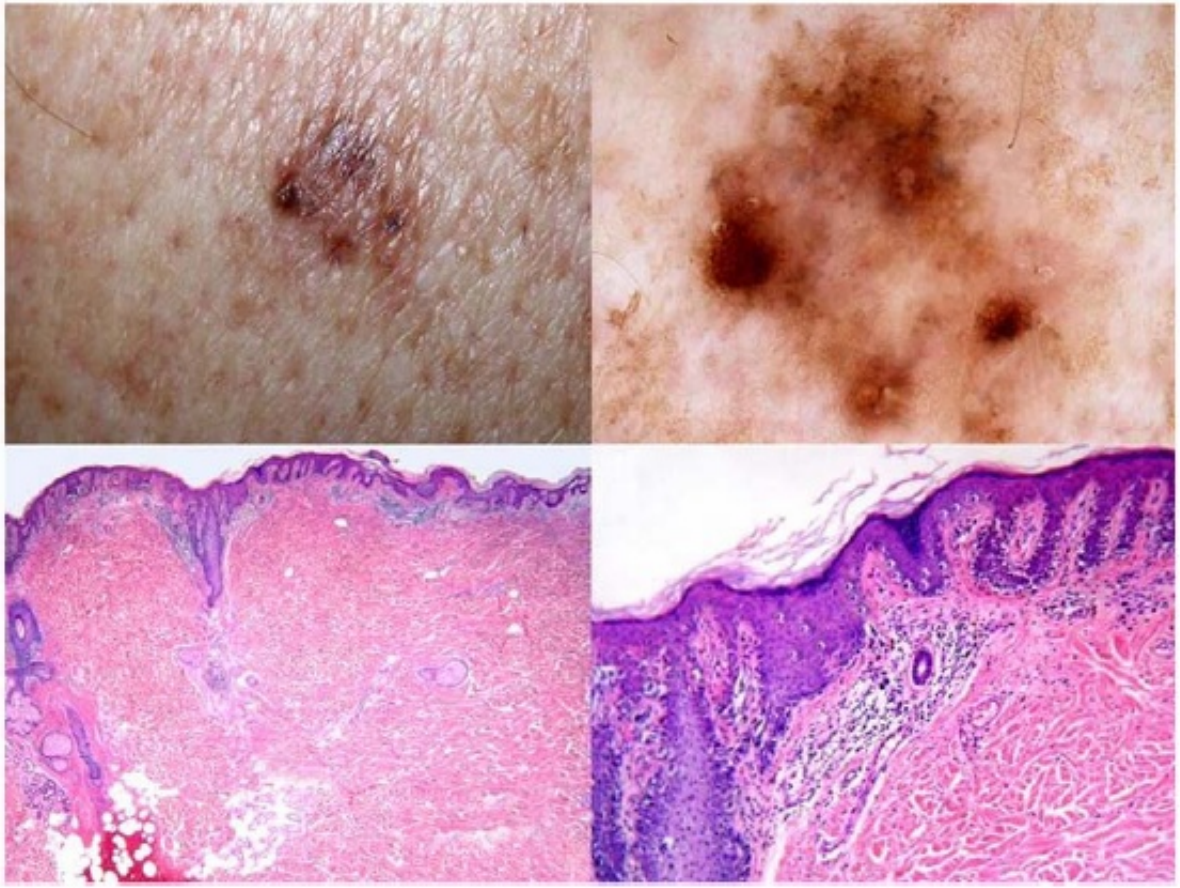


Figure 1. A 69-year-old man with a lesion from the back showing clinical (top left) and dermoscopic (top right) features of regression [16]. Histopathologically, the lesion is medium to large in size and shows a regular epidermal hyperplasia (bottom left). The main feature of atypia is the presence of areas of prevailing single cell proliferation at the junction (bottom right). Lentiginous melanocytic proliferations of the elderly are often controversial from both a both conceptual and a practical point of view. The lesion at issue was diagnosed as melanoma in situ, lentiginous type, [19] by six histopathologists in D1 and by eight histopathologists in D5.
doi:10.1371/journal.pone.0005375.g001

