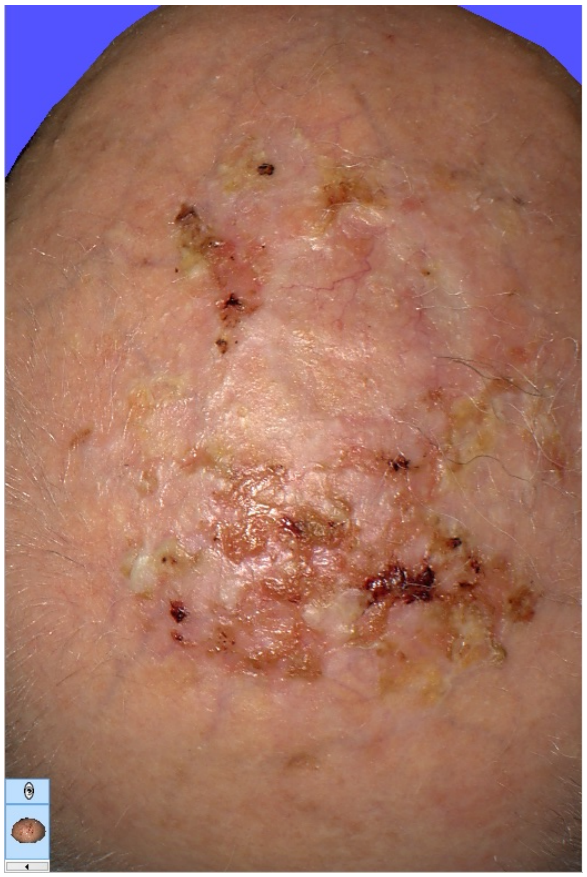
Clinica Dermatologica
Università degli Studi di Brescia
ASST Spedali Civili

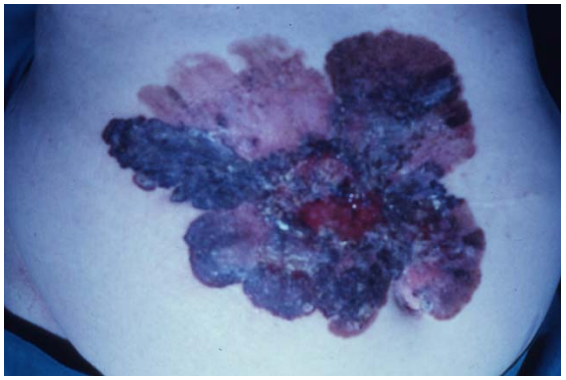
Patogenesi del melanoma. Evidenze cliniche e sperimentali

Piergiacomo Calzavara-Pinton



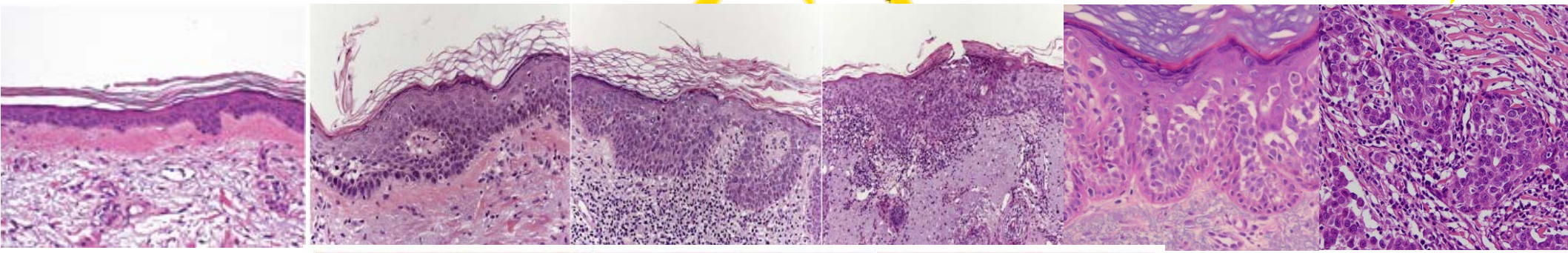
CARCINOMA SPINOCELLULARE

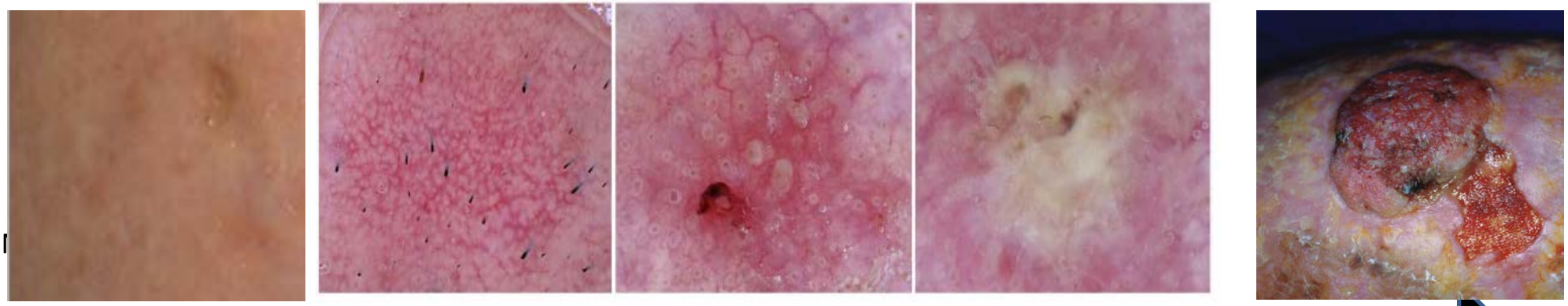
CARCINOMA SQUAMOCELLULARE



MELANOMA

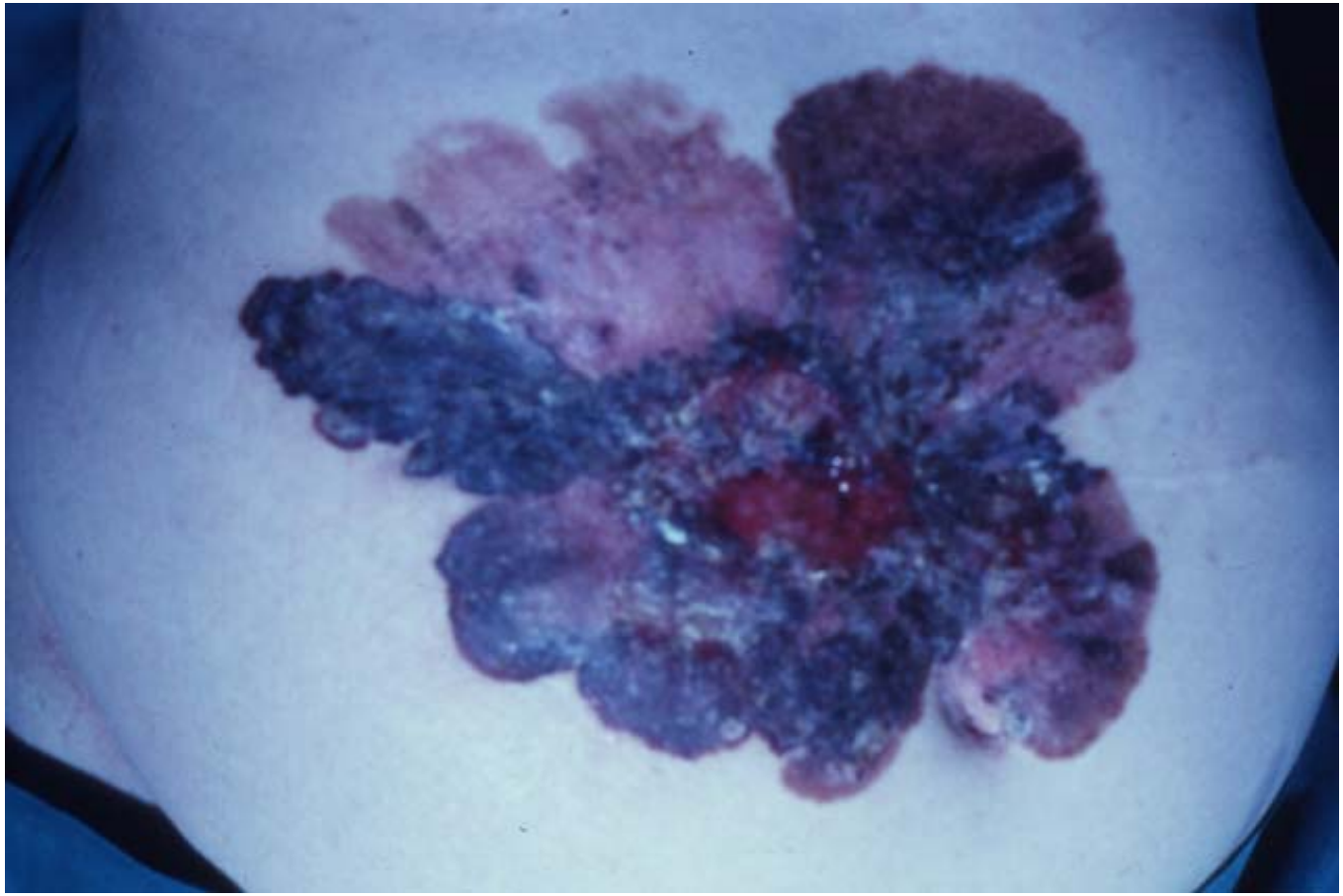
p53± p16± Bcl2+ MYC+ EGFR+ RAS+ Hsp27+ Stat3- Notch-





I° II° III° isSCC

Oncogenes synergy, Aneuploidy, Chromosomal deletions to complex aberrations (translocation chr, isochr, chr amplification), Apoptosis resistance, Clonal expansione

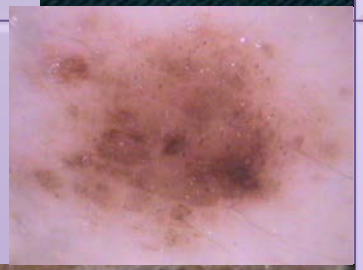


SUN- RELATED RISK FACTORS FOR MELANOMA

		RR (95% CI)
Sunburns		2.0 (1.7-2.4)
Suberythemogenic exposures	Intermittent	1,6 (1,3-2,0)
	Regular	1,0 (0,9-1,0)
	Regular plus marked photoaging	2.0 (1.2-3.3)

*meta-analysis of 60 studies by Gandini et al (2005, 2006, 2007)

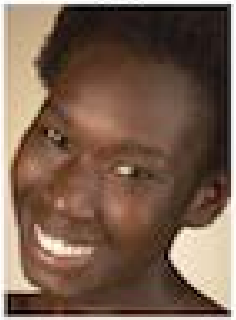
** Berwick et al. J Natl Cancer Inst 2005

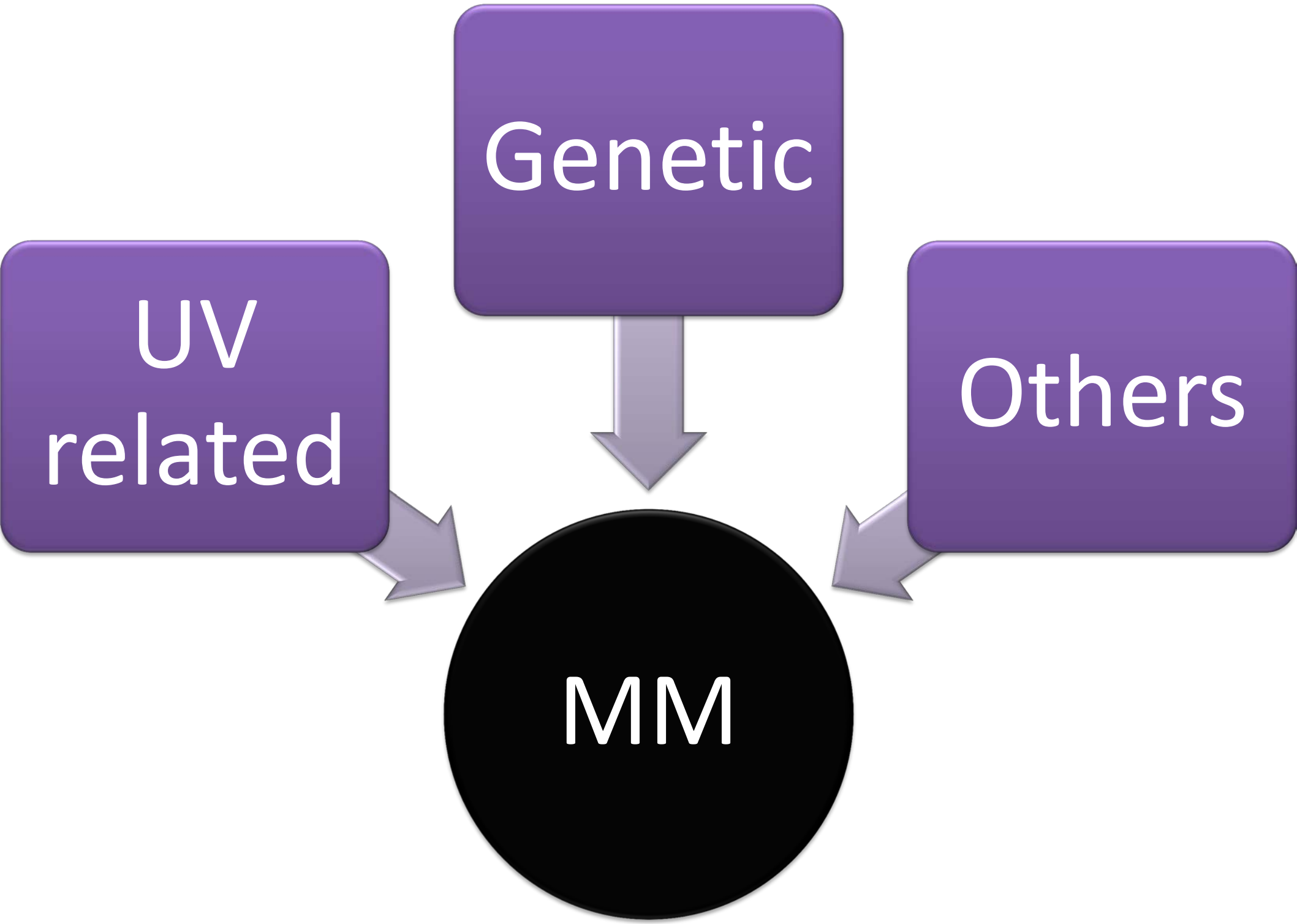
Clinical Type	Chr. sun damage	Sunburns	BRAF	NRAS	KIT
SSM/ NM 	no	yes	50%	20%	0%
LMM 	yes	no	10%	10%	2%
ALM 	no	no	15%	15%	15%
MuM 	no	no	5%	15%	20%
UvM 	no	no	0	0	0

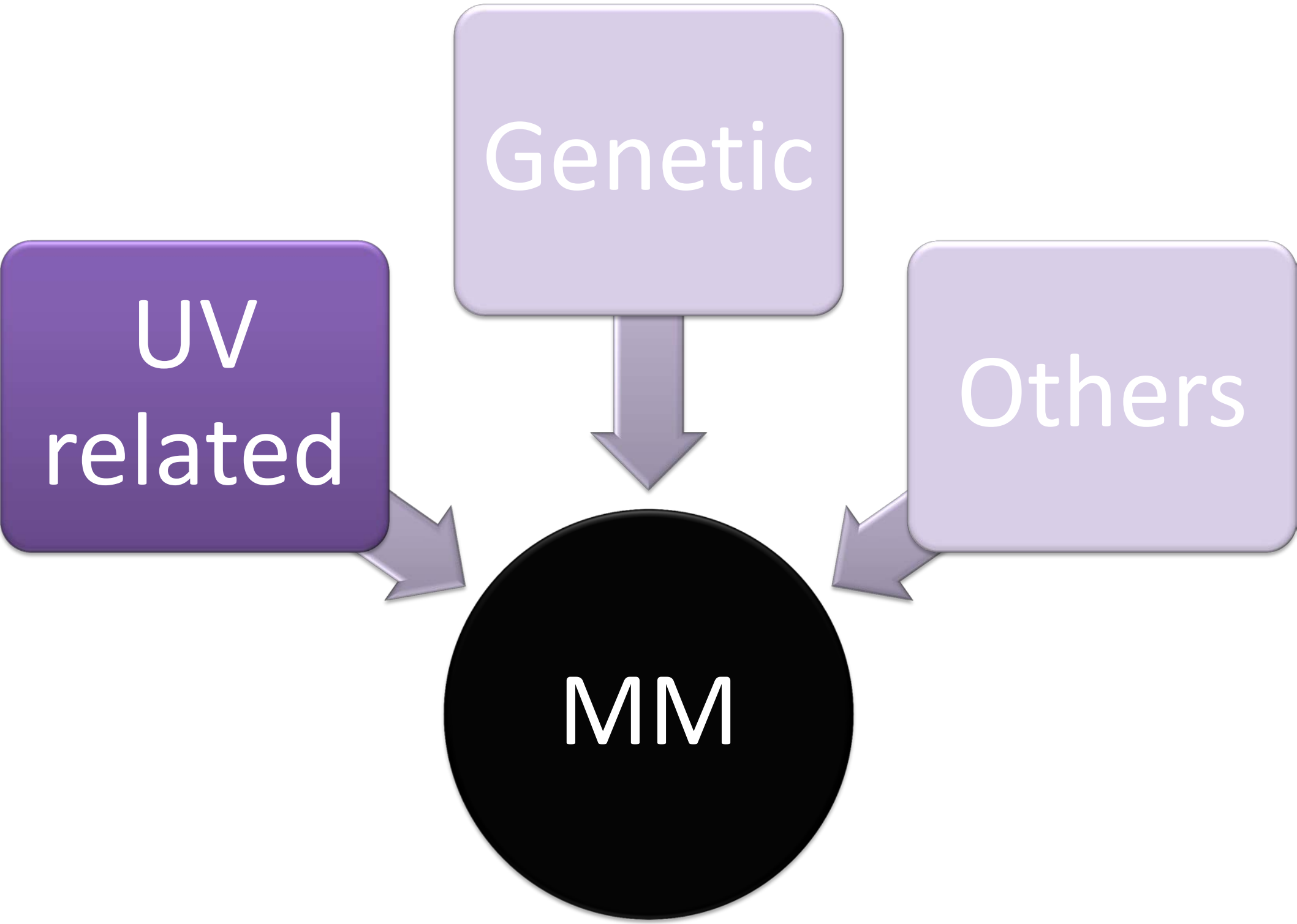
25% GNA; 55%GNA11

SUN- RELATED (?) RISK FACTORS FOR MELANOMA

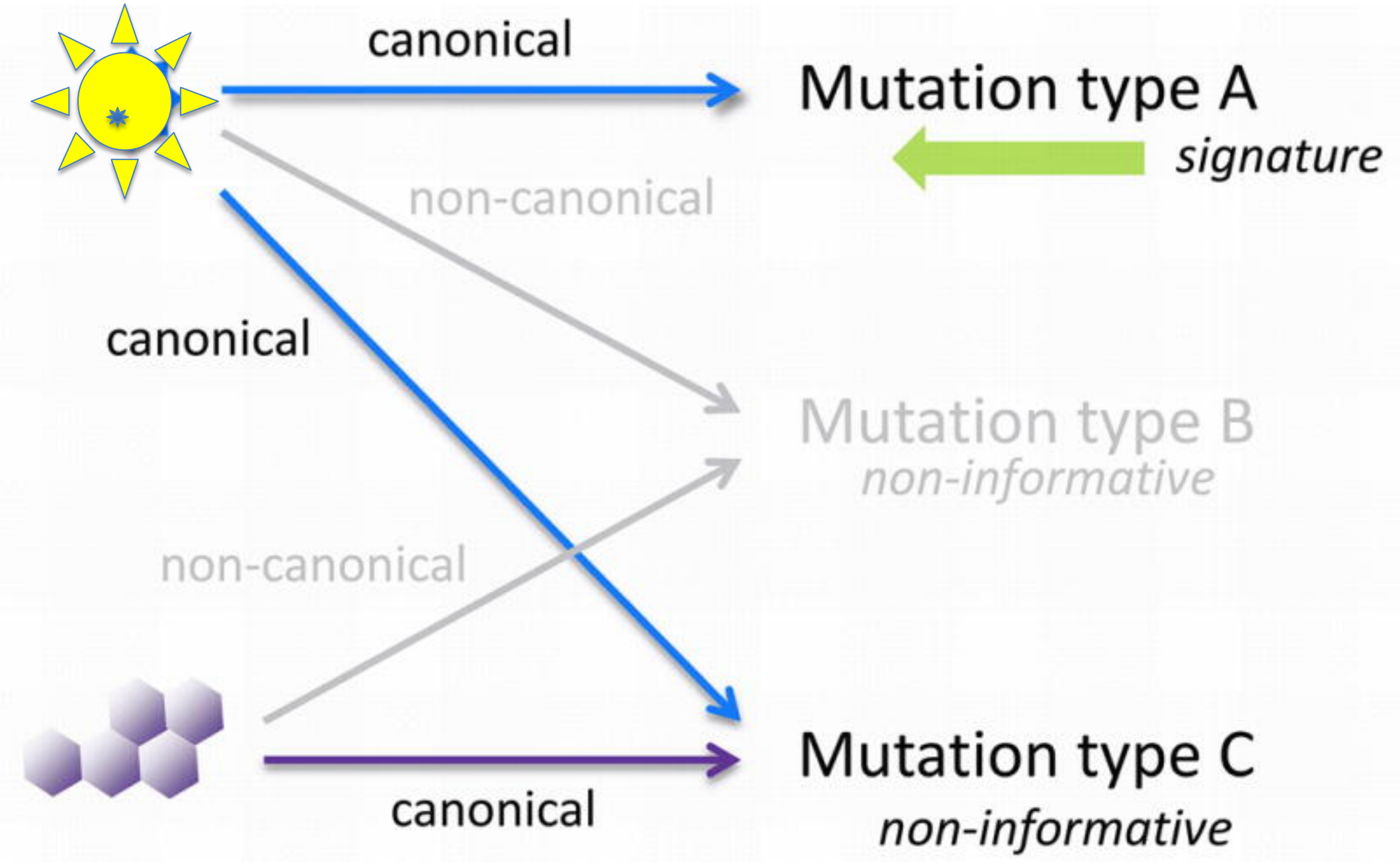
Factor	RR (CI 95%)
Clinically atypical nevi (5 vs. 0)	10,5 (5,1-21,8)
Personal history of melanoma	8,6 (8,3-8,9)
Common melanocytic nevi (>100 vs. <15)	6,9 (4,6-10,3)
Hair colour (red vs. dark)	3,6 (2,6-5,4)
Phototype (I vs. IV)	2,1 (1,7-2,6)
Freckles (many vs. few)	2,1 (1,8-2,5)
Eye colour (blue vs. dark)	1,5 (1,3-1,7)

SKIN TYPE	one	two	three	four	five	six
						
Hair	red, blonde	blonde, red, light brown	chestnut, dark blonde	brown, medium brown, dark brown	dark brown	black
Eyes	blue, grey, green	blue, grey, green, hazel	brown, blue, grey, green, hazel	hazel, brown		
Skin	very pale white, pale white	pale white	white, light brown	medium brown, dark brown		
Tanning Ability	burns very easily, never tans	burns easily, rarely tans	sometimes burns, gradually tans	hardly ever burn, tans very easily		

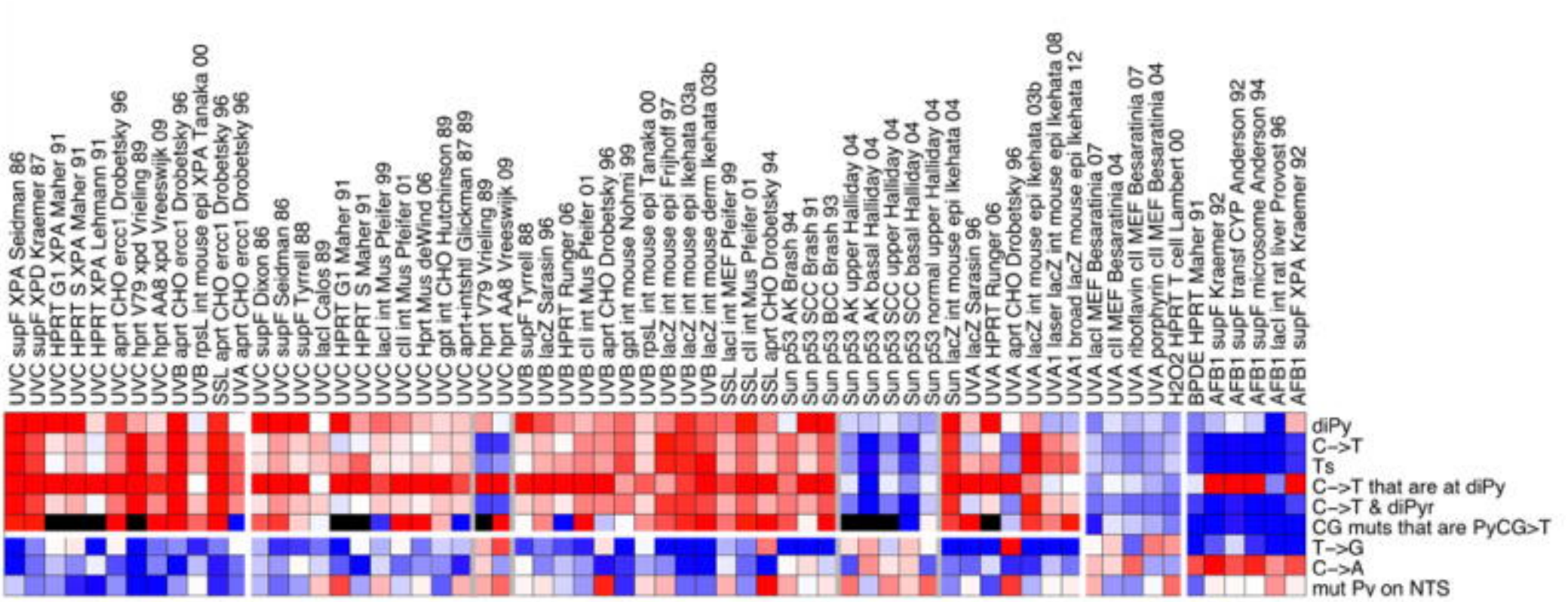

Genetic
UV related
Others
MM


Genetic
UV related
Others
MM

•Canonical mutations and signatures



UV SIGNATURES



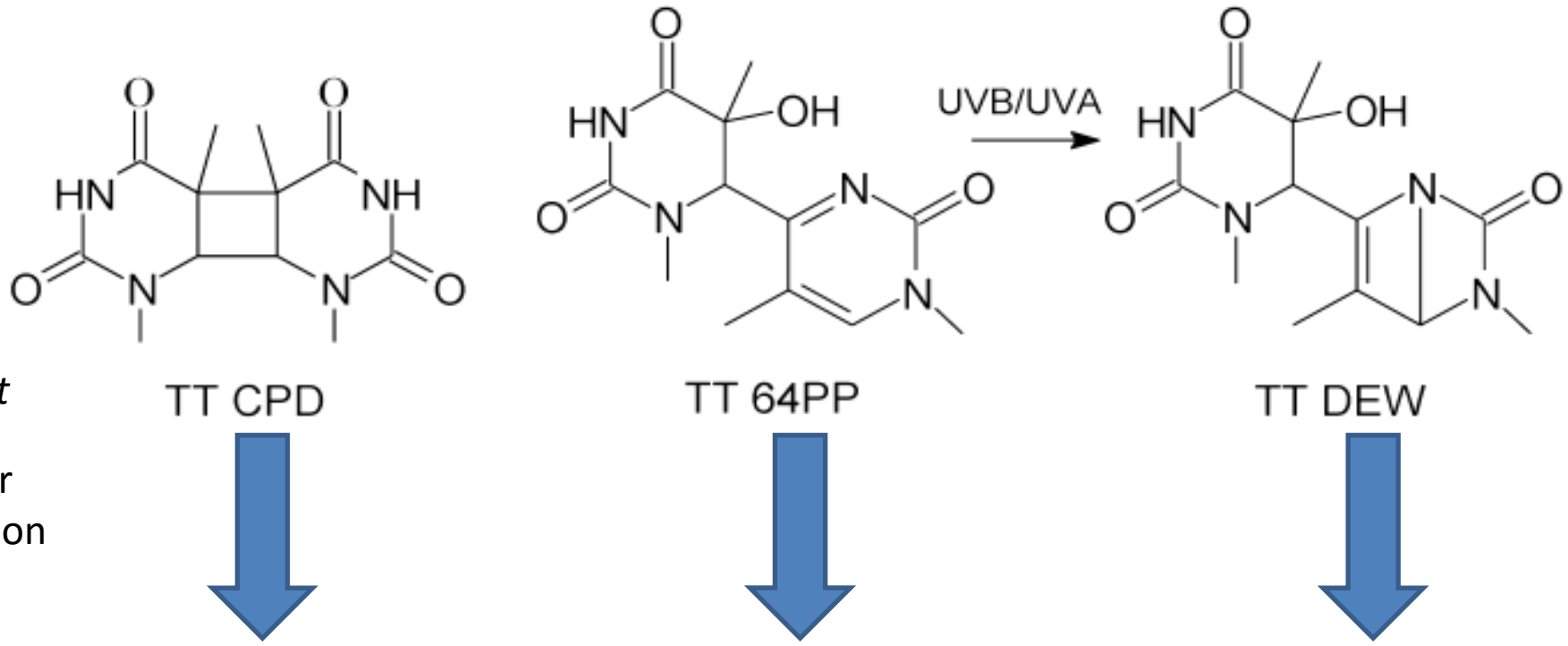
Colors: dark blue, row minimum; white, row average; dark red, row maximum

UVB (uva) FINGERPRINTS/ SIGNATURES

cyclobutane pyrimidine dimers (Thymines dimers)

pyrimidine (6-4) pyrimidone photoproducts (6-4PPs)

DEW = Dewar valence isomer



DNA photoproduct

DNA repair or DNA replication

single C→T or tandem CC→TT transition mutations at bipyrimidine sites

Photochemistry and Photobiology, 2012

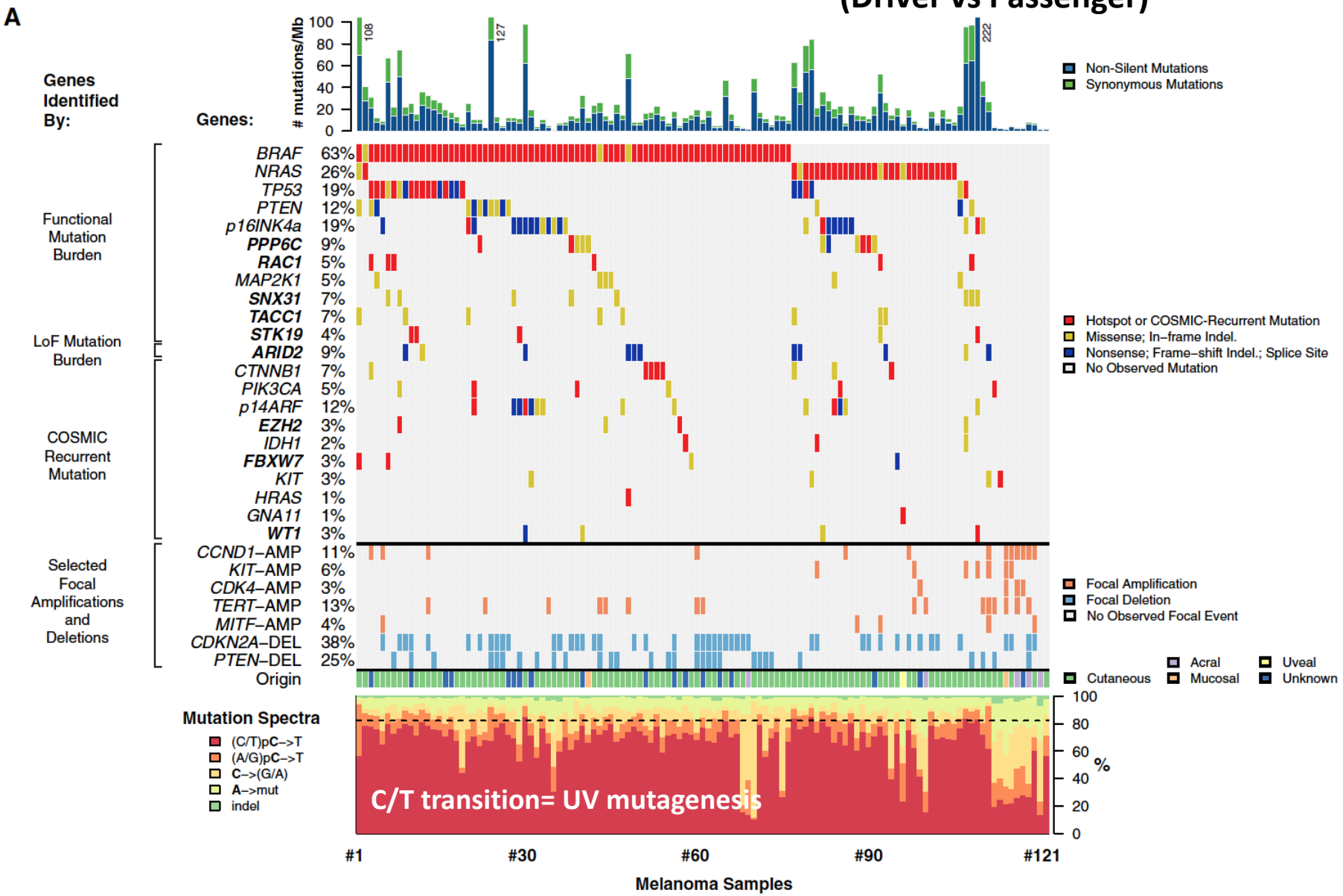
A Landscape of Driver Mutations in Melanoma

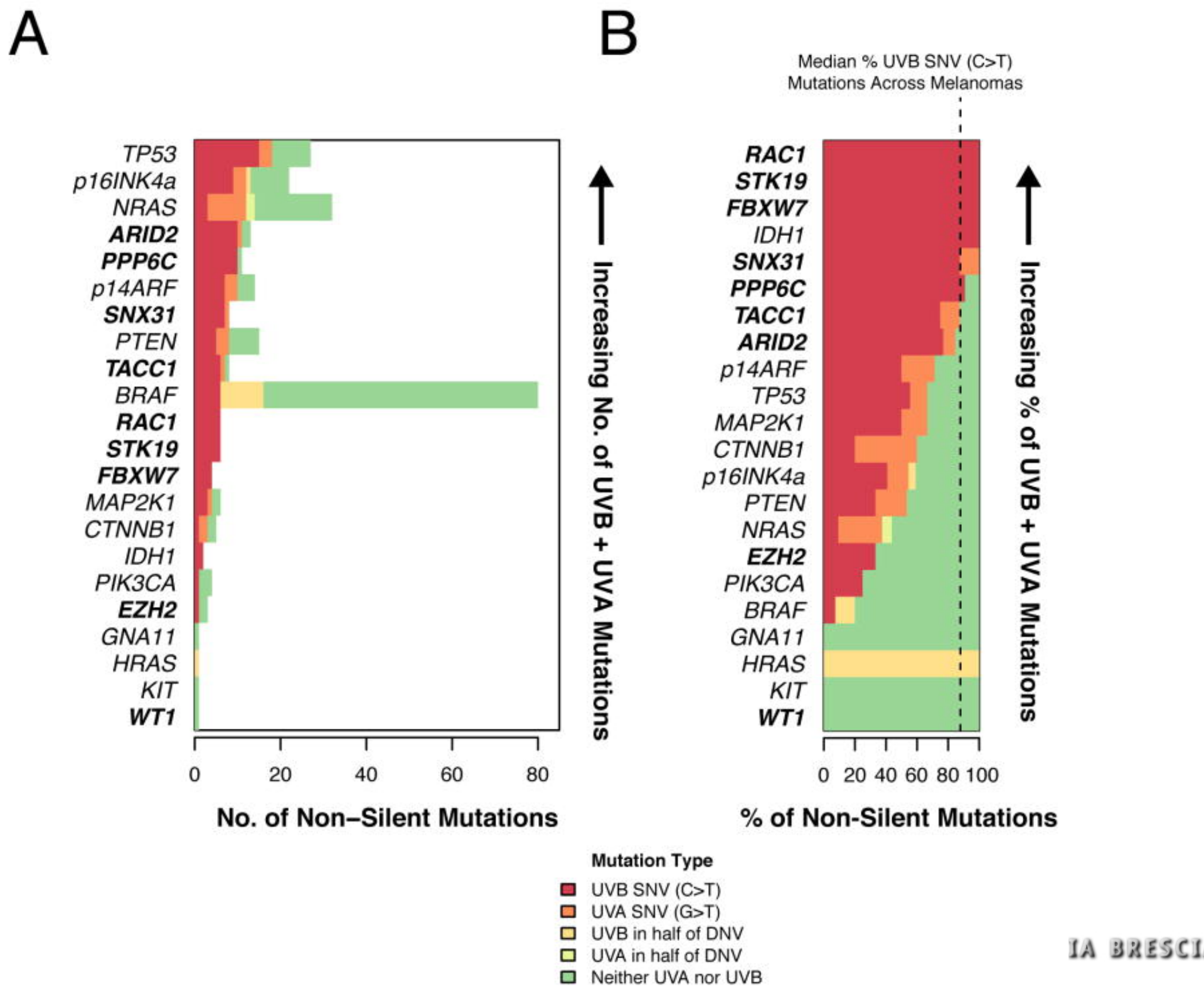
Cell *150*, 251–263, July 20, 2012

Eran Hodis,[1,2,19] Ian R. Watson,[3,10,19] Gregory V. Kryukov,[1,2,12] Stefan T. Arold,[4] Marcin Imielinski,[1] Jean-Philippe Theurillat,[1] Elizabeth Nickerson,[1] Daniel Auclair,[1] Liren Li,[3,10] Chelsea Place,[10] Daniel DiCara,[1] Alex H. Ramos,[1,2] Michael S. Lawrence,[1] Kristian Cibulskis,[1] Andrey Sivachenko,[1] Douglas Voet,[1] Gordon Saksena,[1] Nicolas Stransky,[1] Robert C. Onofrio,[1] Wendy Winckler,[1] Kristin Ardlie,[1] Nikhil Wagle,[1,2] Jennifer Wargo,[13] Kelly Chong,[14] Donald L. Morton,[15] Katherine Stemke-Hale,[5] Guo Chen,[6] Michael Noble,[1] Matthew Meyerson,[1,2,10,11] John E. Ladbury,[4] Michael A. Davies,[5,6] Jeffrey E. Gershenwald,[7,8] Stephan N. Wagner,[16] Dave S.B. Hoon,[14] Dirk Schadendorf,[17] Eric S. Lander,[1,18] Stacey B. Gabriel,[1] Gad Getz,[1] Levi A. Garraway,[1,2,10,11,20,*] and Lynda Chin[1,2,3,9,10,20,*]

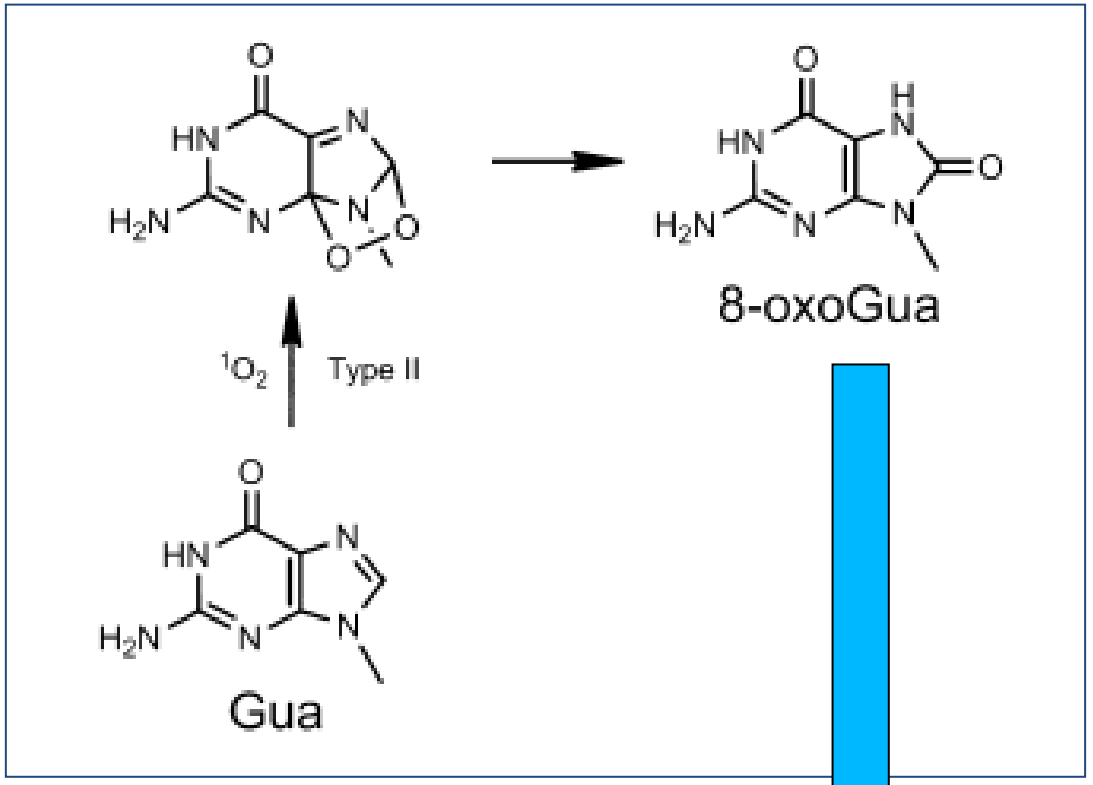
(WES [Illumina HiSeq200]+Affimetrix SNP Array)

High mutational load (Driver vs Passenger)




A
B
Median % UVB SNV (C>T)
Mutations Across Melanomas
TP53
p16INK4a
NRAS
ARID2
PPP6C
p14ARF
SNX31
PTEN
TACC1
BRAF
RAC1
STK19
FBXW7
MAP2K1
CTNNB1
IDH1
PIK3CA
EZH2
GNA11
HRAS
KIT
WT1
Increasing No. of UVB + UVA Mutations
0 20 40 60 80
No. of Non−Silent Mutations
RAC1
STK19
FBXW7
IDH1
SNX31
PPP6C
TACC1
ARID2
p14ARF
TP53
MAP2K1
CTNNB1
p16INK4a
PTEN
NRAS
EZH2
PIK3CA
BRAF
GNA11
HRAS
KIT
WT1
Increasing % of UVB + UVA Mutations
0 20 40 60 80 100
% of Non-Silent Mutations
Mutation Type
UVB SNV (C>T)
UVA SNV (G>T)
UVB in half of DNV
UVA in half of DNV
Neither UVA nor UVB