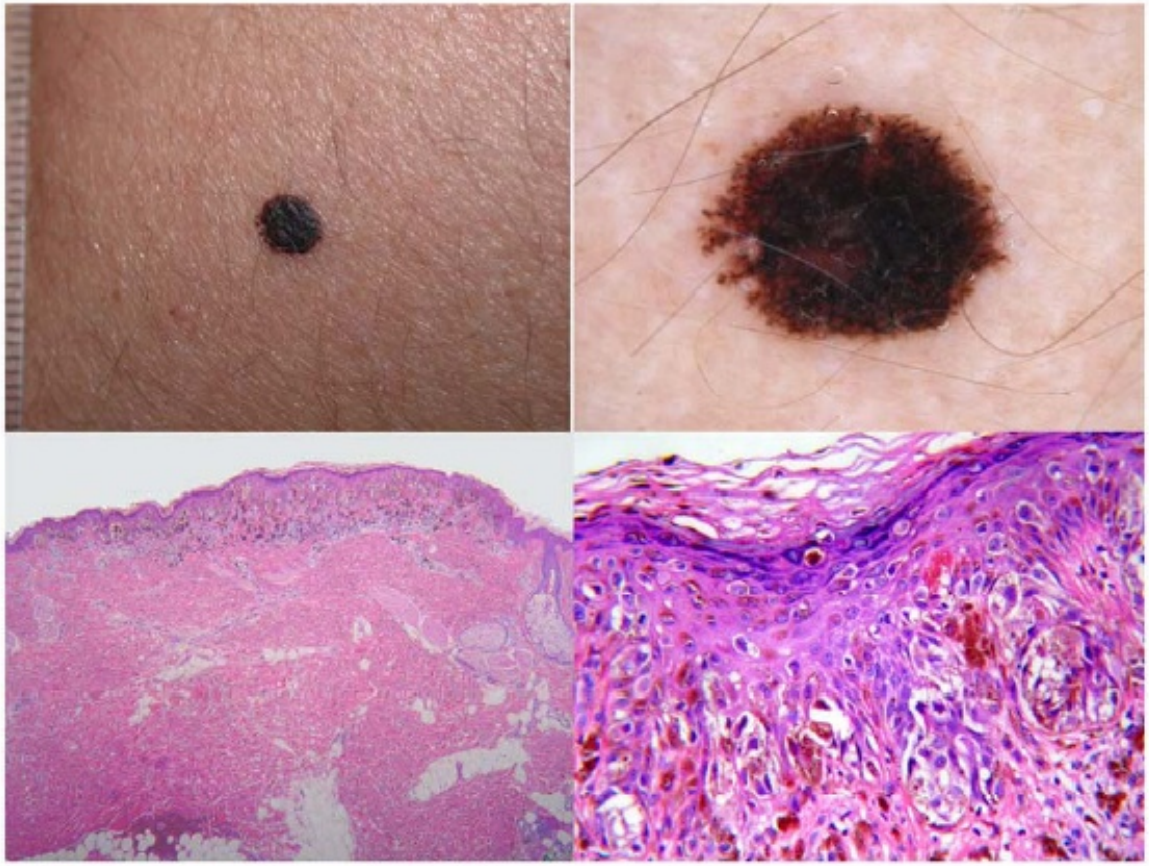
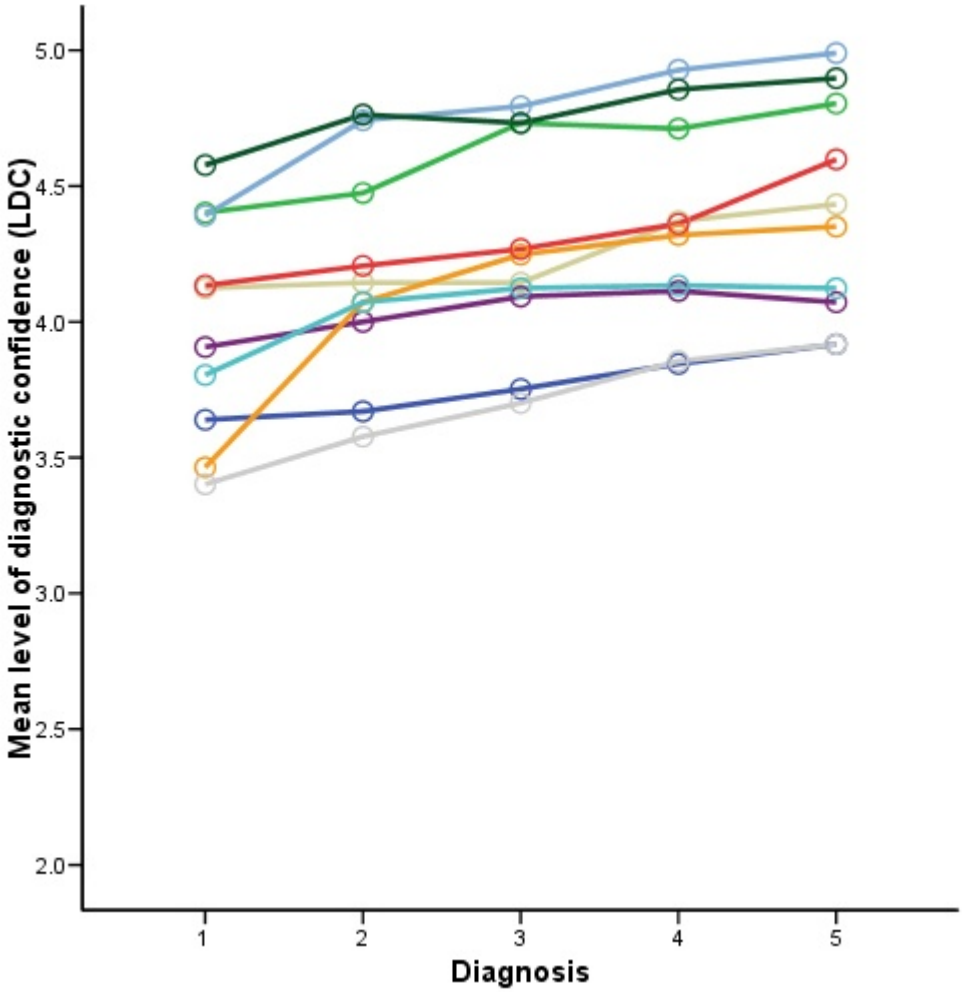


Figure 2. A 20-year-old woman with a lesion from the leg showing clinical (top left) and dermoscopic (top right) features consistent with pigmented Spitz naevus [18]. Histopathology revealed a sharply circumscribed, medium-sized lesion which was mainly characterized by nests of melanocytes at the junction (bottom left; haematoxylin-eosin, ×40). However, in some worrisome microscopic fields, melanocytes at all levels of the epidermis were seen (bottom right; haematoxylin-eosin, ×250). Due to these conflicting features, in the absence of any clinical information the lesion was diagnosed as melanoma by three histopathologists and as naevus by seven histopathologists. With the knowledge of the complete clinical information, the lesion was finally diagnosed as benign by all the histopathologists.
doi:10.1371/journal.pone.0005375.g002

Increase of Level of Diagnostic Confidence



Conclusion

The histopathologic criteria for the diagnosis of MSN can work as such, but the final histopathologic diagnosis is a clinically-aided interpretation.