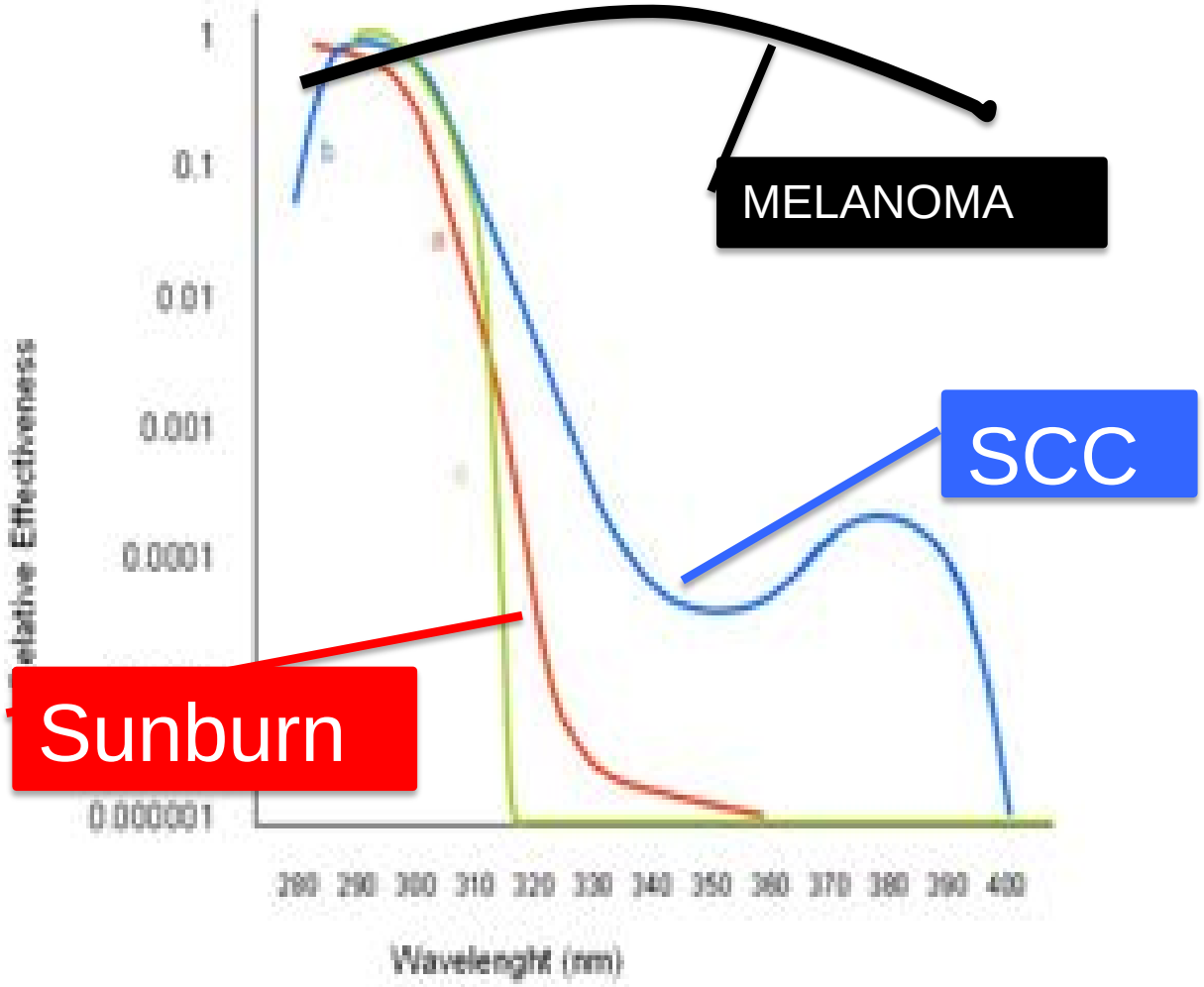
UVA (uvb) FINGERPRINTS/ SIGNATURES

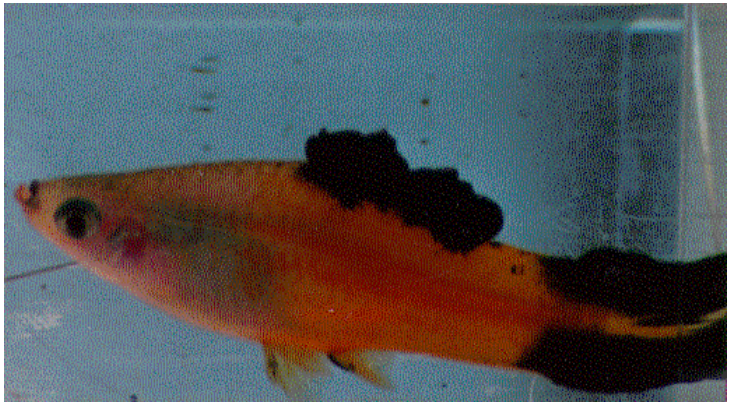


C → T mutation (G:C → A:T)

ACTION SPECTRUM OF MELANOMA

[xiphophorus (Setlow 1993, Wood 2005) and monodelphis domestica (Ley, 1997)]





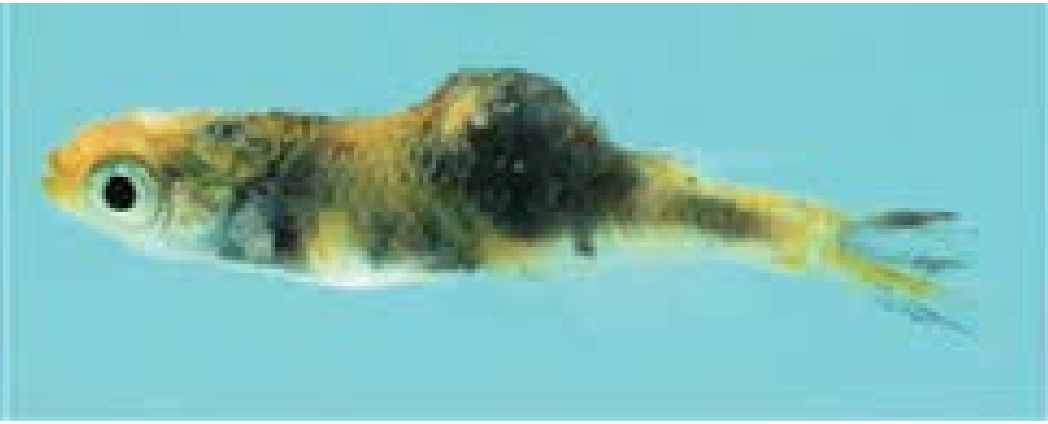
UV causation of melanoma in *Xiphophorus* is dominated by melanin photosensitized oxidant production

Simon R. Wood*, Marianne Berwick†, Ronald D. Ley*, Ronald B. Walter‡, Richard B. Setlow¶||, and Graham S. Timmins*||

*Division of Pharmaceutical Sciences, College of Pharmacy, †Division of Epidemiology, Department of Internal Medicine, and ‡Department of Cell Biology and Physiology, University of New Mexico Health Sciences Center, Albuquerque, NM 87131; §Department of Chemistry and Biochemistry, Molecular Biosciences Research Group, Texas State University, 601 University Drive, San Marcos, TX 78766; and ¶Biology Department, Brookhaven National Laboratory, Upton, NY 11973-5000

Contributed by Richard B. Setlow, December 28, 2005

$$\text{Melanin} \xrightarrow{h\nu} \text{Metastable Reactive Melanin Radical} \xrightarrow{O_2} O_2^{\cdot -},\ H_2O_2,\ HO^{\cdot}.$$



neonatal black C57BL/6-HGF and albino C57BL/6-c-HGF-tyrosinase- mutant transgenic mice

Melanin- independent pathway

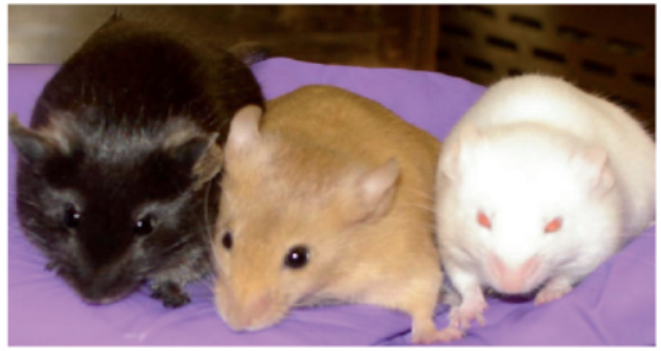
UVB → CPD, 6-4 PD and others… → MM

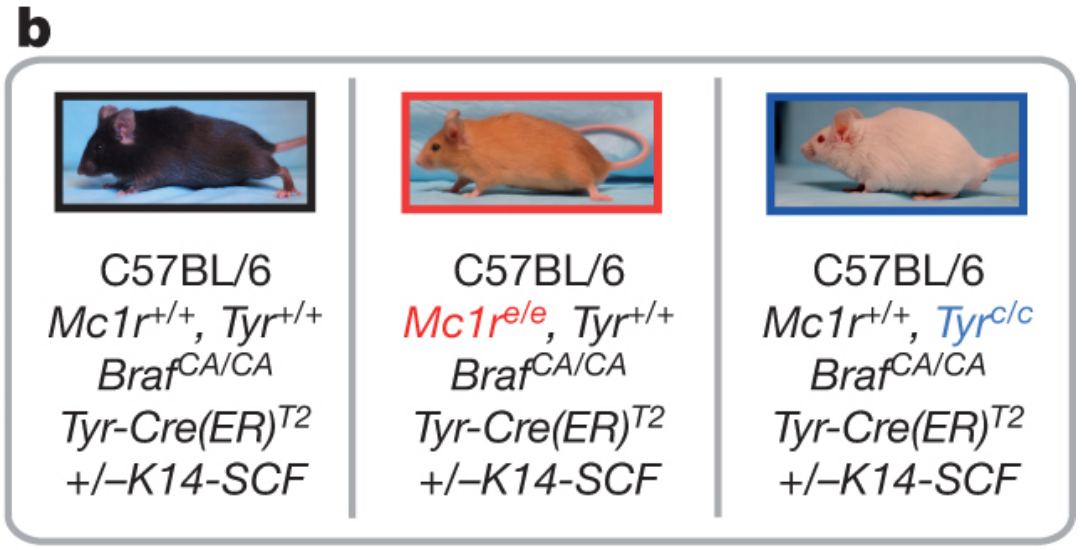
Melanin- dependent pathway

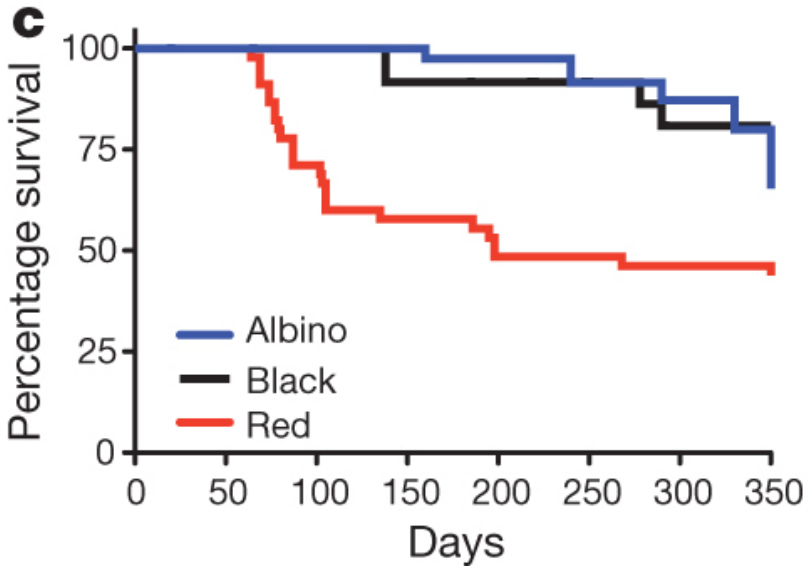
UVA → Melanin → Oxo Dna and others…. → MM

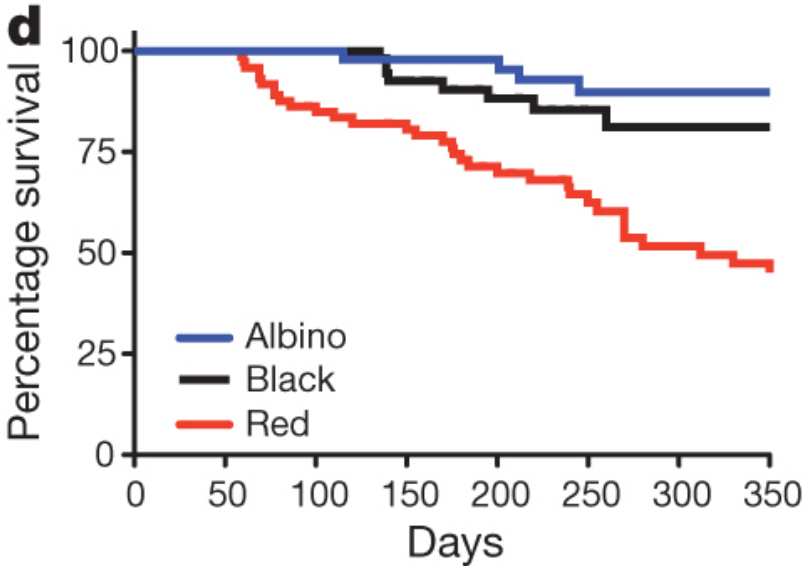
Noonan et al. Melanoma induction by UVA but not UVB requires melanin. Nature, 2013.

Without UVR, *Braf*^{CA} red mice have an increased rate of MM relative to black and albino *Braf*^{CA} animals.







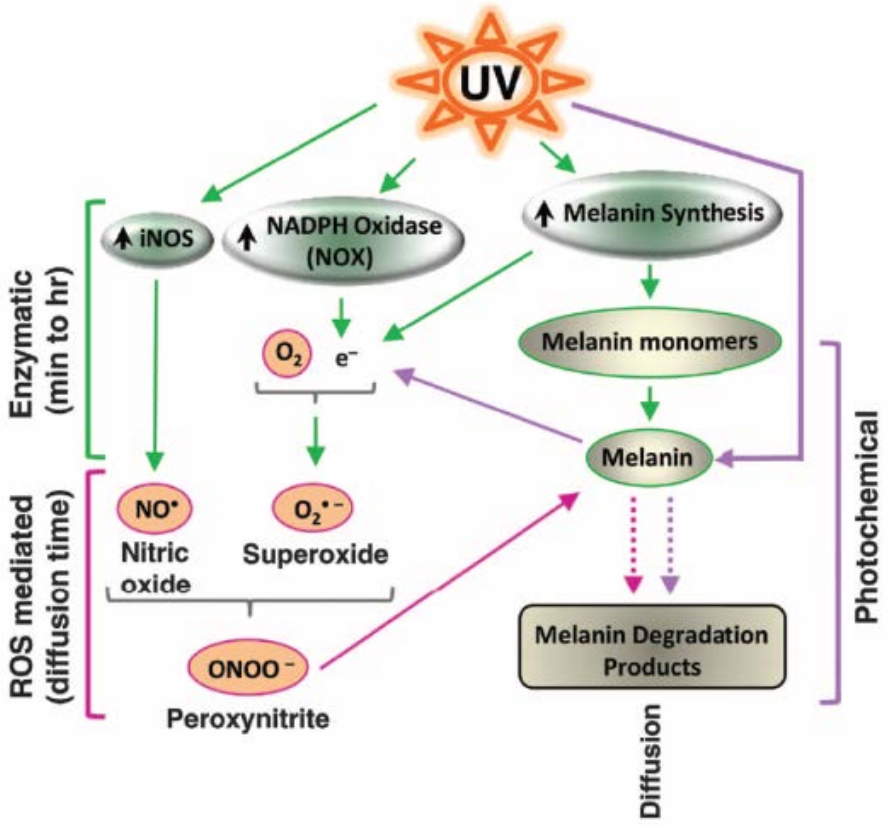


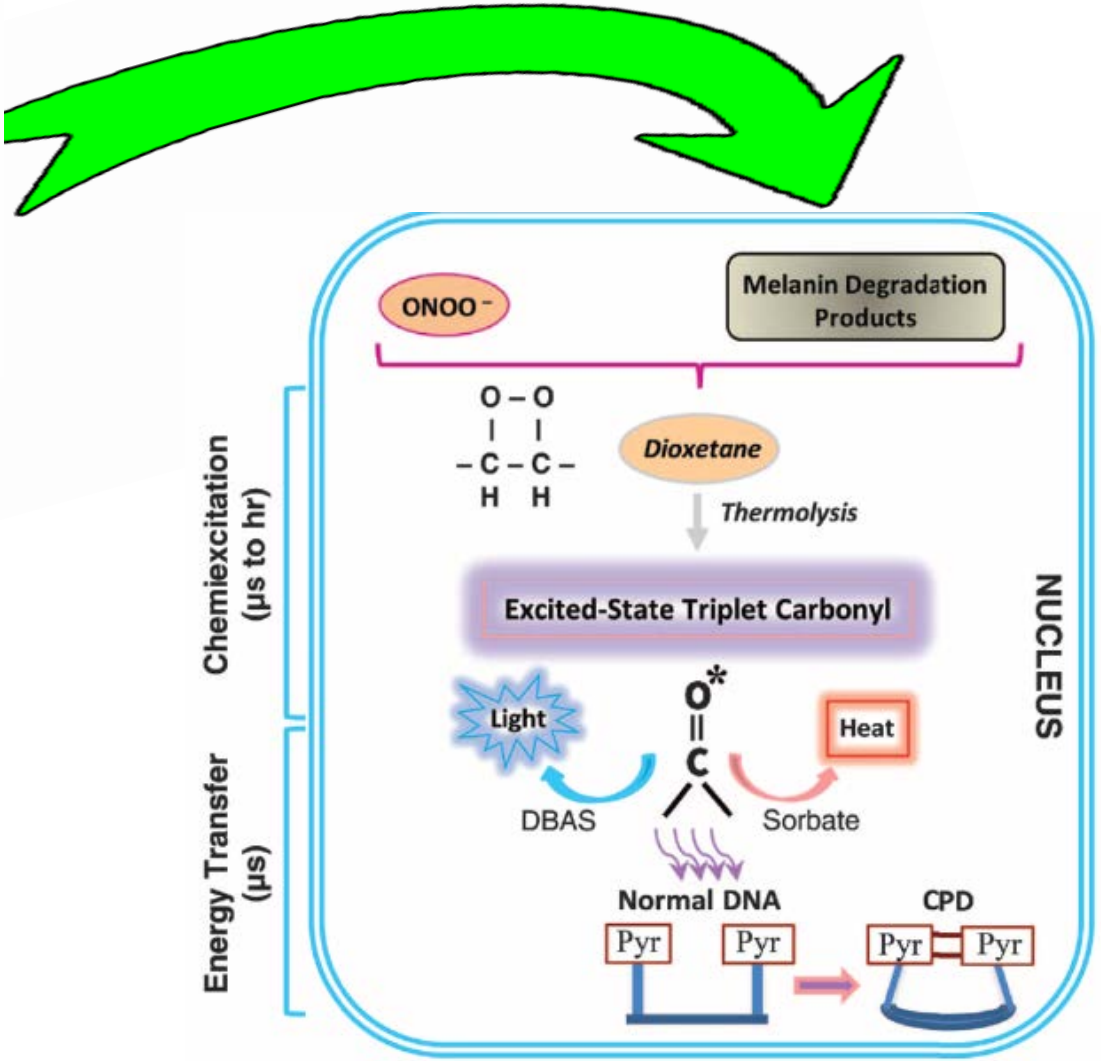
D Mitra *et al.*(2012) nature

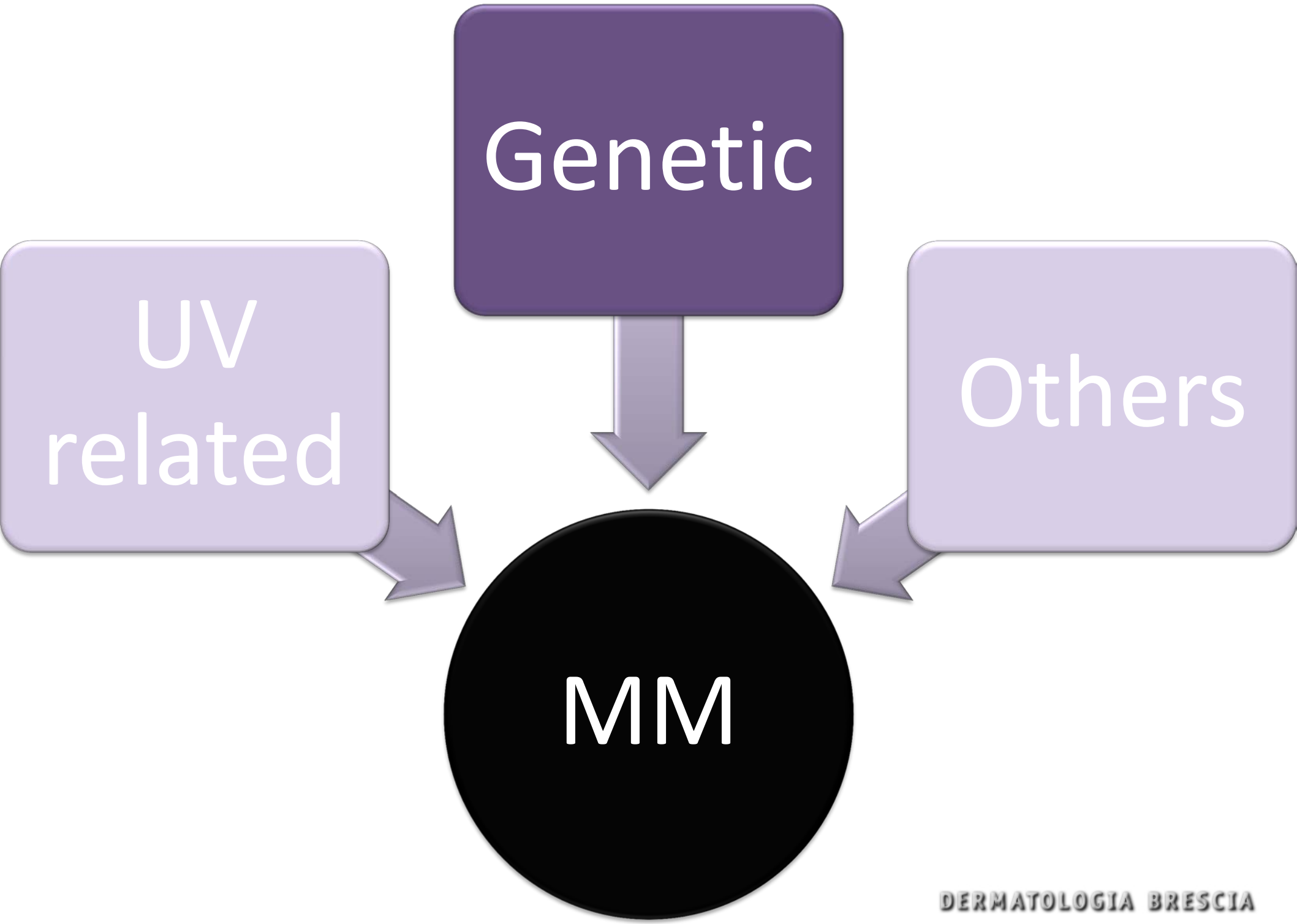
Chemiexcitation of melanin derivatives induces DNA photoproducts long after UV exposure