Clinical data sometimes reverse the initial histopathologic evaluation.

The Histogenesis and Biologic Behavior of Primary Human Melanomas of the Skin

Clark WH Jr and colleagues 1969

- Superficial Spreading Melanoma (SSM)
- Nodular Melanoma (NM)
- Lentigo Maligna Melanoma (LMM)
- Acral Lentiginous Melanoma (ALM)

No significant difference in overall survival or treatment responses between categories when tumors of equivalent tumor thickness were compared

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Distinct Sets of Genetic Alterations in Melanoma

John A. Curtin, Ph.D., Jane Fridlyand, Ph.D., Toshiro Kageshita, M.D., Hetal N. Patel, M.S., Klaus J. Busam, M.D., Heinz Kutzner, M.D., Kwang-Hyun Cho, M.D., Setsuya Aiba, M.D., Ph.D., Eva-Bettina Bröcker, M.D., Philip E. LeBoit, M.D., Dan Pinkel, Ph.D., and Boris C. Bastian, M.D.

ABSTRACT

BACKGROUND

Exposure to ultraviolet light is a major causative factor in melanoma, although the relationship between risk and exposure is complex. We hypothesized that the clinical heterogeneity is explained by genetically distinct types of melanoma with different susceptibility to ultraviolet light.

METHODS

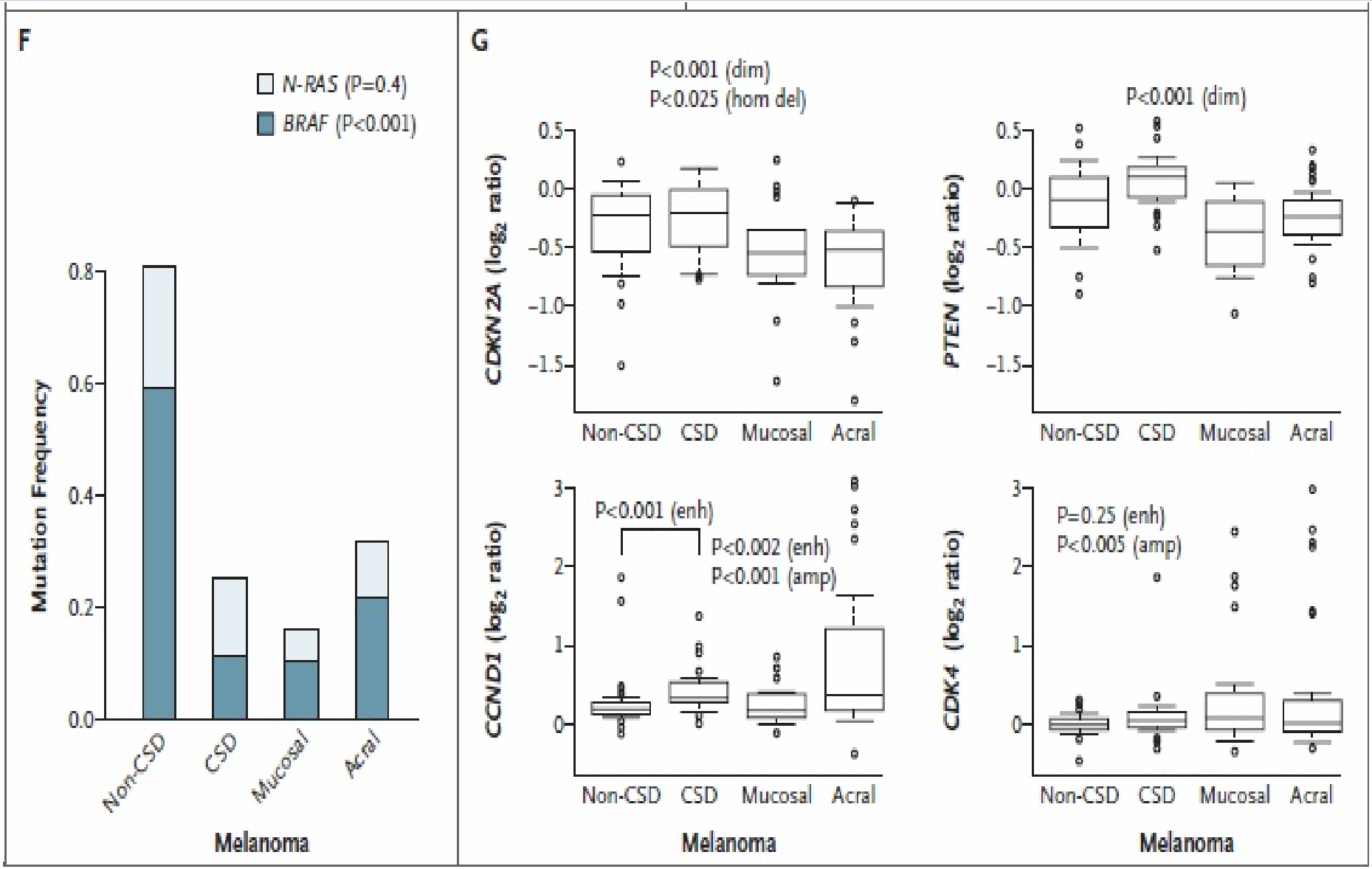
We compared genome-wide alterations in the number of copies of DNA and mutational status of *BRAF* and *N-RAS* in 126 melanomas from four groups in which the degree of exposure to ultraviolet light differs: 30 melanomas from skin with chronic sun-induced damage and 40 melanomas from skin without such damage; 36 melanomas from palms,

From the Comprehensive Cancer Center (J.A.C., J.F., H.N.P., D.P., B.C.B.) and the Departments of Epidemiology and Biostatistics (J.F.) and Dermatology and Pathology (P.E.L., B.C.B.), University of California, San Francisco, San Francisco; the Department of Dermatology, Kumamoto University School of Medicine, Kumamoto, Japan (T.K.); the Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York (K.J.B.); DermPath, Friedrichshafen, Germany (H.K.); the Department of Dermatology, Seoul National University College of Medicine, Seoul, South Korea

New Melanoma Classification?

Curtin JA and colleagues 2005

- Melanoma arising on skin with evidence of chronic sun-induced damage (CSD Melanoma)
- Melanoma arising on skin without evidence of chronic sun-induced damage (non-CSD Melanoma)
- Acral Melanoma
- Mucosal Melanoma


F
N-RAS (P=0.4)
BRAF (P<0.001)
Mutation Frequency
0.8
0.6
0.4
0.2
0.0
Non-CSD
CSD
Mucosal
Acral
Melanoma
G
P<0.001 (dim)
P<0.025 (hom del)
CDKN 2A (log2 ratio)
0.5
0.0
-0.5
-1.0
-1.5
Non-CSD CSD Mucosal Acral
P<0.001 (dim)
PTEN (log2 ratio)
0.5
0.0
-0.5
-1.0
-1.5
Non-CSD CSD Mucosal Acral
P<0.001 (enh)
P<0.002 (enh)
P<0.001 (amp)
CCND1 (log2 ratio)
3
2
1
0
Non-CSD CSD Mucosal Acral
Melanoma
P=0.25 (enh)
P<0.005 (amp)
CDK4 (log2 ratio)
3
2
1
0
Non-CSD CSD Mucosal Acral
Melanoma

Melanocytic Nevi, Solar Keratoses, and Divergent Pathways to Cutaneous Melanoma

David C. Whiteman, Peter Watt, David M. Purdie, Maria Celia Hughes, Nicholas K. Hayward, Adèle C. Green

Background: Some melanomas form on sun-exposed body sites, whereas others do not. We previously proposed that melanomas at different body sites arise through different pathways that have different associations with melanocytic nevi and solar keratoses. We tested this hypothesis in a case–case comparative study of melanoma patients in Queensland, Australia. *Methods:* We randomly selected patients from among three prespecified groups reported to the population-based Queensland Cancer Registry: those with superficial spreading or nodular melanomas of the trunk (n = 154, the reference group), those with such melanomas of the head and neck (n = 77, the main comparison group), and those with lentigo maligna melanoma (LMM) (n = 75, the chronic sun-exposed group). Each participant completed a questionnaire, and a research nurse counted melanocytic nevi and solar keratoses. We calculated exposure odds ratios (ORs) and 95% confidence intervals (CIs) to quantify the association between factors of interest and each melanoma group. *Results:* Patients with head and neck melanomas, compared with patients with melanomas of the trunk, were statistically significantly less likely to have more than 60 nevi (OR = 0.34, 95% CI = 0.15 to 0.79) but were statistically significantly more likely to have more than 20 solar keratoses (OR = 3.61, 95% CI = 1.42 to 9.17) and also tended to have a past history of excised solar skin lesions (OR = 1.87, 95% CI = 0.89 to 3.92). Patients with LMM were also less likely than patients with truncal melanomas to have more than 60 nevi (OR = 0.32, 95% CI = 0.14 to 0.75) and tended toward more solar keratoses (OR = 2.14, 95% CI = 0.88 to 5.16). *Conclusions:* Prevalences of nevi and solar keratoses differ markedly between patients with head and neck melanomas or LMM and patients with melanomas of the trunk. Cutaneous melanomas may arise through two pathways, one associated with melanocyte proliferation and the other with chronic exposure to sunlight. [J Natl Cancer Inst 2003;95: 806–12]

involving disruption of one or more molecular, cellular, and immunologic control mechanisms.

We have previously suggested a "divergent pathway" model for the development of cutaneous melanoma *(9)*. Under this model, people with an inherently low propensity for melanocyte proliferation require chronic sun exposure to drive clonal expansion of transformed epidermal melanocytes. If we assume that the hypothesis is correct, then melanomas arising in this group of people should occur on habitually sun-exposed body sites such as the face. In contrast, among people with an inherently high propensity for melanocyte proliferation (as characterized by high nevus counts), we predict that exposure to sunlight is required early in the process of carcinogenesis, after which host factors drive melanoma development. This group of patients would be expected to have less solar damage than the former group of melanoma patients and would be expected to develop their tumors on body sites with unstable melanocyte populations such as the trunk. We tested this divergent pathway hypothesis for the development of melanoma according to anatomical site in a population-based epidemiologic study.

Patients and Methods

We used a case–case study design to test our hypothesis, in which one group of patients with melanoma served as the reference group (*see* below) to which all other groups of patients were compared. Patients with incident cases of cutaneous melanoma were ascertained from the computerized records of the Queensland Cancer Registry (notification of melanoma is compulsory). Approval to undertake the study was granted by the Queensland Institute of Medical Research Human Research Ethics Committee.