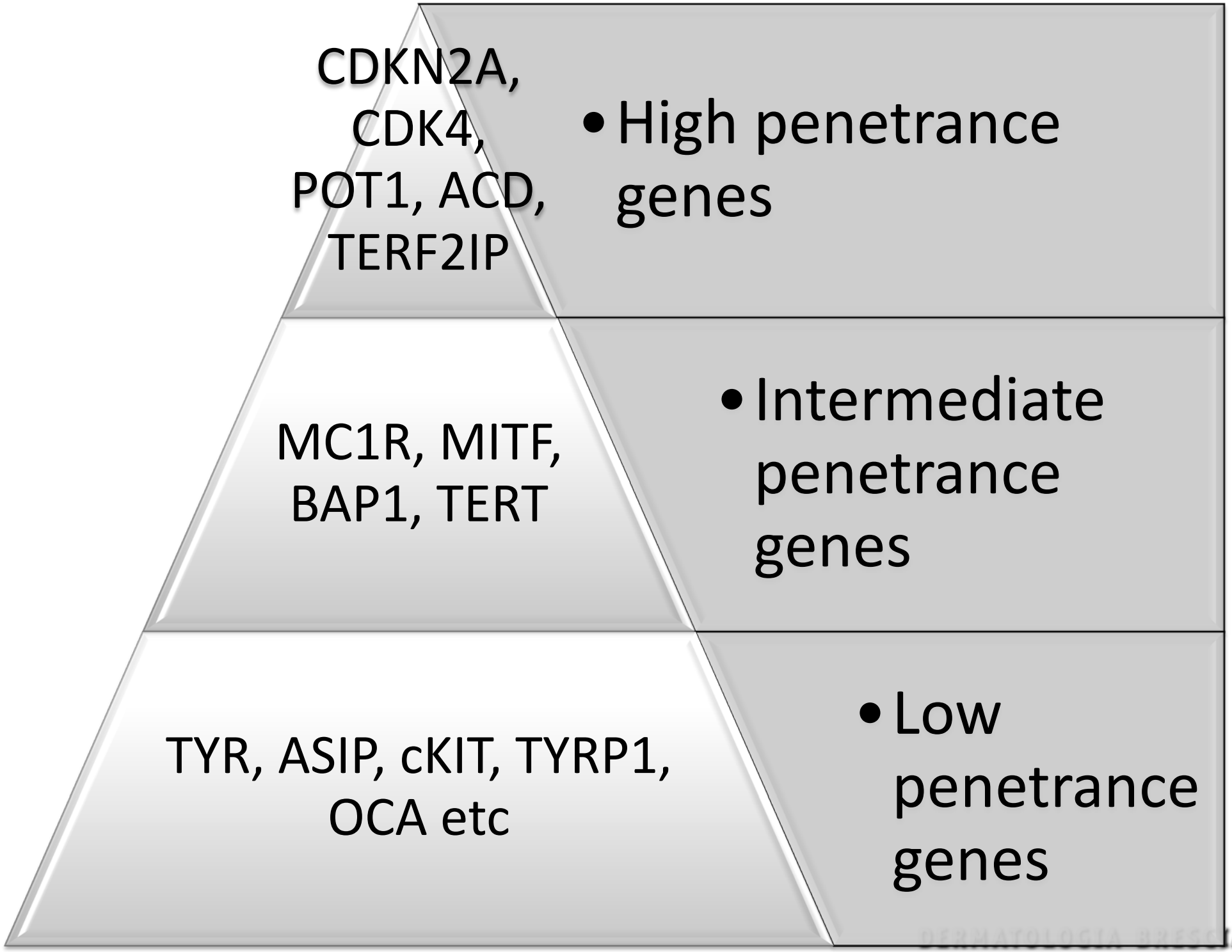
Sanjay Premi,[1] Silvia Wallisch,[1] Camila M. Mano,[1,2] Adam B. Weiner,[1]* Antonella Bacchiocchi,[3] Kazumasa Wakamatsu,[4] Etelvino J. H. Bechara,[2,5]† Ruth Halaban,[3,6] Thierry Douki,[7]† Douglas E. Brash[1,6]‡

Science, 2015








CDKN2A, CDK4, POT1, ACD, TERF2IP
• High penetrance genes
MC1R, MITF, BAP1, TERT
• Intermediate penetrance genes
TYR, ASIP, cKIT, TYRP1, OCA etc
• Low penetrance genes

Four factors associated with increased frequency of CDKN2A mutations

- ✓ Increased number of CMM patients in a family
- ✓ CMM patients with multiple primary melanoma tumors (also sporadic)
- ✓ Early age at melanoma diagnosis
- ✓ Occurrence of pancreatic cancer

Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents

Alisa M Goldstein, May Chan, Mark Harland, Nicholas K Hayward, Florence Demenais, D Timothy Bishop, Esther Azizi, Wilma Bergman, Giovanna Bianchi-Scarra, William Bruno, Donato Calista, Lisa A Cannon Albright, Valerie Chaudru, Agnes Chompret, Francisco Cuellar, David E Elder, Paola Ghiorzo, Elizabeth M Gillanders, Nelleke A Gruis, Johan Hansson, David Hogg, Elizabeth A Holland, Peter A Kanetsky, Richard F Kefford, Maria Teresa Landi, Julie Lang, Sancy A Leachman, Rona M MacKie, Veronica Magnusson, Graham J Mann, Julia Newton Bishop, Jane M Palmer, Susana Puig, Joan A Puig-Butille, Mitchell Stark, Hensin Tsao, Margaret A Tucker, Linda Whitaker, Emanuel Yakobson, The Lund Melanoma Study Group, and the Melanoma Genetics Consortium (GenoMEL)

J Med Genet 2007;**44**:99–106. doi: 10.1136/jmg.2006.043802

MC1R

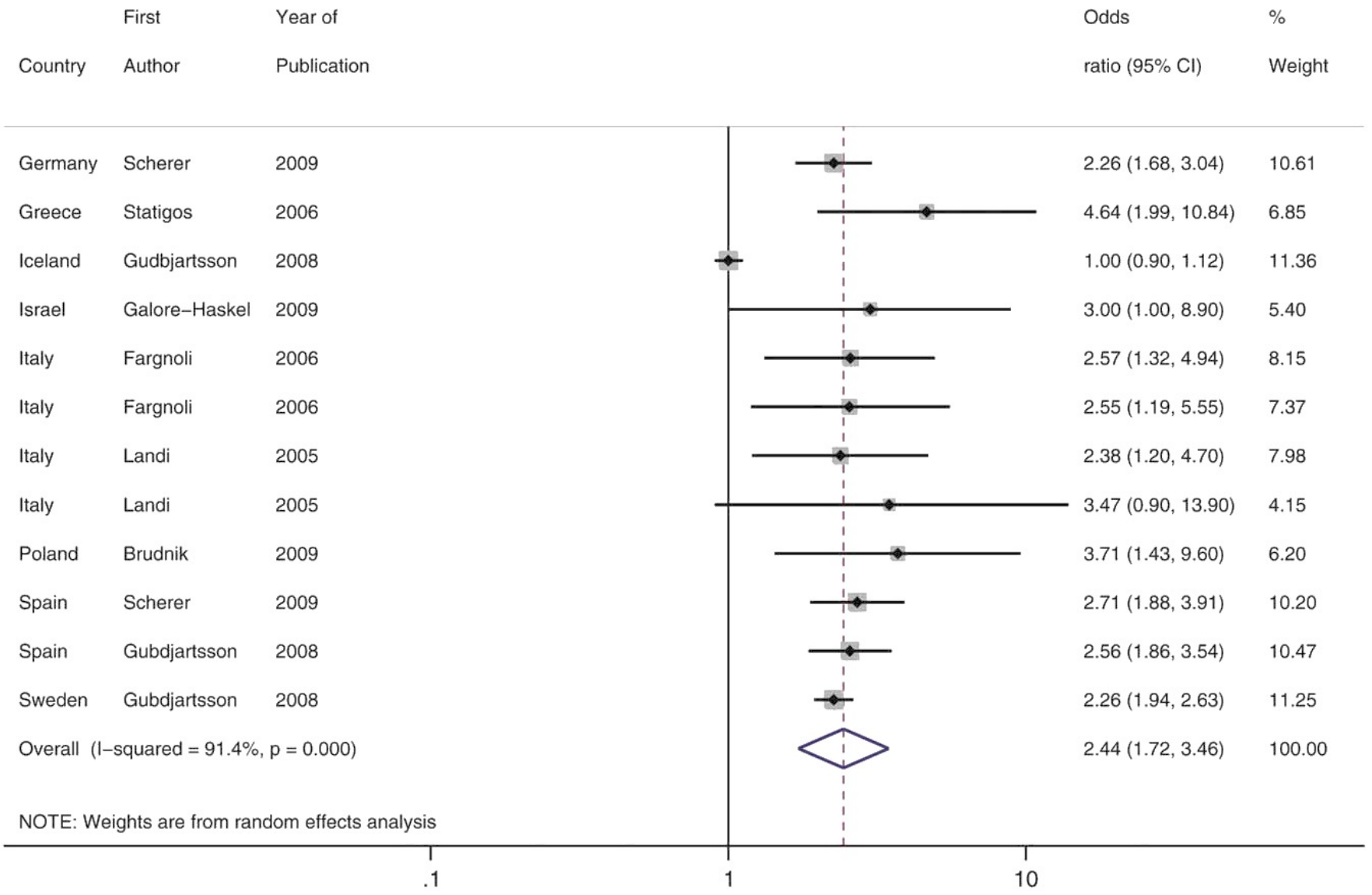
Low/Medium Penetrance Gene

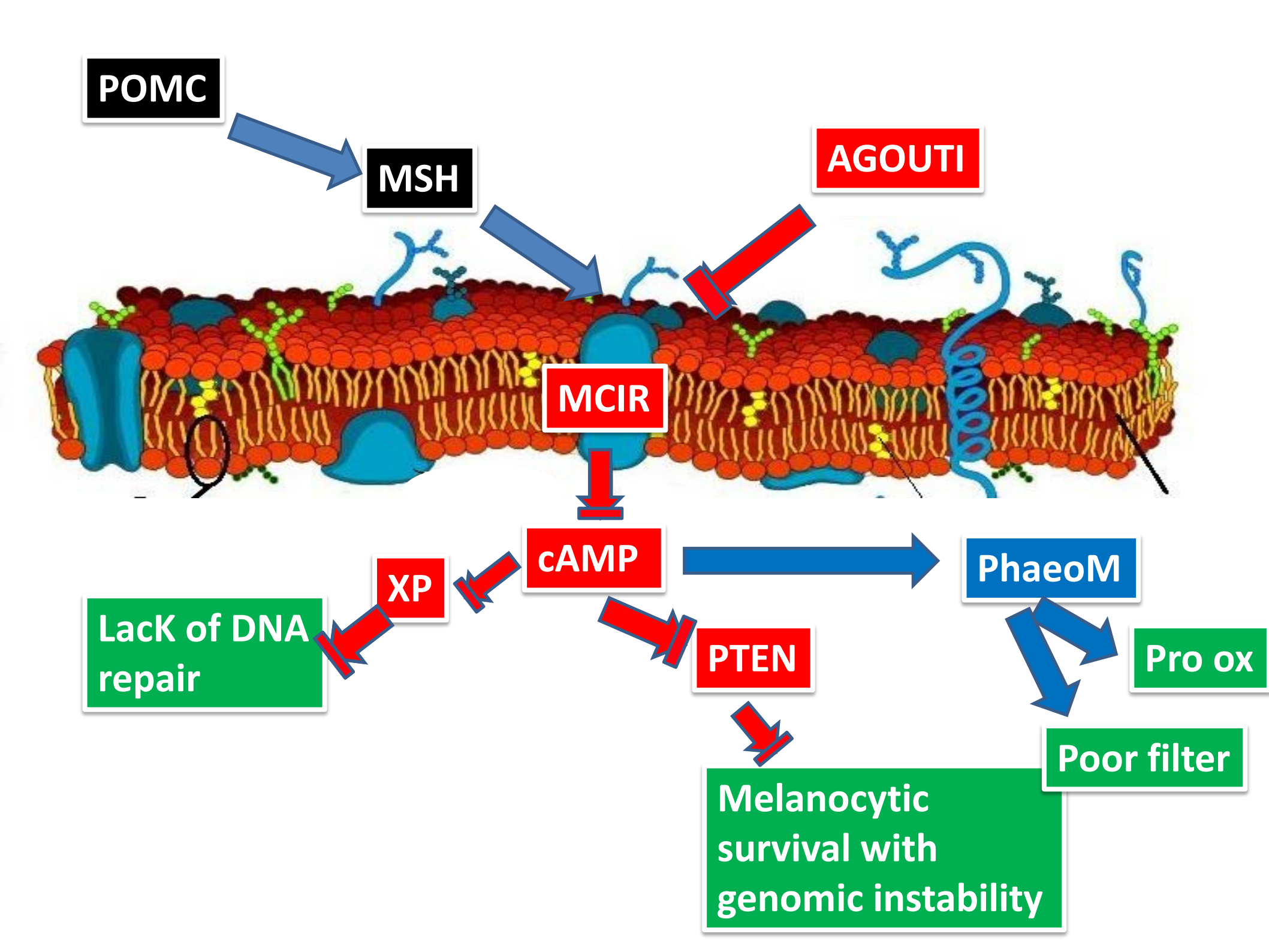
- RED HAIR POLIMORPHISMS
  - Increased risk for MM
  - Increased risk for MPM
  - Decrease the age of onset (10 yrs earlier)

Cutaneous phenotype and *MC1R* variants as modifying factors for the development of melanoma in *CDKN2A* G101W mutation carriers from 4 countries

Alisa M. Goldstein[1*], Valerie Chaudru[2], Paola Ghiorzo[3], Celia Badenas[4], Josep Malvehy[5], Lorenza Pastorino[3], Karine Laud[6], Benjamin Hulley[1], Marie-Francoise Avril[7], Joan A. Puig-Butille[4], Annie Miniere[6], Rosa Marti[8], Agnes Chompret[6], Francisco Cuellar[5], Isabel Kolm[5], Montserrat Mila[4], Margaret A. Tucker[1], Florence Demenais[2], Giovanna Bianchi-Scarra[3], Susana Puig[5] and Brigitte Bressac de-Paillerets[6]

Melanocortin 1 receptor and risk of cutaneous melanoma: a meta-analysis and estimates of population burden Williams PF et al. 2011




POMC
MSH
AGOUTI
MCIR
cAMP
XP
LacK of DNA repair
PTEN
Melanocytic survival with genomic instability
PhaeoM
Pro ox
Poor filter

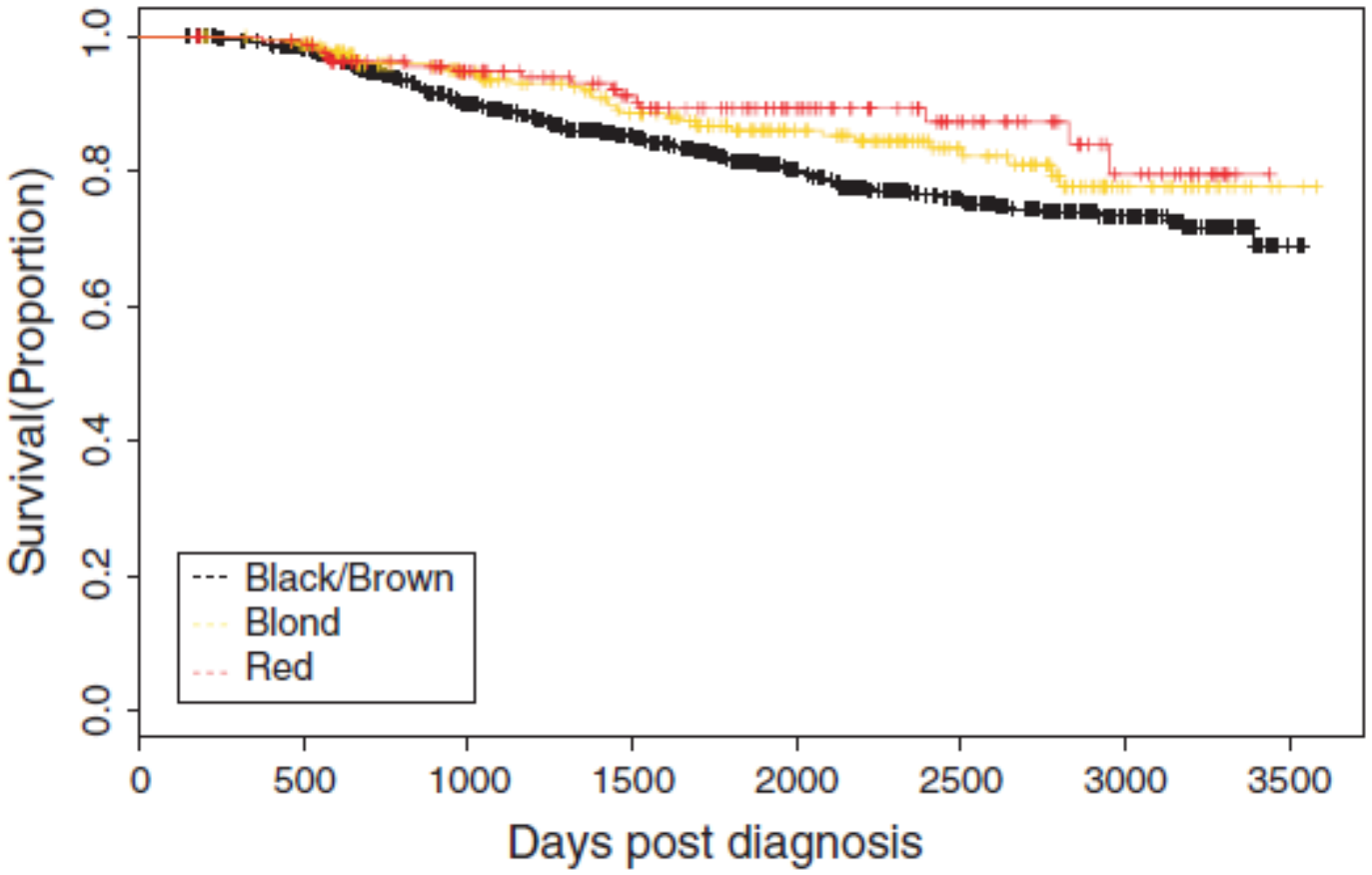
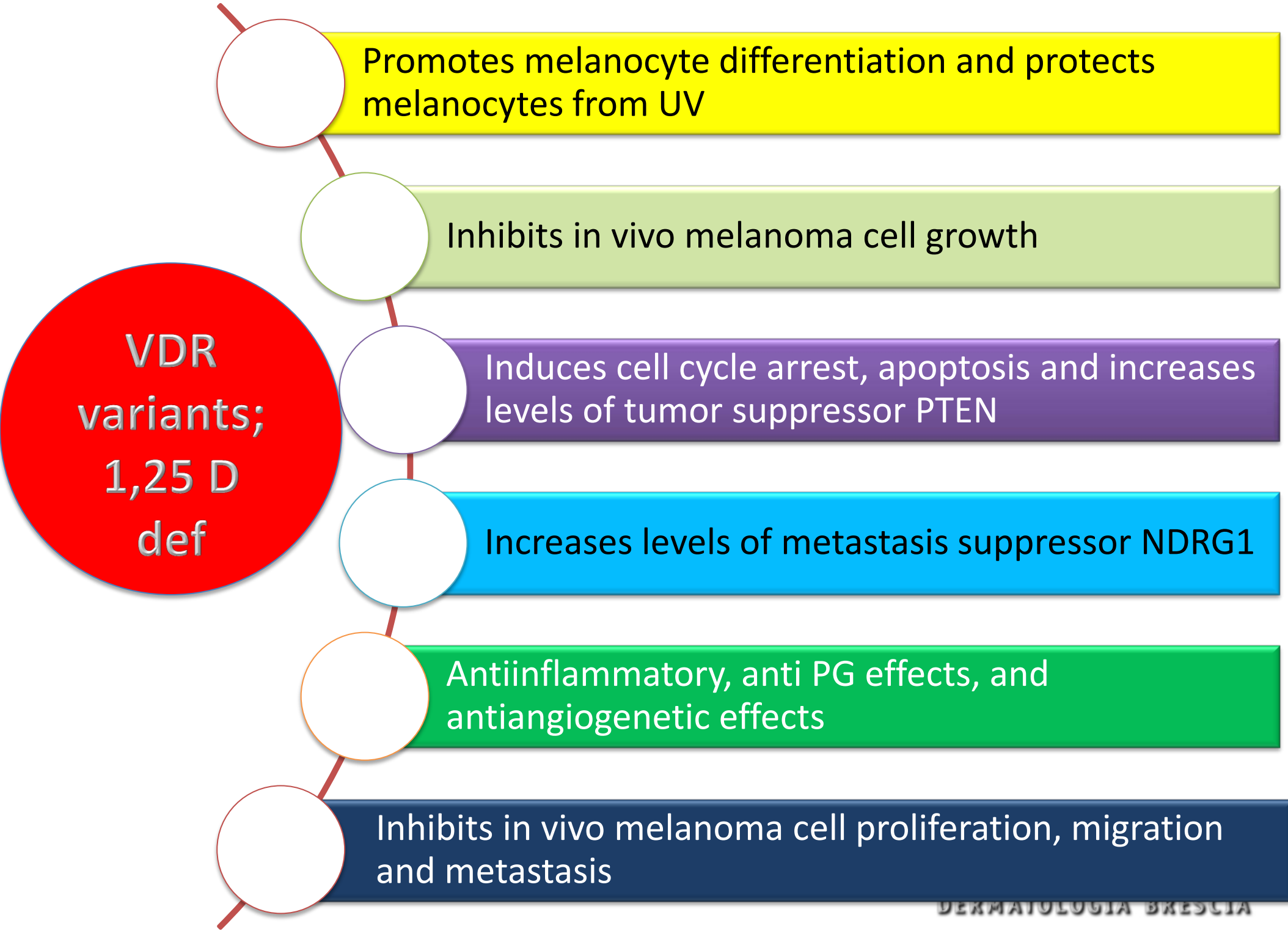


Figure 2. Kaplan–Meier curve showing differences in overall survival by hair color in the Leeds melanoma cohort (Black/brown = 965; Blond = 268; Red = 164; Log rank test, P = 0.02).