Patients

Patients eligible for inclusion in the study were all residents of the greater Brisbane region (population = 1.5 million; latitude = 27°S) who had their first histologic diagnosis of primary cutaneous melanoma between January 1, 1998, and December

OPEN ACCESS Freely available online

PLOS MEDICINE

Improving Melanoma Classification by Integrating Genetic and Morphologic Features

Amaya Viros[1], Jane Fridlyand[2,3], Juergen Bauer[1], Konstantin Lasithiotakis[4], Claus Garbe[4], Daniel Pinkel[2,5], Boris C. Bastian[1,2,6*]

1 Department of Dermatology, University of California San Francisco, San Francisco, California, United States of America, **2** University of California San Francisco (UCSF) Comprehensive Cancer Center, University of California San Francisco, San Francisco, California, United States of America, **3** Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, United States of America, **4** Department of Dermatology, University of Tübingen, Tübingen, Germany, **5** Department of Laboratory Medicine, University of California San Francisco, San Francisco, California, United States of America, **6** Department of Pathology, University of California San Francisco, San Francisco, California, United States of America

Funding: Supported by grants from the National Cancer Institute (P01 CA025874, R01 CA094963). The funding agency did not have a role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Academic Editor: Jonathan Rees, University of Edinburgh, United Kingdom

Citation: Viros A, Fridlyand J, Bauer

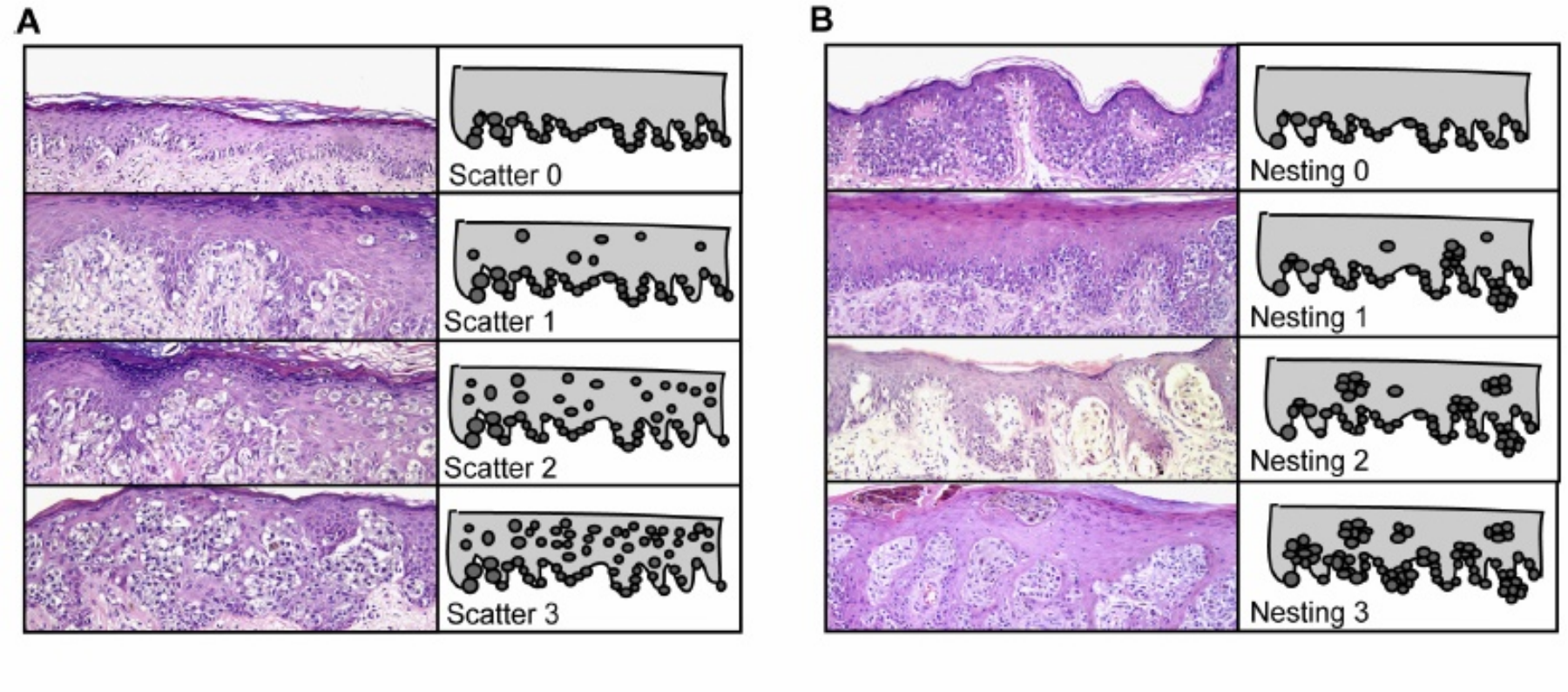
ABSTRACT

Background

In melanoma, morphology-based classification systems have not been able to provide relevant information for selecting treatments for patients whose tumors have metastasized. The recent identification of causative genetic alterations has revealed mutations in signaling pathways that offer targets for therapy. Identifying morphologic surrogates that can identify patients whose tumors express such alterations (or functionally equivalent alterations) would be clinically useful for therapy stratification and for retrospective analysis of clinical trial data.