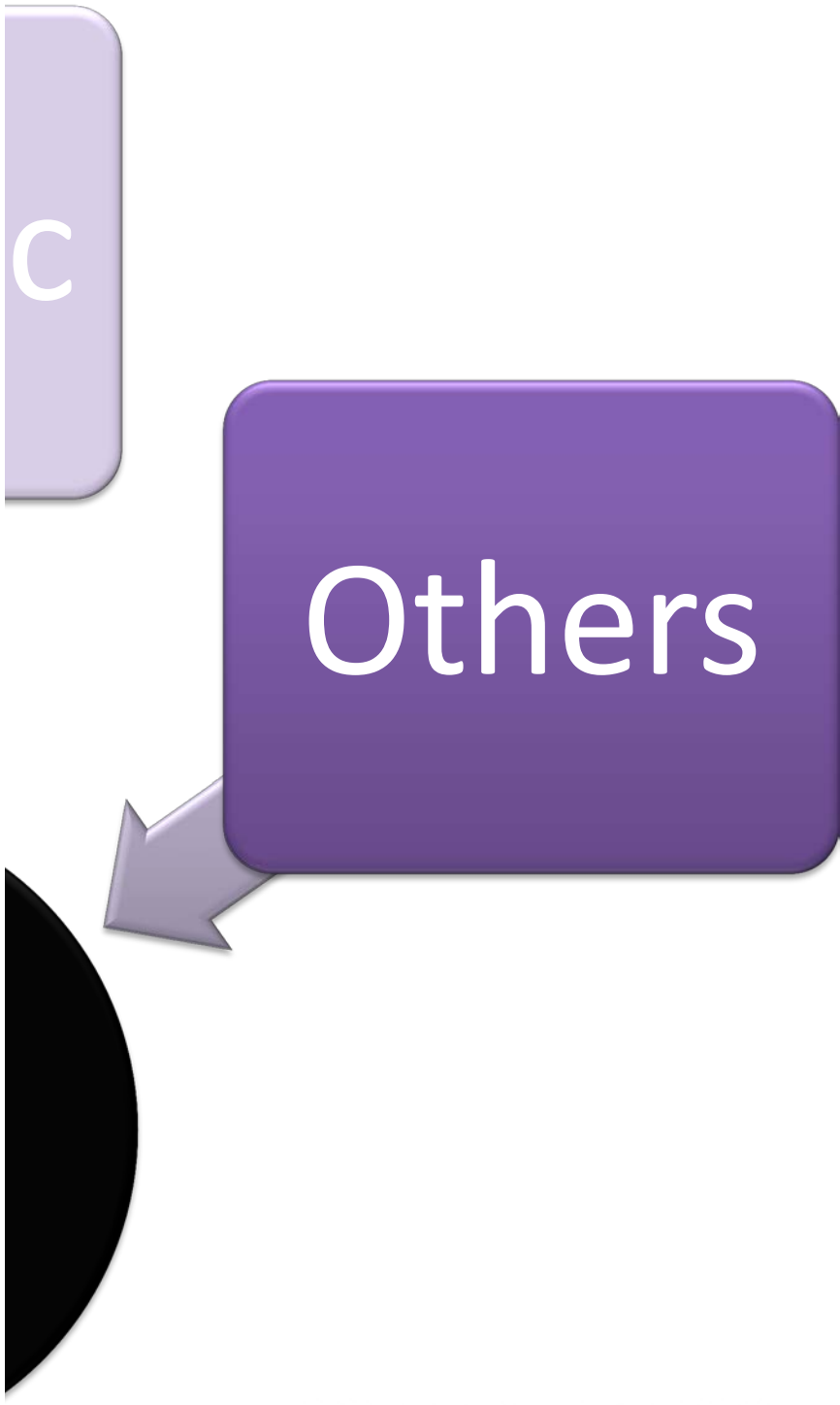
Inherited variants in the *MC1R* gene and survival from cutaneous melanoma: a BioGenoMEL study

John R. Davies[1], Juliette Randerson-Moor[1], Kairen Kukalizch[1], Mark Harland[1], Rajiv Kumar[2], Srinivasan Madhusudan[3], Eduardo Nagore[4], Johan Hansson[5], Veronica Höiom[5], Paola Ghiorzo[6], Nelleke A. Gruis[7], Peter A. Kanetsky[8], Judith Wendt[1,9], Dace Pjanova[10], Susana Puig[11,12], Philippe Saiag[13], Dirk Schadendorf[14], Nadem Soufir[15,16,17], Ichiro Okamoto[9], Paul Affleck[1], Zaida García-Casado[18], Zighereda Ogbah[11,12], Aija Ozola[10], Paola Queirolo[19], Antje Sucker[14], Jennifer H. Barrett[1], Remco van Doorn[7], D. Timothy Bishop[1] and Julia Newton-Bishop[1]

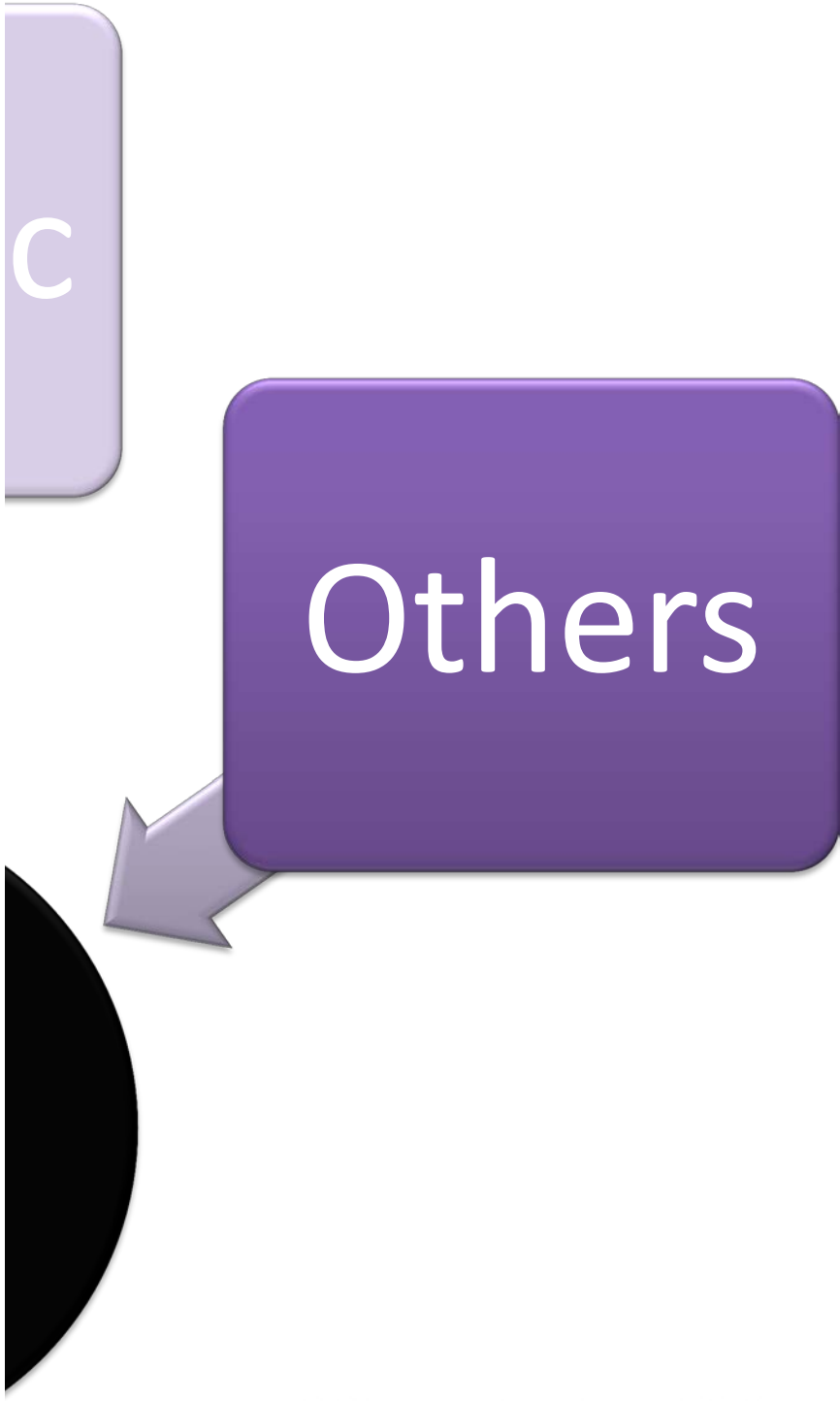
Pigment Cell Melanoma Res. **25**; 384–394



- Obesity
- Estrogens
- Oral chemicals
  1. PCB
  2. Pesticides
  3. Phototoxic drugs
  4. Sildenafil
- Topical chemicals
- Psoralens
- Sunscreens (?)

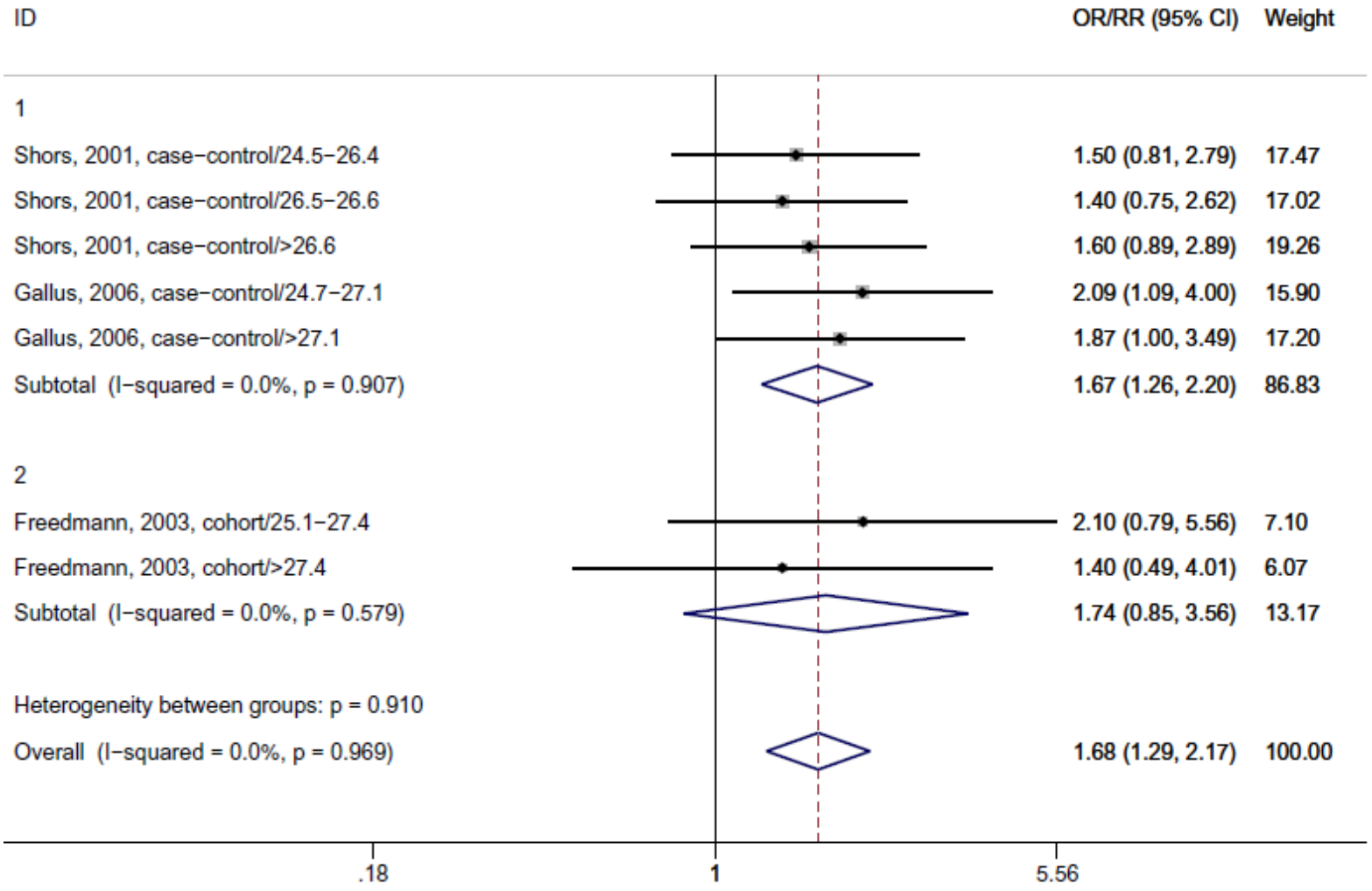


- **Obesity**
- Estrogens
- Oral chemicals
  1. PCB
  2. Pesticides
  3. Phototoxic drugs
  4. Sildenafil
- Topical chemicals
- Psoralens
- Sunscreens (?)



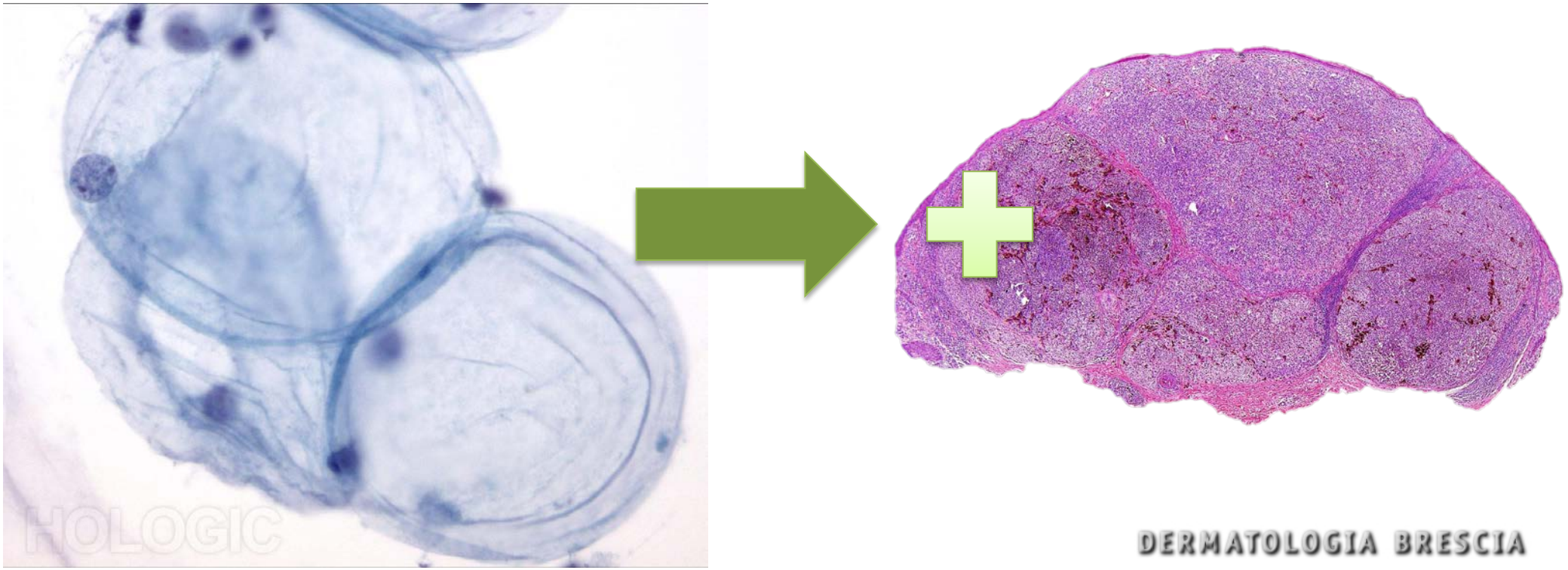
Obesity and risk of malignant melanoma: A meta-analysis of cohort and case–control studies

Theodoros N. Sergentanis [a], Antonios G. Antoniadis [a], Helen J. Gogas [b],

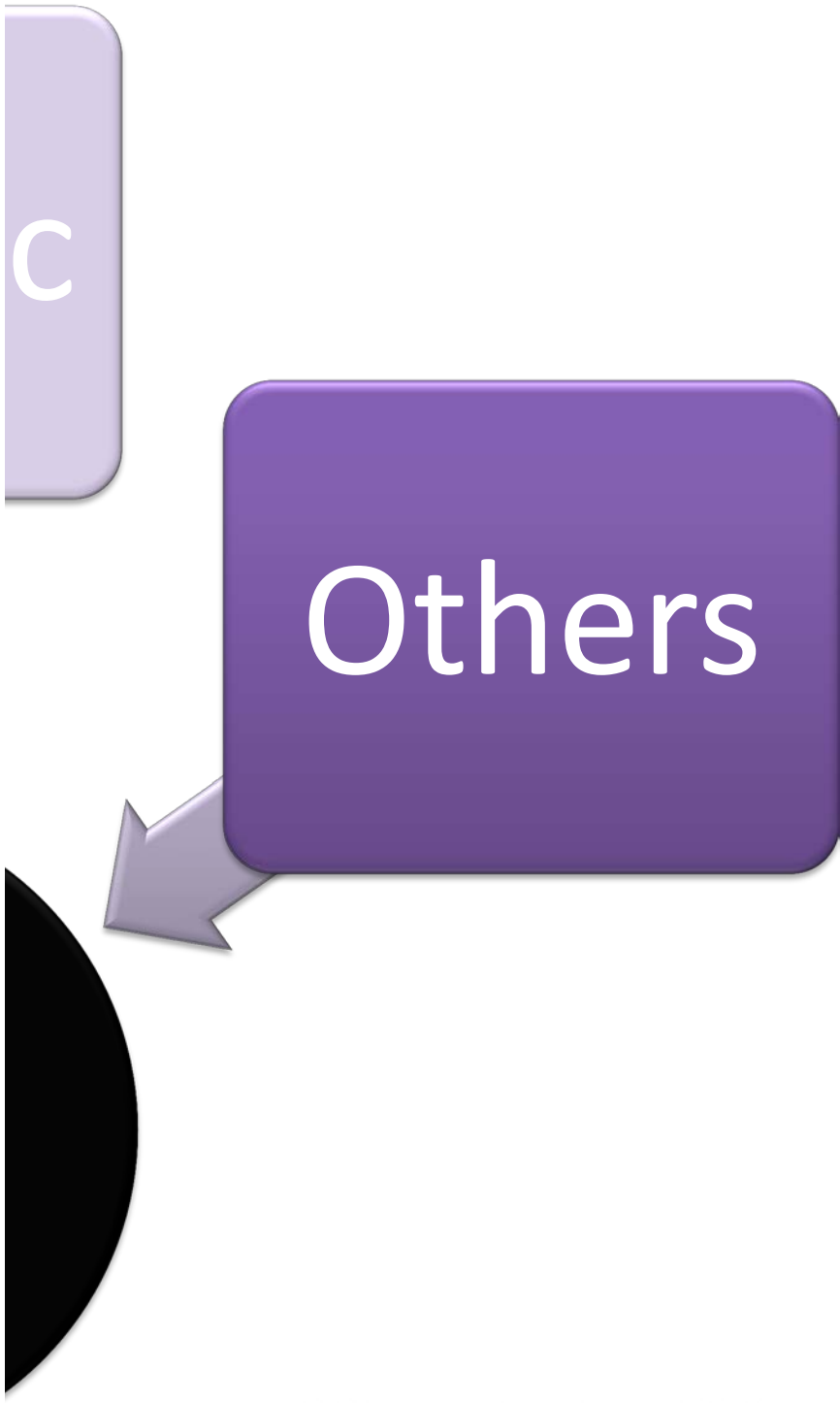


Kwan HY. Subcutaneous Adipocytes Promote Melanoma Cell Growth by Activating the Akt Signaling Pathway *J Biol Chem* 2014

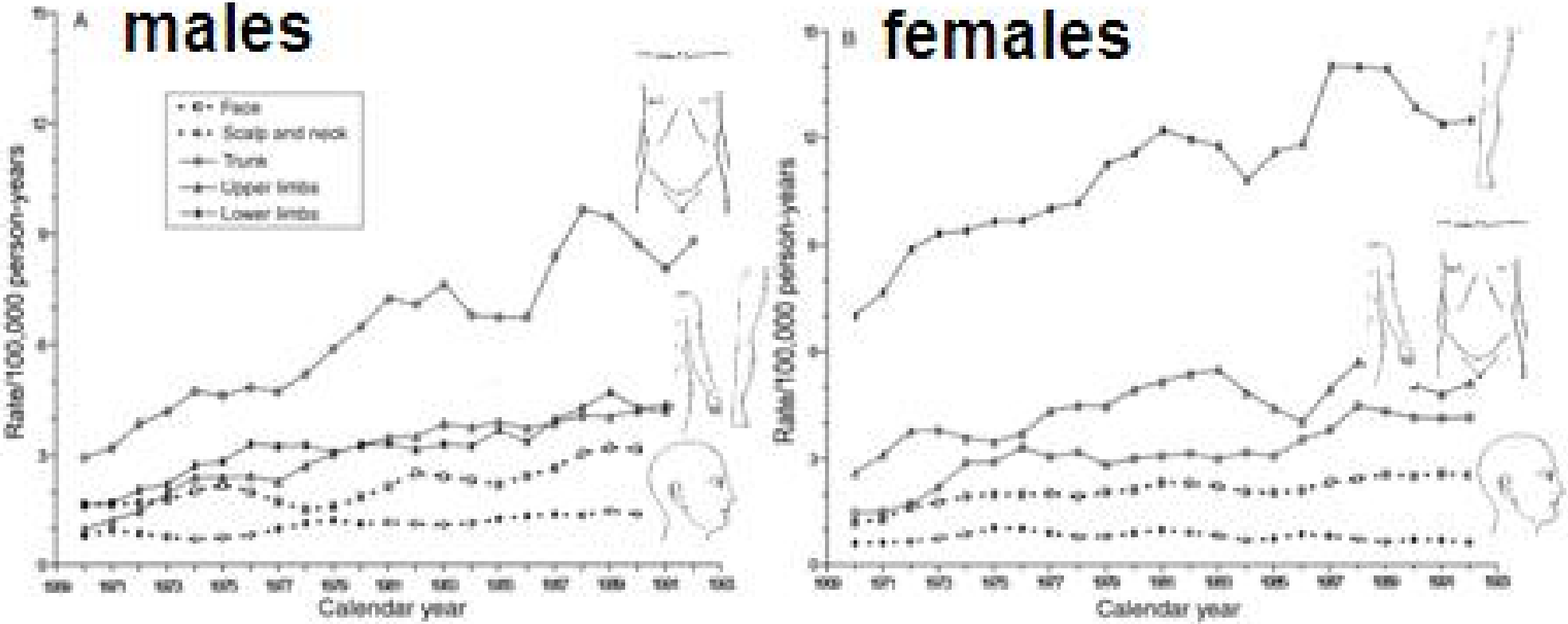
- Subcutaneous adipocytes may be an exogenous source of a FFA (palmitic acid) for melanoma growth by activating Akt signaling in a PTEN-independent manner.



- Obesity
- **Estrogens**
- Oral chemicals
  1. PCB
  2. Pesticides
  3. Phototoxic drugs
  4. Sildenafil
- Topical chemicals
- Psoralens
- Sunscreens (?)



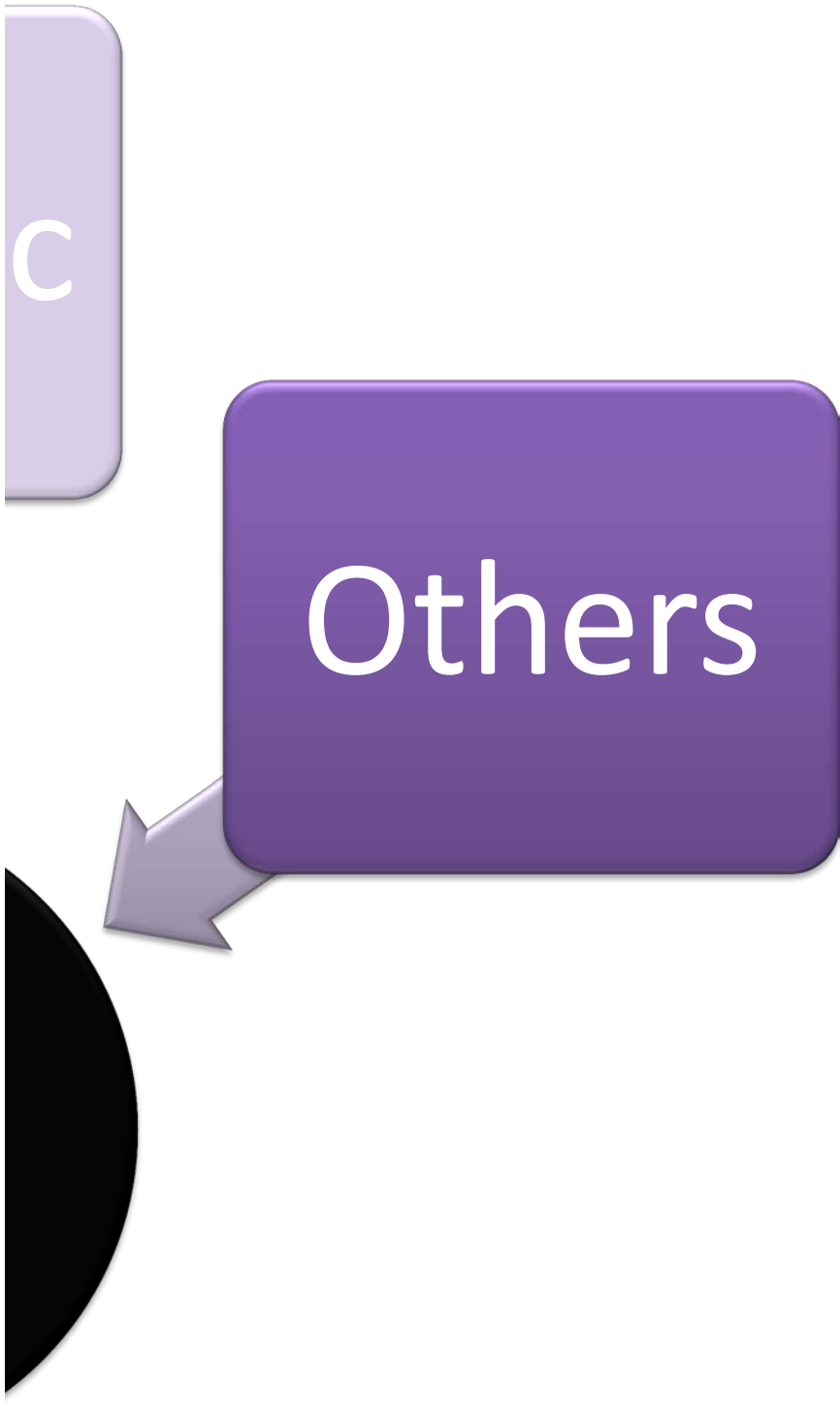
Age-standardized incidence rates of melanoma by sex and anatomical site, 1969-1993.



Bulliard, J.-L. et al. Int J. Epidemiol. 2000 29:416-423; doi:10.1093/ije/29.3.416

International Journal of Epidemiology

- Obesity
- Estrogens
- **Oral chemicals**
  1. **PCB**
  2. **Pesticides**
  3. Phototoxic drugs
  4. Sildenafil
- Topical chemicals
- Psoralens
- Sunscreens (?)



- Obesity
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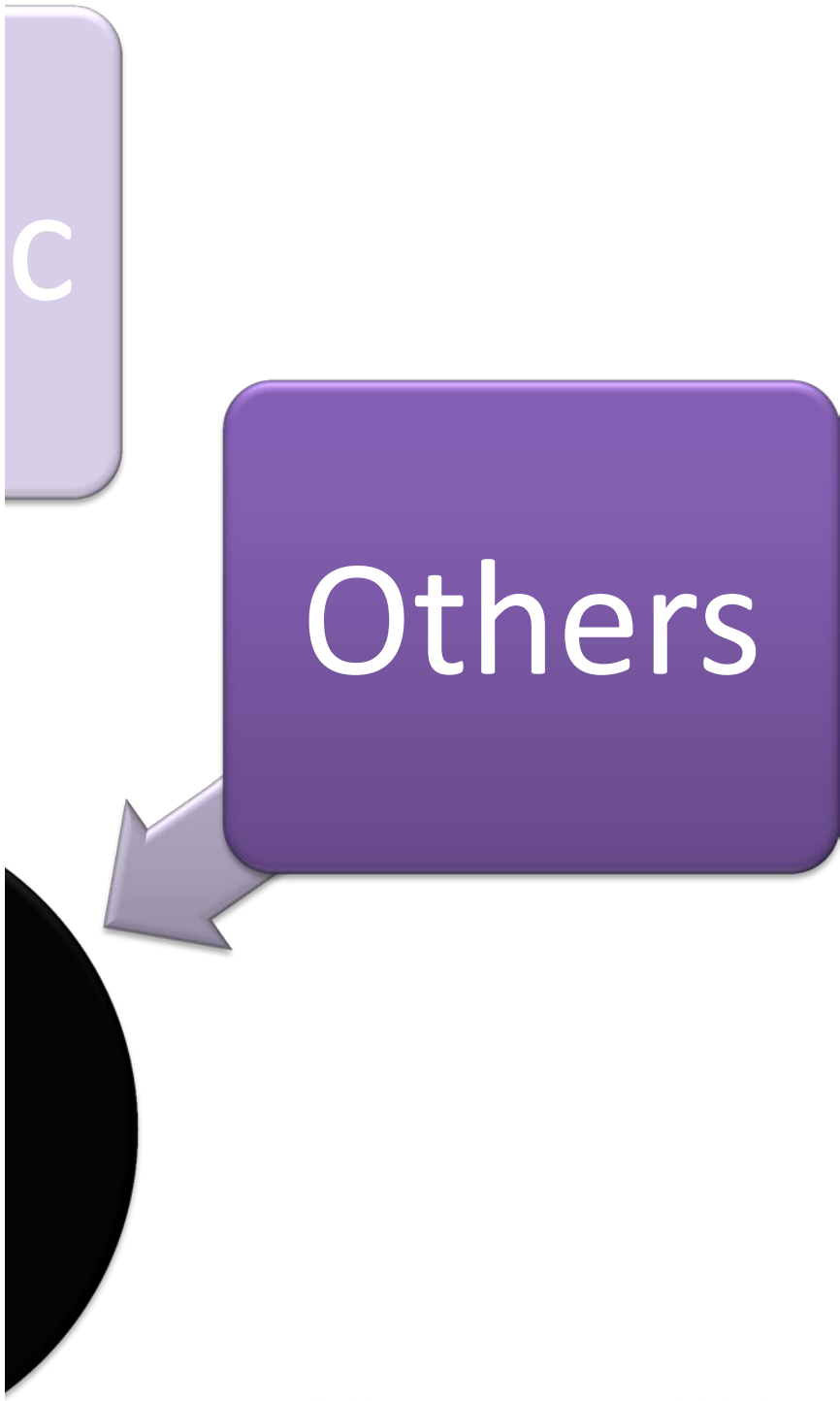
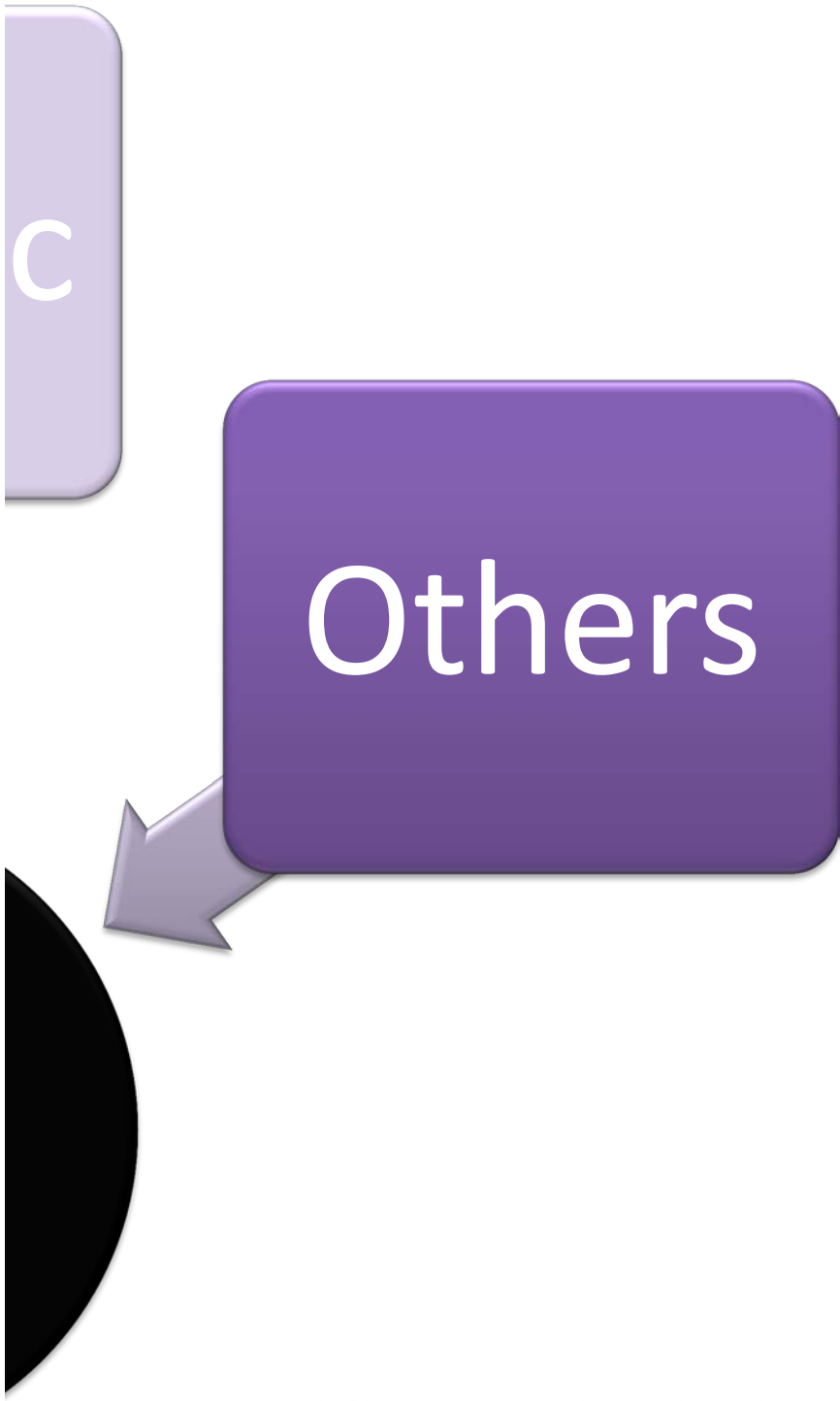


PHOTOSENSITIVE ORAL DRUGS ASSOCIATE WITH MELANOMA AND NMSC RISK

- DRUG PHOTOSENSITIZATION TIPICALLY IN THE UVA RANGE
- UVA PHOTOSENSITIZATION IN THE SHORT TERM IS RARELY NOTED BY SUNBURN
- UVA PHOTOSENSITIZATION IN THE LONG TERM MAY INITIATE AND PROMOTE SKIN CARCINOGENESIS
- DRUGS ASSOCIATED WITH SKIN CARCINOGENESIS IN LONG TERM STUDIES: THIAZIDE DIURETICS, ANTIMICROBIALS, FANS, PSYCHATRIC ETC

- Obesity
- Estrogens
- **Oral chemicals**
  1. PCB
  2. Pesticides
  3. Phototoxic drugs
  4. **Sildenafil**
- Topical chemicals
- Psoralens
- Sunscreens (?)



From: **Sildenafil Use and Increased Risk of Incident Melanoma in US Men: A Prospective Cohort Study**

JAMA Intern Med. 2014;():. doi:10.1001/jamainternmed.2014.594

Table 2. Hazard Ratios for Incident Melanoma, Squamous Cell Carcinoma, and Basal Cell Carcinoma Associated With Use of Sildenafil Citrate[a]

Diagnosis	Person-years	Cancer Cases, No.	Hazard Ratio (95% CI)	
			Age Adjusted	Multivariate Adjusted[b]
Melanoma				
No sildenafil use	193 935	128	1 [Reference]	1 [Reference]
Sildenafil use	10 935	14	1.93 (1.11-3.37)	1.84 (1.04-3.22)
Squamous cell carcinoma				
No sildenafil use	190 716	548	1 [Reference]	1 [Reference]
Sildenafil use	10 714	32	0.90 (0.63-1.29)	0.84 (0.59-1.20)
Basal cell carcinoma				
No sildenafil use	190 716	2838	1 [Reference]	1 [Reference]
Sildenafil use	10 714	192	1.12 (0.97-1.30)	1.08 (0.93-1.25)

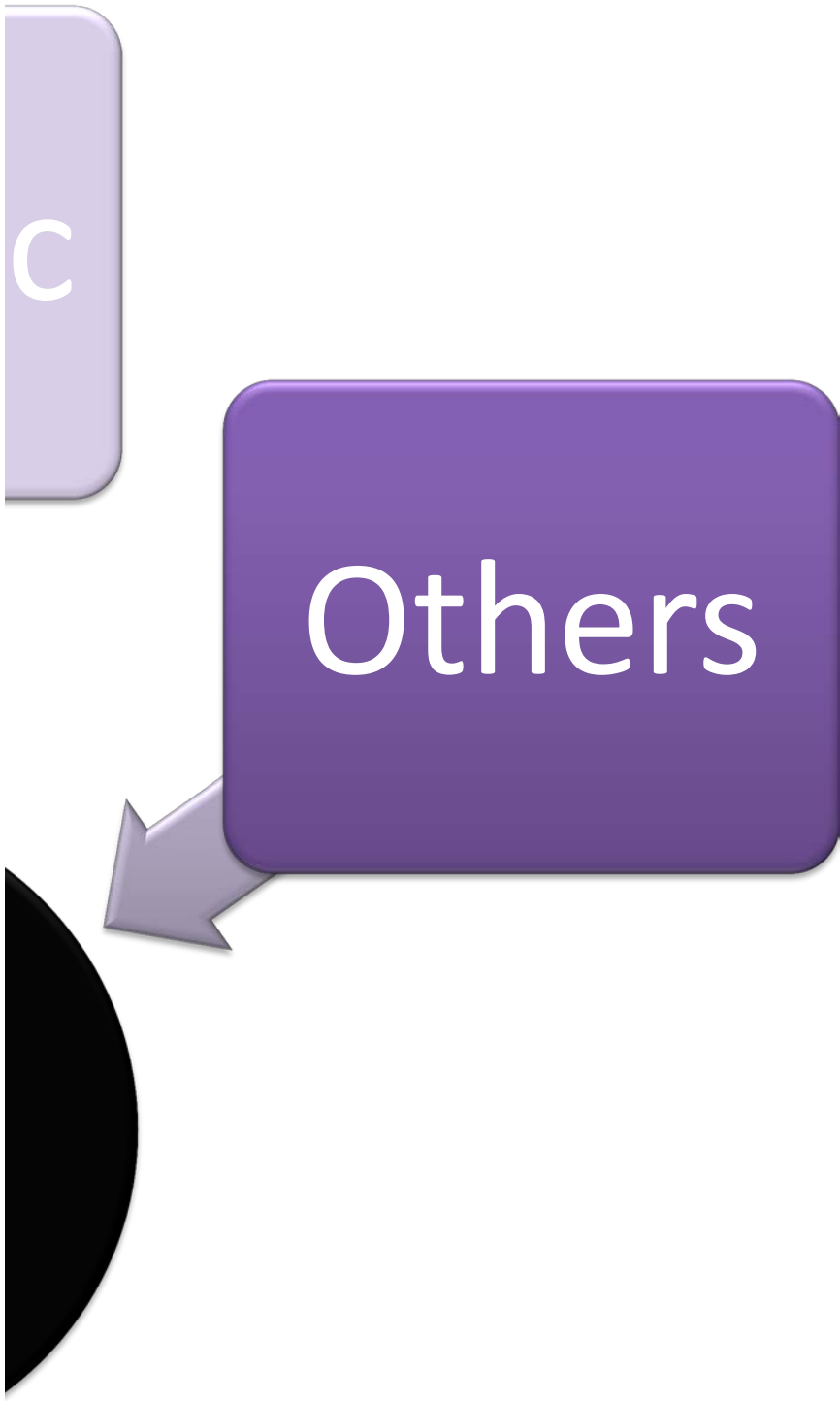
[a] Data from the Health Professionals' Follow-up Study (2000-2010).

[b] Adjusted for age (continuous variable), body mass index (<24.9, 25-29.9, or ≥30 [calculated as weight in kilograms divided by height in meters squared]); smoking (never, past, or current); physical activity (in quintiles, metabolic equivalent hours per week); childhood reaction to sun (tan without burn, burn, or painful burn/blisters); number of sunburns (0, 1-2, 3-5, or ≥6); mole count (0, 1-2, 3-5, or ≥6); hair color (red, blond, light brown, or dark brown/black); family history of melanoma (yes or no); sun exposure at high school age and age 25 to 35, 36 to 59, and ≥60 y (<5, 6-10, or ≥11 h/wk for each); UV index at birth and age 15 and 30 y (≤5, 6, or ≥7); and other treatment for erectile dysfunction.

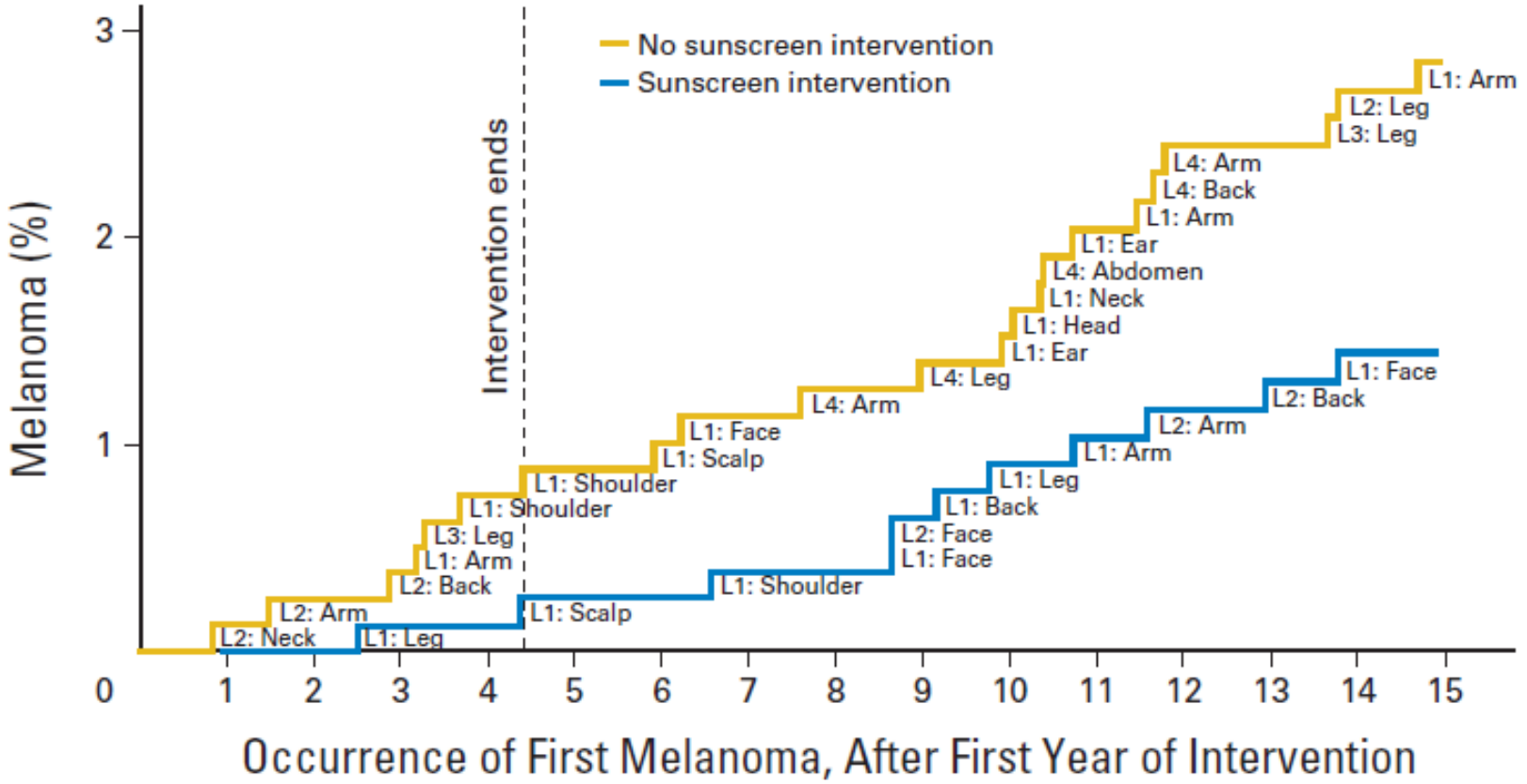
Figure Legend:

Hazard Ratios for Incident Melanoma, Squamous Cell Carcinoma, and Basal Cell Carcinoma Associated With Use of Sildenafil Citrate[a]

- Obesity
- Estrogens
- Oral chemicals
  1. PCB
  2. Pesticides
  3. Phototoxic drugs
  4. Sildenafil
- **Topical chemicals**
  1. **Furocoumarins**
  2. **Sunscreens (?)**



Unintentional Sun Exposure
Melanoma Incidence after 1 Y. of Intervention



Persons at risk

No sunscreen intervention	809	806	804	803	798	792	789	784	780	773	764	752	745	740	738
Sunscreen intervention	812	808	804	800	795	788	782	780	773	769	763	754	747	744	741

J Clin Oncol. 2011; 29: 257-63

Pigment Cell Melanoma Res. 23; 835–837

Sunscreen prevention of melanoma in man and mouse

Heather L. P. Klug[1], Janet A. Tooze[2], Cari Graff-Cherry[3], Miriam R. Anver[3], Frances P. Noonan[4], Thomas R. Fears[5], Margaret A. Tucker[5], Edward C. De Fabo[4] and Glenn Merlino[6]

[1]Regional Academic Health Center-Edinburg, The University of

strate for the first time significant sunscreen prevention in UV-dependent, melanoma-prone transgenic mice, and propose that when applied properly should be preventive in people.