Methodology/Principal Findings

Morphogenetic Correlation of Melanoma



Phenotypic characteristics will become surrogate markers for genetic knowledge

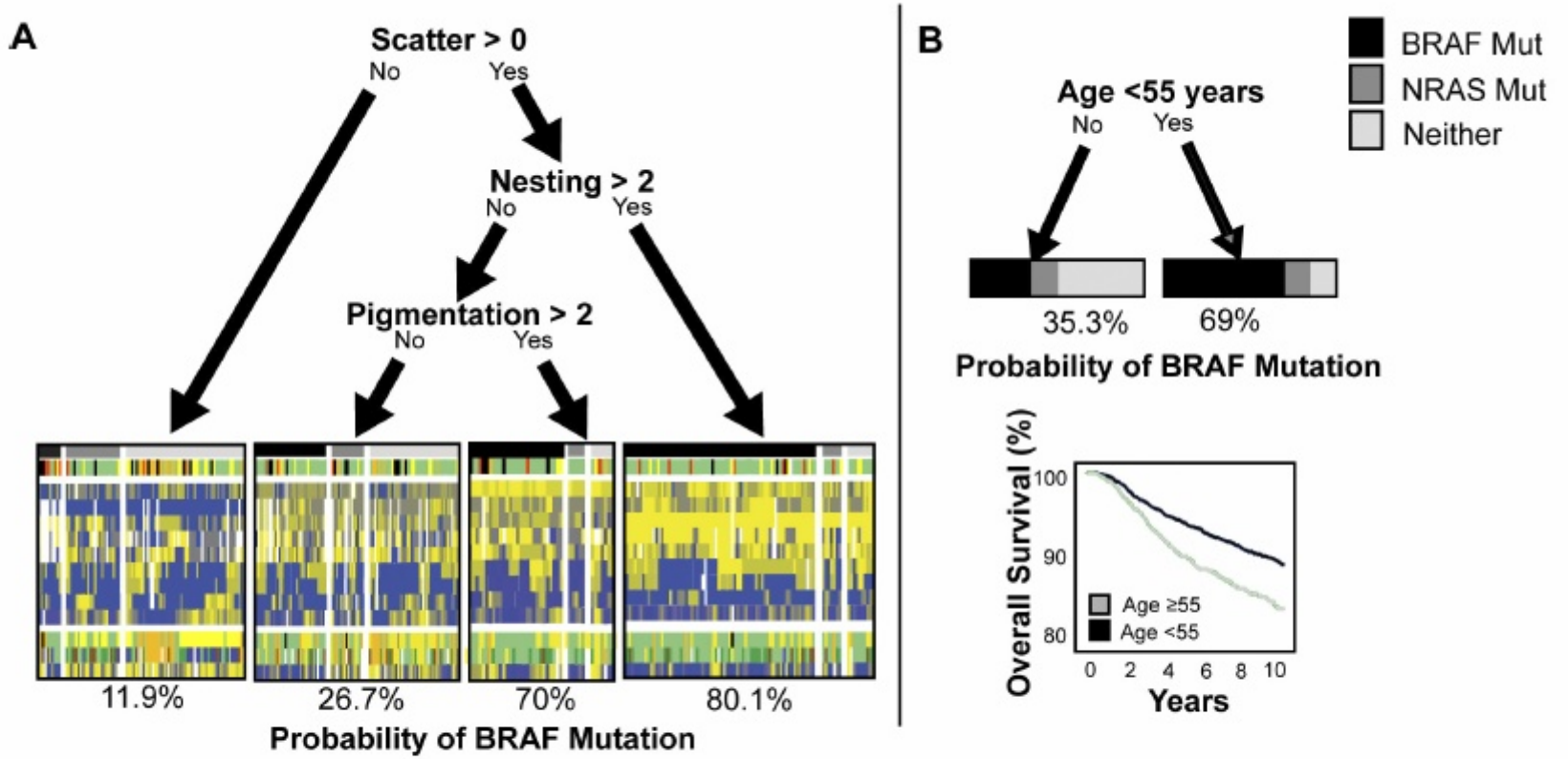


Figure 3. Prediction Algorithms of *BRAF* Mutation

Prediction trees for *BRAF* mutation status with morphologic variables (A) or variables in the Southern German Tumor Registry (B).

(A) Terminal nodes display heatmaps showing samples by mutation status, ordered and coded as in Figure 2A.

(B) The prediction tree for *BRAF* mutation using the variables of age, sex, body site, and WHO type also recorded in melanoma registries identifies an age cutoff of 55 y as the single best predictor of *BRAF* mutation status. Kaplan Meier survival analysis from the Southern German Tumor Registry shows a significant ($p < 0.0001$) decrease in survival when stratified by this age cutoff.

doi:10.1371/journal.pmed.0050120.g003

The Vision beyond Classification

Development of a melanoma classification system that combines analysis of known genetic factors with histopathology may produce a clinically powerful method for managing individual patients and guiding research in the immediate future.

A. Viros 2008

How wide and deep

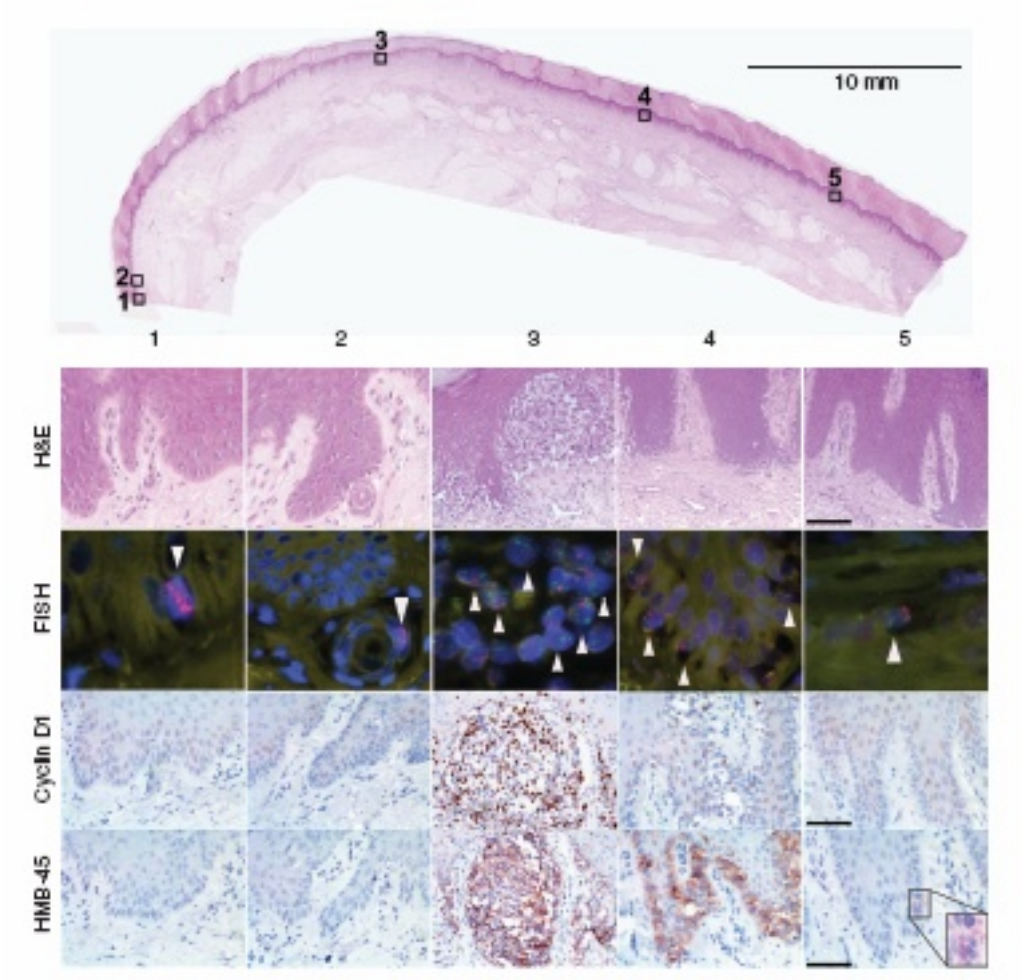
is wide and deep enough?

Distribution and Significance of Occult Intraepidermal Tumor Cells Surrounding Primary Melanoma

Jeffrey P. North[1,2], Toshiro Kageshita[3], Daniel Pinkel[4,5], Philip E. LeBoit[4,6] and Boris C. Bastian[4,6]

Primary melanoma can recur at the excision site if not excised with a safety margin of surrounding uninvolved skin. To characterize the nature of residual melanoma in the skin surrounding primary tumors targeted by safety margins, we used array comparative genomic hybridization and fluorescent *in situ* hybridization to detect and spatially map aberrations in the skin adjacent to acral melanomas. Melanocytic cells with genetic amplifications in histopathologically normal skin (field cells) were detected exclusively in the epidermis in 84% of 19 cases, with a mean extension of 6.1 mm (*in situ* melanomas) and 4.5 mm (invasive melanomas) beyond the histopathological margin. Genetic profiling of these field cells indicated that they represent an early phase of disease preceding melanoma *in situ*. The extent of field cells did not correlate with tumor depth or diameter, indicating that tumor depth is not suited to predict the extent of field cells. These results demonstrate that, on acral sites, melanoma field cells extend significantly into seemingly normal skin. These field cells provide a plausible explanation for the tendency of certain melanoma types to recur locally despite apparently having undergone complete excision.

Journal of Investigative Dermatology (2008) **128,** 2024–2030; doi:10.1038/jid.2008.41; published online 6 March 2008