Human epidemiologic studies of melanoma prevention are limited by recall bias, insufficient statistical power, and non-uniform estimations of sun exposure

Sunscreen use	Number of controls[a]	Number of cases[b]	Total	OR[c] (95% CI)
No use	202	147	349	Referent
Ever use	743	570	1313	0.90 (0.70–1.19)
Total	945	717	1662	
Burn easily	186	160	346	0.85 (0.62–1.19)
Do not burn	557	410	967	0.91 (0.70–1.19)
Total	743	570	1313	

All OR adjusted for ambient residential UV intensity, number of hours outdoors, tan type, number of sunburns, gender, age group, and study site

The paradox of the sunscreen use and skin cancer

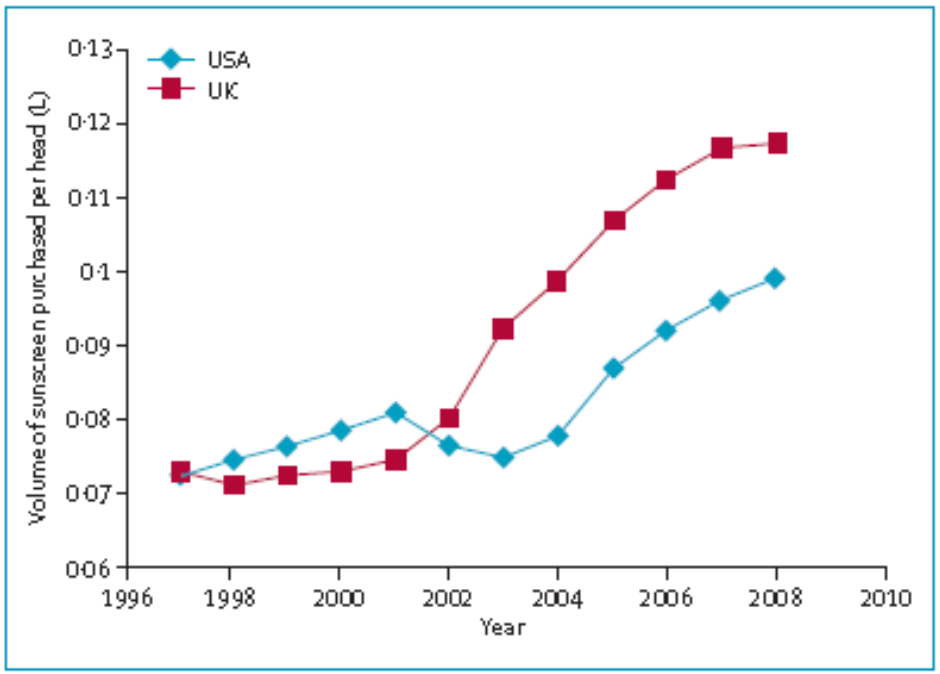
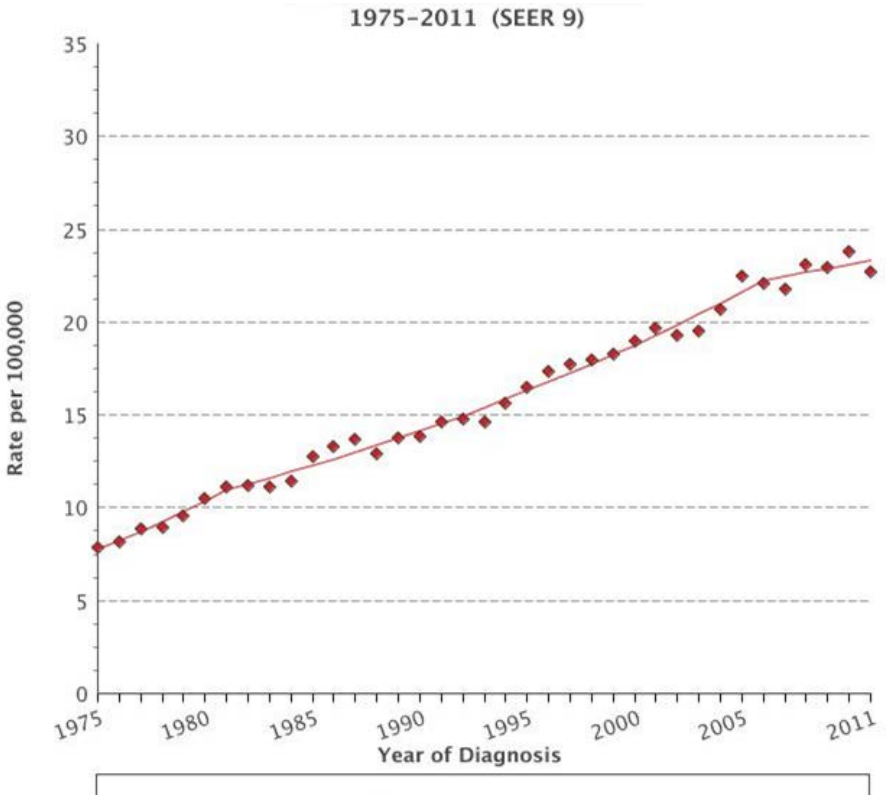


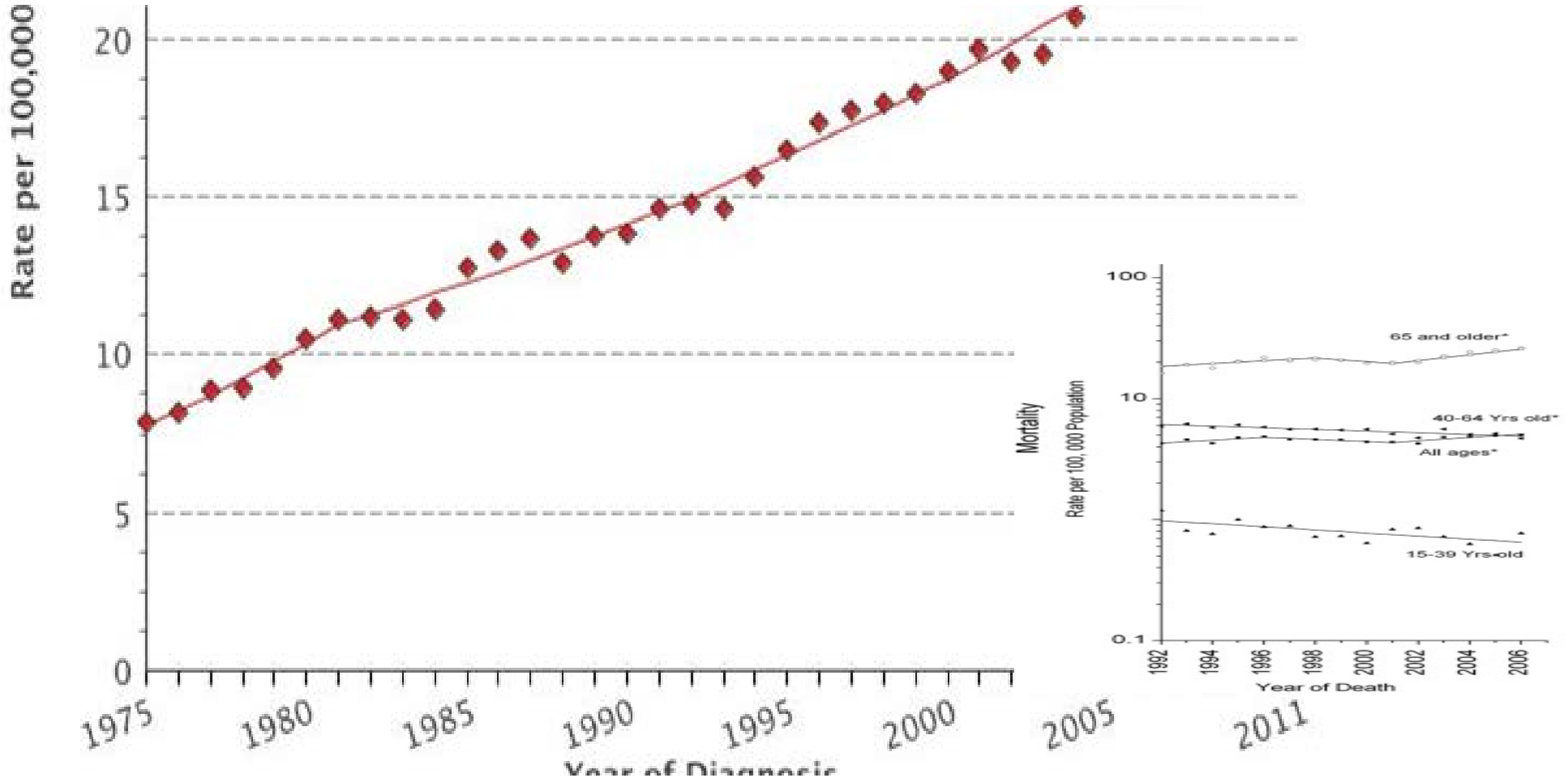
Figure: Purchase of sunscreen products by volume per head over time in the USA and UK[3,4]



Madan V et al, Lancet, 376: 161-2, 2010.


Thank you

MELANOMA: INCREASING INCIDENCE AND STEADY MORTALITY



Age-Adjusted SEER Incidence Rates
By Cancer Site
All Ages, All Races, Both Sexes
1975-2011 (SEER 9)

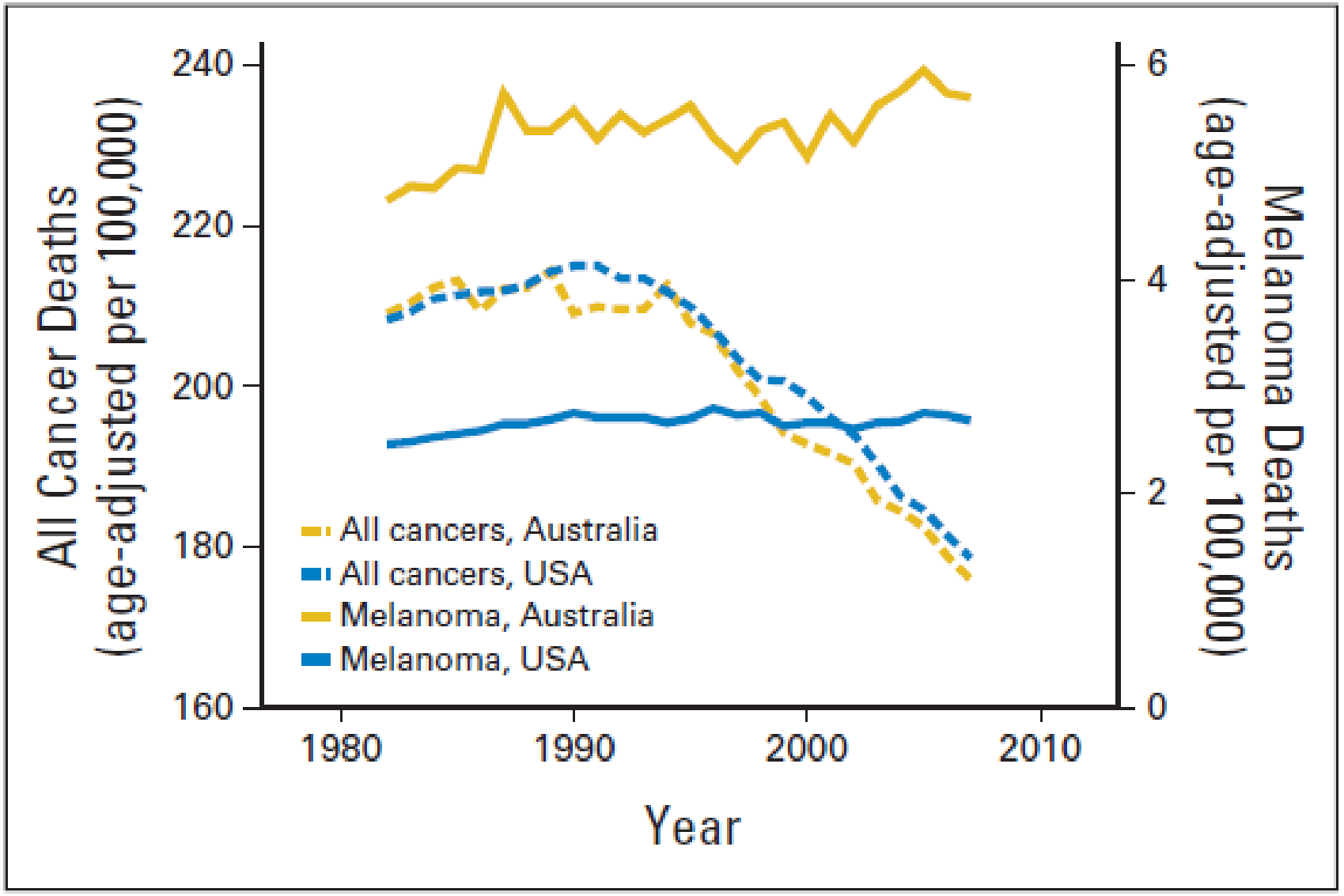


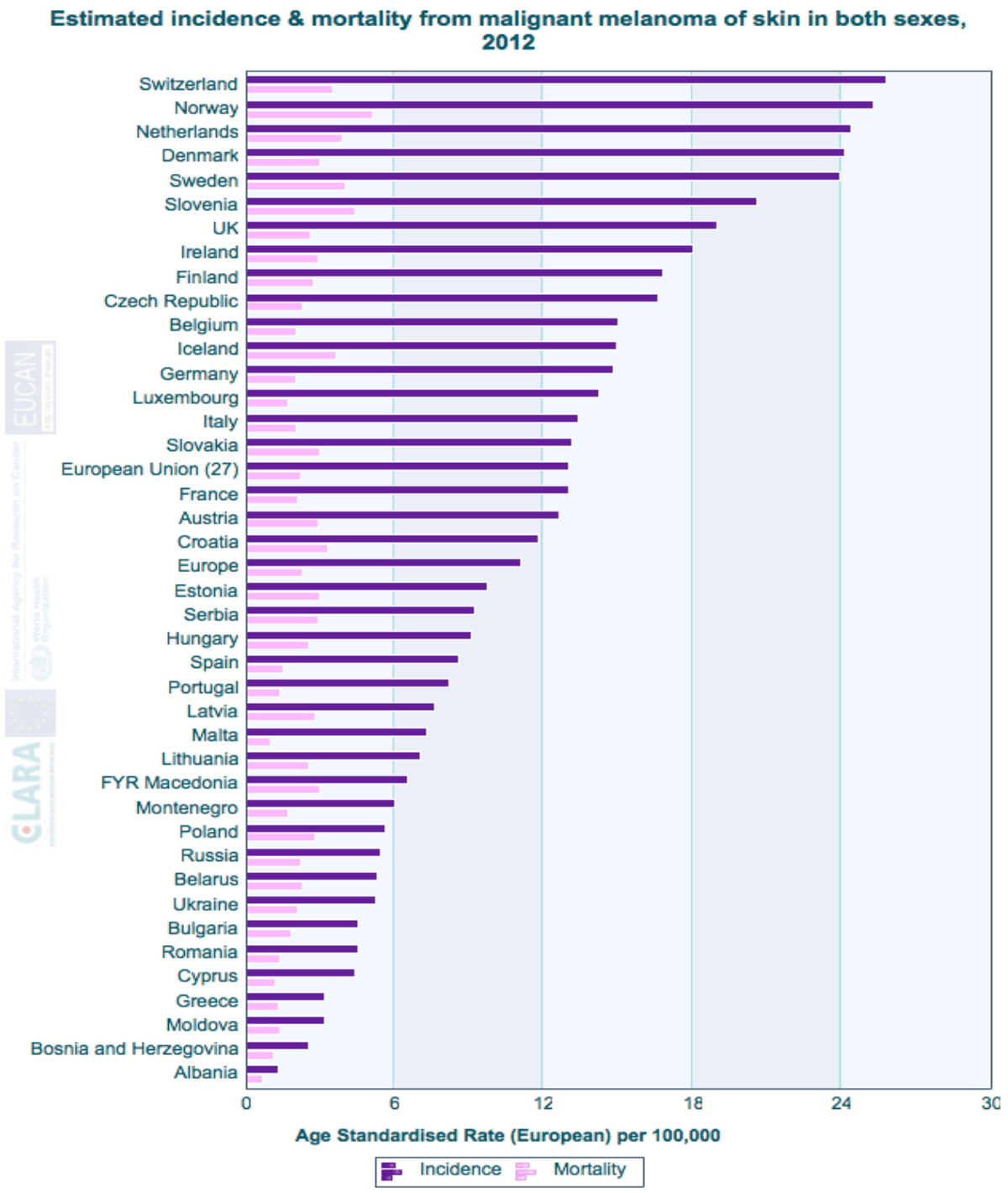
Fig 1. Age-adjusted total cancer and melanoma mortality in the United States (USA) and Australia, 1982 to 2007.[2,2a]

Targeting Oncogenic Drivers and the Immune System in Melanoma

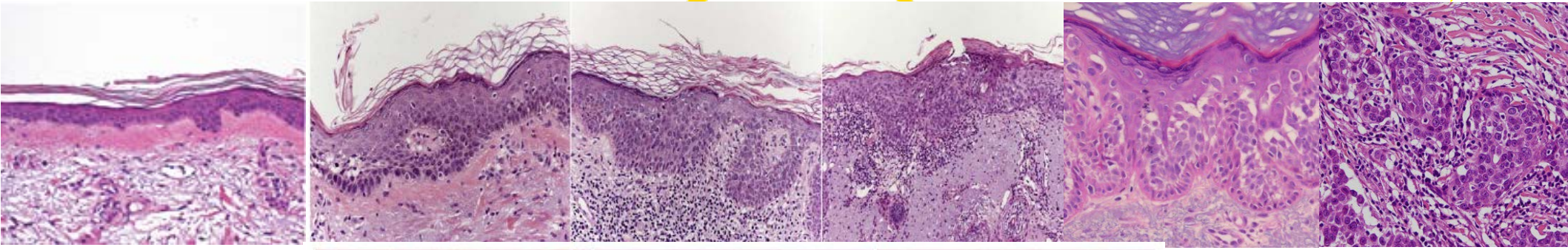
Grant A. McArthur and Antoni Ribas

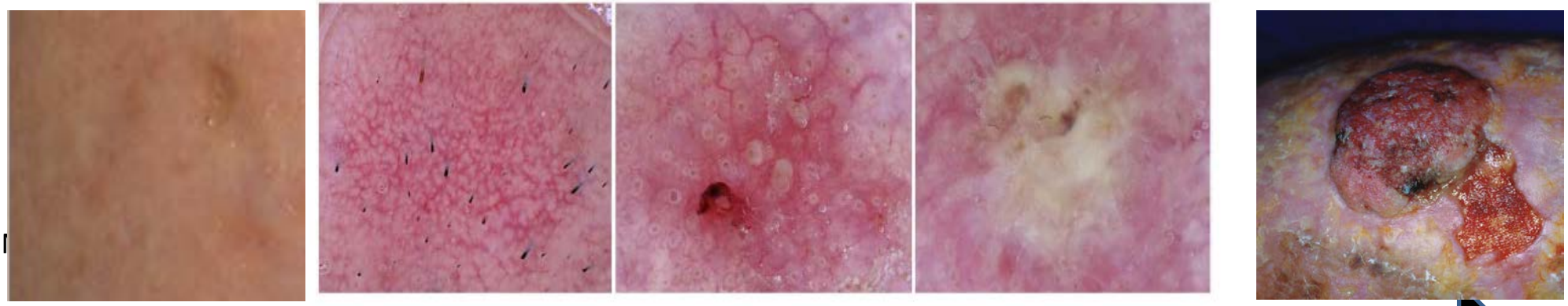
J Clin Oncol 31:499-506. © 2012 by American Society of Clinical Oncology

Melanoma Eucan



p53± p16± Bcl2+ MYC+ EGFR+ RAS+ Hsp27+ Stat3- Notch-



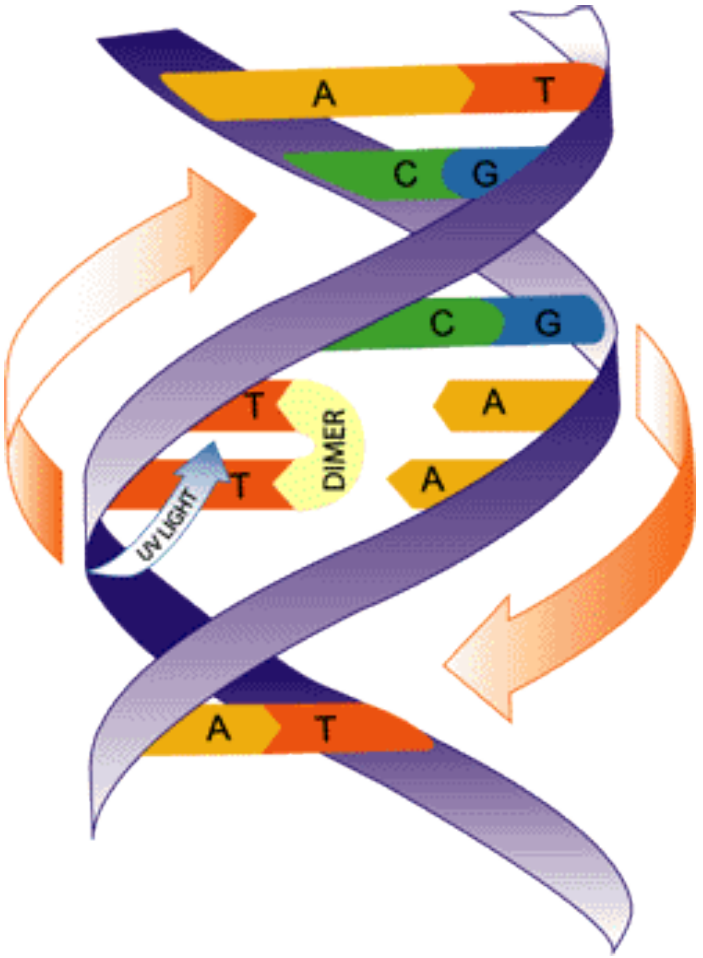


I° II° III° isSCC

Oncogenes synergy, Aneuploidy, Chromosomal deletions to complex aberrations (translocation chr, isochr, chr amplification), Apoptosis resistance, Clonal expansione

Fattori genetici

- Next-generation sequencing, have increased the opportunities for the discovery of inherited germline high- (CDKN2A and others), intermediate-, and low-risk susceptibility genes and somatic genes.
- (Hill VK et al 2013)



Genetic alterations in RAS regulated pathway in Acral Lentiginous Melanoma

Joan Anton Puig-Butillé[1,2], **Celia Badenas**[1,2], **Zighereda Ogbah**[3], **Cristina Carrera**[1,3], **Paula Aguilera**[1,3], **Josep Malvehy**[1,3], and **Susana Puig**[1,3]

Abstract

Studies integrating clinicopathological and genetic features have revealed distinct patterns of genomic aberrations in Melanoma. Distributions of *BRAF* or *NRAS* mutations and gains of several oncogenes differ among melanoma subgroups while 9p21 deletions are found in all melanoma subtypes.