3
4
5
2
1
10 mm
1
2
3
4
5
H&E
FISH
Cyclin D1
HMB-45

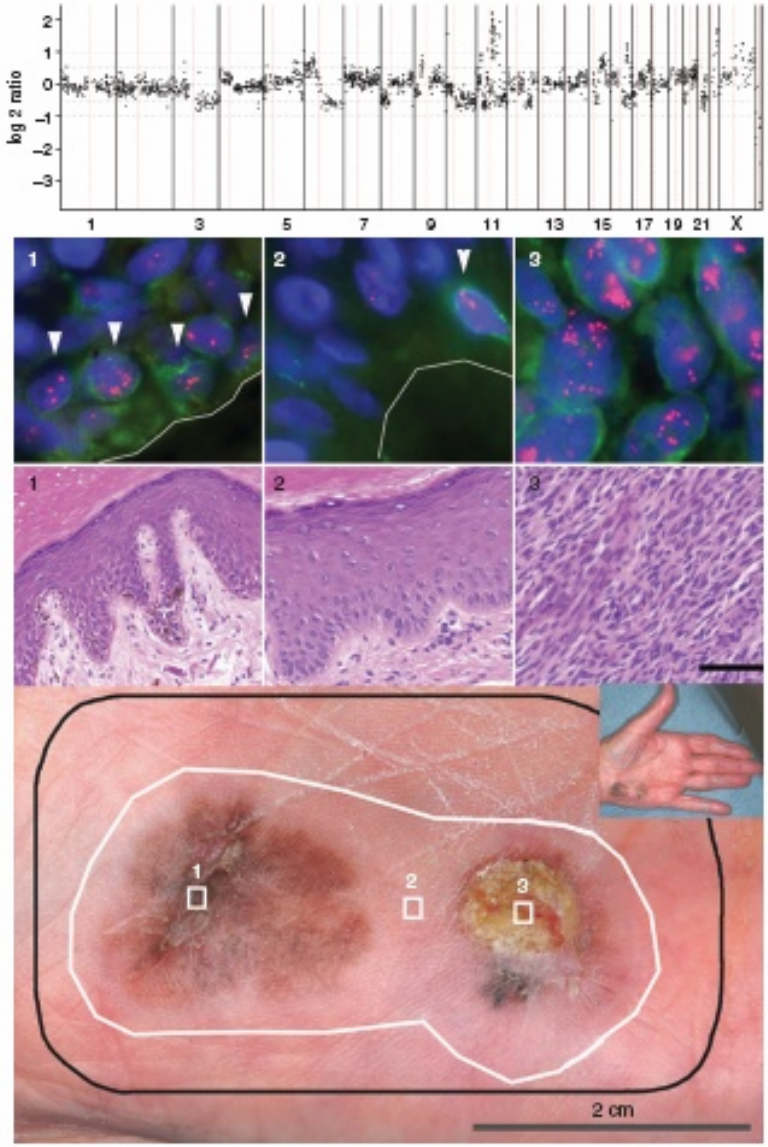

log 2 ratio
2
1
0
−1
−2
−3
1
3
5
7
9
11
13
15
17
19
21
X
1
2
3
1
2
3
1
2
3
2 cm

Table 1. Case characteristics

Case no.	Age	Sex	Site	Tumor depth	Histologic width	FC width beyond H&E	FC at margin	Patient follow-up after excision
AM 134	85	F	Sole	*In situ*	32.5 mm	1.5 mm	–	No recurrence 60 months
AM 159	66	F	Sole	*In situ*	16.0 mm	—	–	No recurrence 57 months
AM 136	75	F	Sole	*In situ*	24.0 mm	3.0 mm	–	No recurrence 52 months
AM 179	—[1]	—[1]	—[1]	*In situ*	25.5 mm	6.0, 6.5[2]	+	No recurrence 38 months
AM 117	40	M	Sole	*In situ*	40.0 mm	3.0 mm	+	No recurrence 94 months
AM 118	73	M	Sole	0.4 mm	28.0 mm	10.5, 12.5[2]	+	Regional+systemic metastasis 54 months, died 57 months
AM 180	—[1]	—[1]	—[1]	1.6 mm	14.0 mm	4.0 mm	–	Recurrence 32 months, dead 39 months
AM 108	63	M	Sole	1.8 mm	17.0 mm	—	–	No recurrence 68 months
AM 169	66	M	Sole	2.3 mm	39.5 mm	4.5 mm	+	Dead 47 months (stroke), no recurrence
AM 165	74	F	Sole	2.5 mm	30.5 mm	2.5 mm	–	No recurrence 60 months
AM 125	83	M	Sole	2.7 mm	9.5 mm	6.5 mm	–	Inguinal skin metastasis 9 months, still alive 58 months
AM 133	84	F	Sole	2.8 mm	14.5 mm	2.5 mm	–	No recurrence 60 months
AM 130	69	F	Sole	2.9 mm	12.0 mm	3.0 mm	–	No recurrence 56 months
AB 1	84	F	Palm	3.0 mm	10.0 mm	9.0, 5.0[2]	–	No recurrence 23 months
AM 50	—[1]	M	Sole	3.2 mm	24.0 mm	4 mm	–	No recurrence 12 months
AM 110	63	M	Sole	3.5 mm	18.0 mm	2 mm	–	No recurrence 88 months
AM 126	77	M	Toe nail	4.1 mm	22.5 mm	4.5 mm	–	Inguinal LN metastasis 25 months, died 32 months
AM 132	57	M	Toe nail	4.8 mm	15.5 mm	—	–	No recurrence 65 months
AM 114	77	M	Sole	9.5 mm	42.5 mm	6.5 mm	+	Incomplete operation/stage 4, died 12 months

FC, field cell; LN, lymph node.
[1]Data not available.
[2]Field cells extended past the histologic margin to both sides of the melanoma; distances in mm.

INTERNATIONAL DERMOSCOPY SOCIETY

ids

- HOMEPAGE
- FREE MEMBERSHIP
- REPRESENTATIVES
- ARTICLES AND AIMS
- LIST OF MEMBERS
- SUPP. MEMBERS
- LINKS
- STUDIES
- EDUCATION
- MEETINGS
- CASE OF THE MONTH
- MEMBERS AREA
- CONTACTS
- DISCLAIMER
- IMPRESSUM

HOMEPAGE

Welcome to the web page of the International Dermoscopy Society (IDS).

Our **membership is worldwide** and currently **more than 70 different countries are represented**.

Individuals may join by direct application for free membership. Our organization conducts a world congress every 5 years and multiple national meetings throughout the world are planned to be held. The First World Congress of Dermoscopy has been held in Rome, Italy, in 2001.

The IDS has been founded in 2003 by H. Peter Soyer, Rainer Hofmann-Wellenhof and Giuseppe Argenziano to promote clinical research in dermoscopy and to represent a clinically oriented international organization with a thrust towards helping and improving education in dermoscopy.

We welcome your participation in the International Dermoscopy Society!

For registered members: Please visit our new MEMBERS AREA with discussion forum!

First Congress of the International Dermoscopy Society

First Congress of the International Dermoscopy Society (IDS)
Naples, Italy, April 27-29, 2006

www.dermoscopy-ids.org

The Official Organ of the IDS:
Dermatology
International Journal for Clinical and Investigative Dermatology

2nd congress of the international dermoscopy society

12-14 november 2009
barcelona, spain
hotel fira palace