In the study, status of genes involved in cell cycle progression and apoptosis were evaluated in a panel of 17 frozen primary acral melanomas.

NRAS—mutations were found in 17% of the tumours. In contrast, *BRAF* mutations were not found. Gains of *AURKA* gene (20q13.3) were detected in 37.5% of samples, gains of *CCND1* gene (11q13) or *TERT* gene (5p15.33) in 31.2% and gains of NRAS gene (1p13.2) in 25%. Alterations in 9p21 were identified in 69% of tumours. Gains of 11q13 and 20q13 were mutually exclusive; and 1p13.2 gain was associated with 5p15.33.

Our findings showed that alterations in RAS related pathways are present in 87.5% of acral lentiginous melanomas.

Exp Dermatol. 2013 February ; 22(2): 148–150.

✓ **BRAF** (B-Raf proto-oncogene, serine/threonine kinase)

Mutations of the *BRAF* gene in human cancer

Helen Davies[1,2], Graham R. Bignell[1,2], Charles Cox[1,2], Philip Stephens[1,2], Sarah Edkins[1], Sheila Clegg[1], Jon Teague[1], Hayley Woffendin[1], Mathew J. Garnett[3], William Bottomley[1], Neil Davis[1], Ed Dicks[1], Rebecca Ewing[1], Yvonne Floyd[1], Kristian Gray[1], Sarah Hall[1], Rachel Hawes[1], Jaime Hughes[1], Vivian Kosmidou[1], Andrew Menzies[1], Catherine Mould[1], Adrian Parker[1], Claire Stevens[1], Stephen Watt[1], Steven Hooper[3], Rebecca Wilson[3], Hiran Jayatilake[4], Barry A. Gusterson[5], Colin Cooper[6], Janet Shipley[6], Darren Hargrave[7], Katherine Pritchard-Jones[7], Norman Maitland[8], Georgia Chenevix-Trench[9], Gregory J. Riggins[10], Darell D. Bigner[10], Giuseppe Palmieri[11], Antonio Cossu[12], Adrienne Flanagan[13], Andrew Nicholson[14] Judy W. C. Ho[15], Suet Y. Leung[16], Siu T. Yuen[16], Barbara L. Weber[17], Hilliard F. Seigler[18], Timothy L. Darrow[18], Hugh Paterson[3], Richard Marais[3], Christopher J. Marshall[3], Richard Wooster[1,6], Michael R. Stratton[1,4] & P. Andrew Futreal[1]

COSMIC
Catalogue of somatic mutations in cancer

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Cosmic » Gene » Analysis » BRAF

Histogram | Mutations | Fusions | Tissue | Distribution | CNV & Expr

Mutation Distribution Pie Charts

Distribution Overview | Substitutions (coding strand) | Substitutions (both strands) | Deletions | Insertions

Color	Mutation Type	Mutant samples	Percentage
	Substitution nonsense	2	0.03
	Substitution missense	6287	93.65
	Substitution synonymous	28	0.42
	Insertion inframe	5	0.07
	Insertion frameshift	0	0.00
	Deletion inframe	0	0.00
	Deletion frameshift	0	0.00
	Complex	21	0.31
	Other	410	6.11
	Total	6713	100

Note:The sum of mutant samples might not be equal to "Total" because each number represents the total number of unique samples in that category, so a sample having mutations in one or more categories would be counted once in total. This total is used to calculate the percentage so it might not add up to 100% either.

Filters

Gene: BRAF

Position: Start 1 — End 743

Sequence Type: cDNA / Amino Acid

Sites: Skin

Histology: Malignant Melanoma

Systematic Screen | Somatic Status | Tumour Source | Mutation Type | Copy Number Variation | Gene Expression

Apply | Reset

Help | Contact us | Legal | Cookies policy | Data sharing

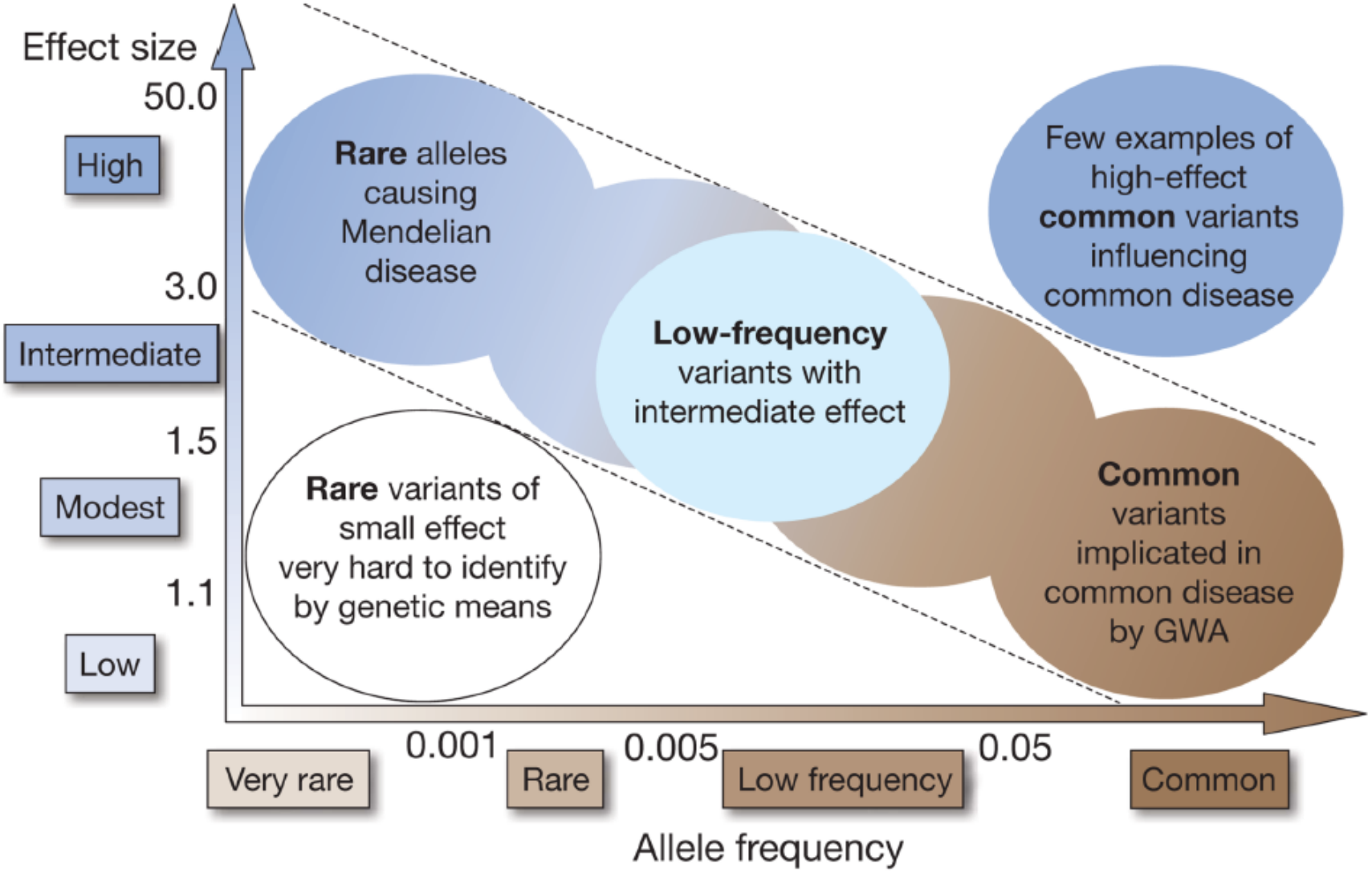


Figure 1. Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio)

Most emphasis and interest lies in identifying associations with characteristics shown within diagonal dotted lines. Adapted from ref. 42.

Finding the missing heritability of complex diseases

Teri A. Manolio[1], Francis S. Collins[2], Nancy J. Cox[3], David B. Goldstein[4], Lucia A. Hindorff[5], David J. Hunter[6], Mark I. McCarthy[7], Erin M. Ramos[5], Lon R. Cardon[8], Aravinda Chakravarti[9], Judy H. Cho[10], Alan E. Guttmacher[1], Augustine Kong[11], Leonid Kruglyak[12], Elaine Mardis[13], Charles N. Rotimi[14], Montgomery Slatkin[15], David Valle[9], Alice S. Whittemore[16], Michael Boehnke[17], Andrew G. Clark[18], Evan E. Eichler[19], Greg Gibson[20], Jonathan L. Haines[21], Trudy F. C. Mackay[22], Steven A. McCarroll[23], and Peter M. Visscher[24]

Nature. 2009 October 8; 461(7265): 747–753.

Sunny Holidays before and after Melanoma Diagnosis Are Respectively Associated with Lower Breslow Thickness and Lower Relapse Rates in Italy

Sara Gandini[1*], Esther De Vries[2], Giulio Tosti[3], Edoardo Botteri[1], Giuseppe Spadola[3], Patrick Maisonneuve[1], Chiara Martinoli[4], Arien Joosse[2], Pier Francesco Ferrucci[4], Federica Baldini[3], Emilia

Figure 2b. Group 1, at diagnosis:
Percentages of very thick CM (Breslow>4mm) by weeks of sunny holidays

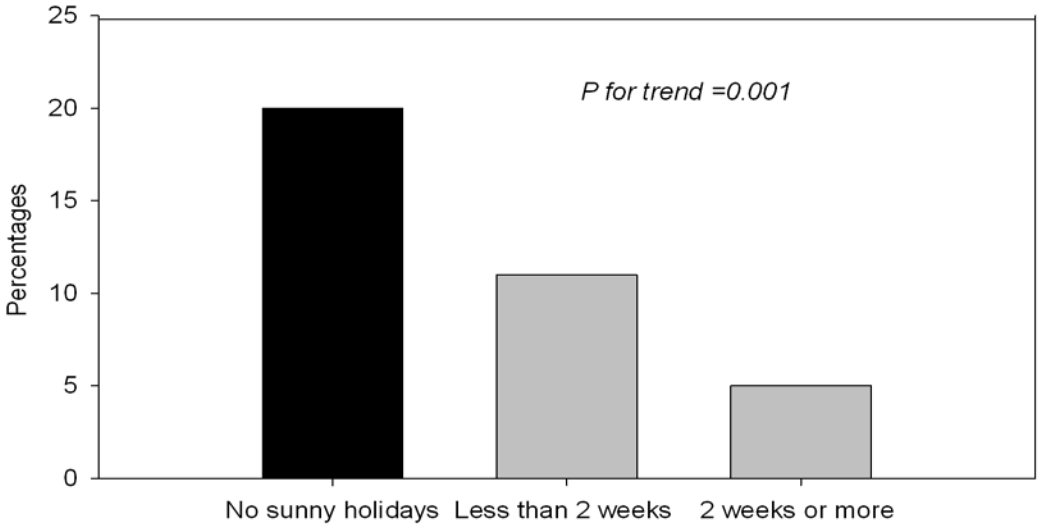
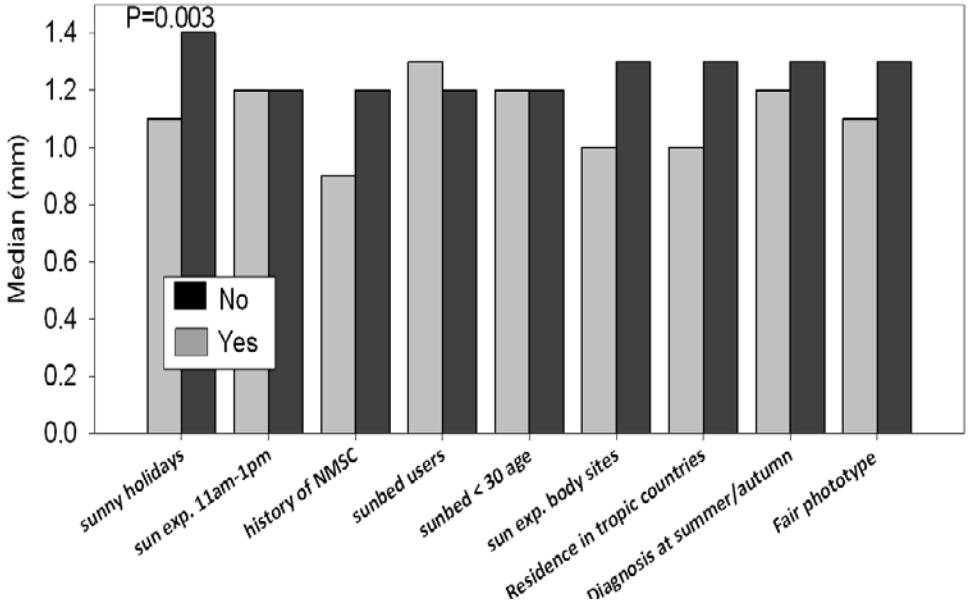


Figure 3a. Group 1, at diagnosis: Breslow thickness by UV exposure indicators



MELANOMA SURVIVAL

NE

Sunny Holidays before and after Melanoma Diagnosis Are Respectively Associated with Lower Breslow Thickness and Lower Relapse Rates in Italy

Sara Gandini[1*], Esther De Vries[2], Giulio Tosti[3], Edoardo Botteri[1], Giuseppe Spadola[3], Patrick Maisonneuve[1], Chiara Martinoli[4], Arjen Joosse[2], Pier Francesco Ferrucci[4], Federica Baldini[3], Emilia Cocorocchio[4], Elisabetta Pennacchioli[3], Francesco Cataldo[3], Barbara Bazolli[1], Alessandra Clerici[1], Massimo Barberis[5], Veronique Bataille[6☯], Alessandro Testori[3☯]

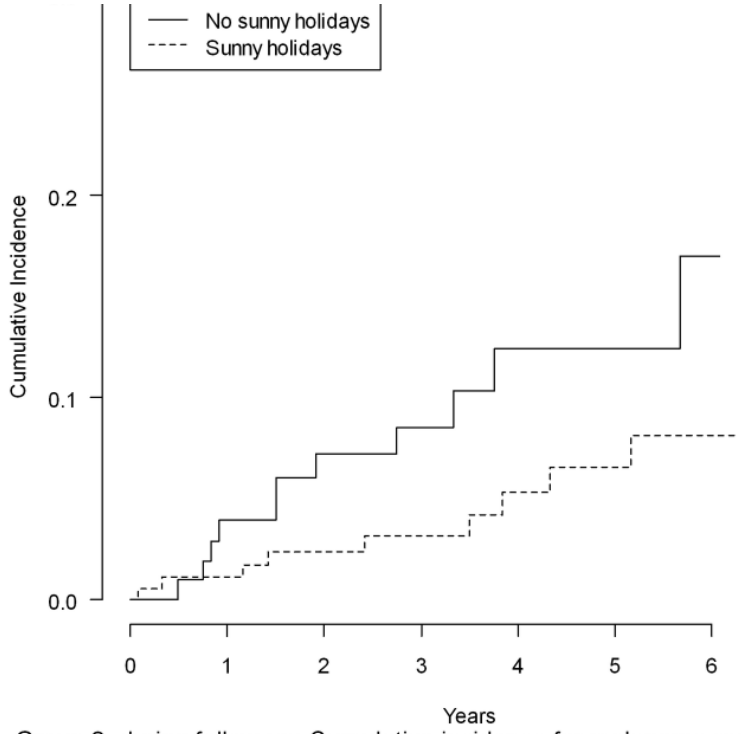
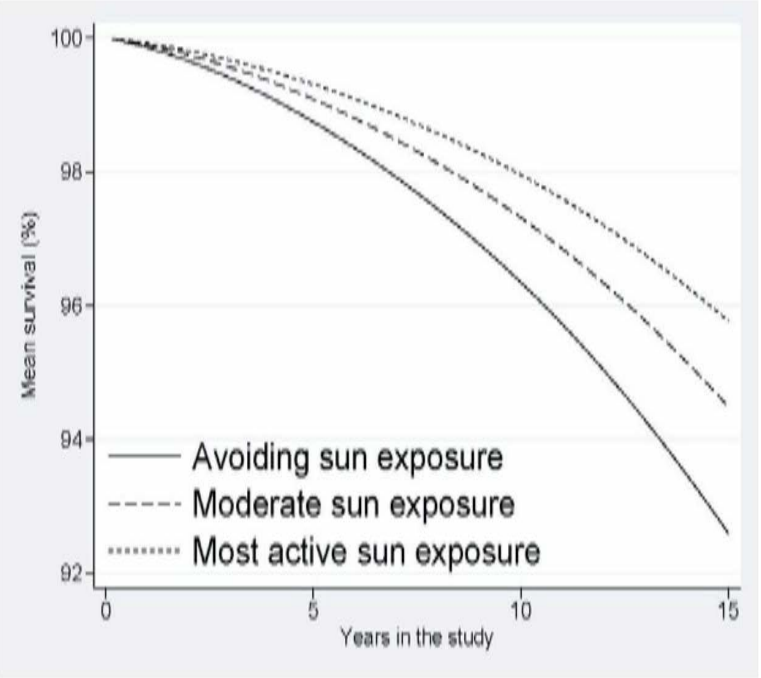


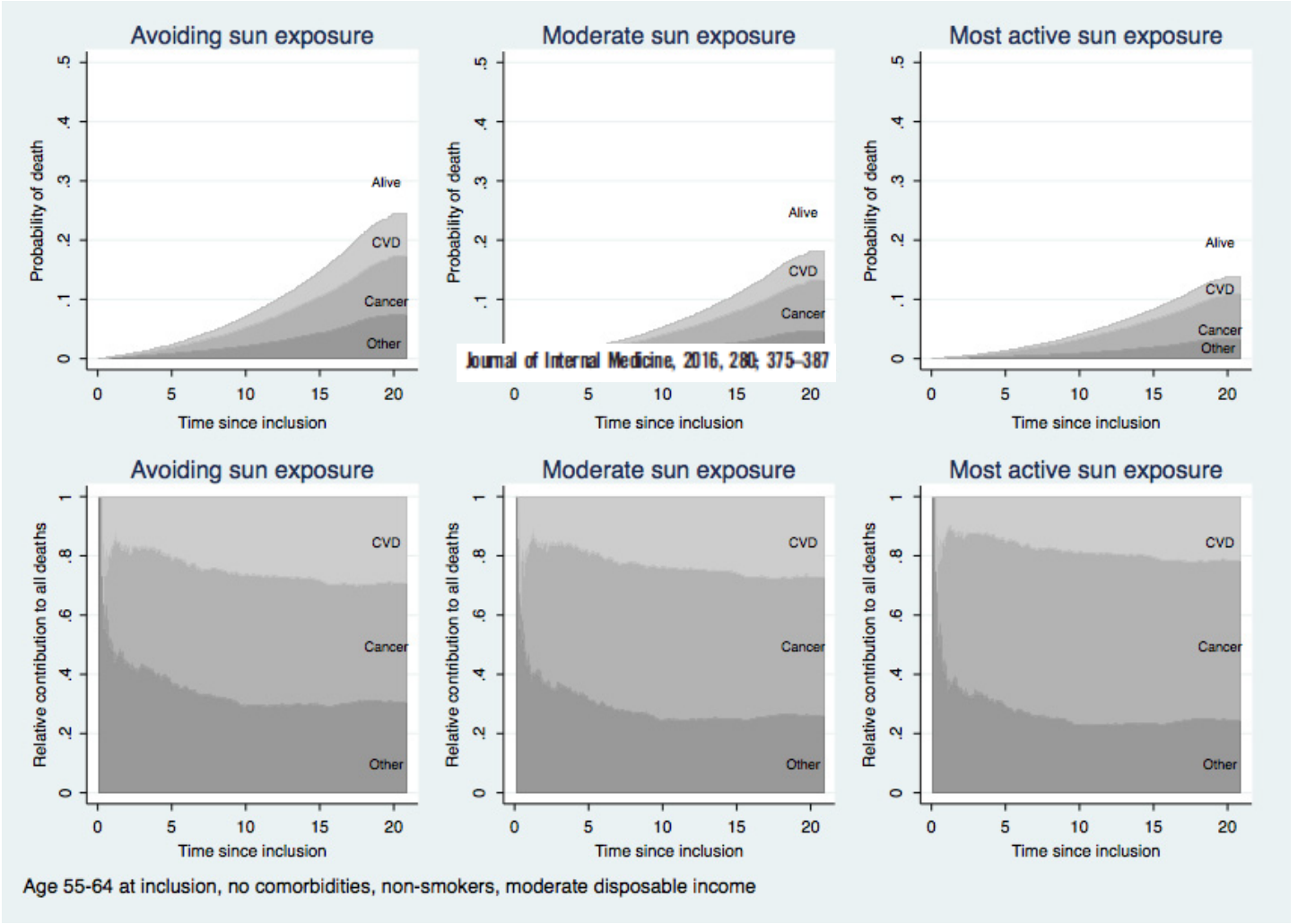
Figure 4b. Group 2, during follow-up: Cumulative incidence for melanoma recurrence by sunny holida

Avoidance of sun exposure is a risk factor for all-cause mortality: results from the MISS cohort Pelle G. Lindqvist, 2013



Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the Melanoma in Southern Sweden cohort

P. G. Lindqvist[1], E. Epstein[2], K. Nielsen[3], M. Landin-Olsson[4], C. Ingvar[5] & H. Olsson[6]



Journal of Internal Medicine, 2016, 280; 375–387

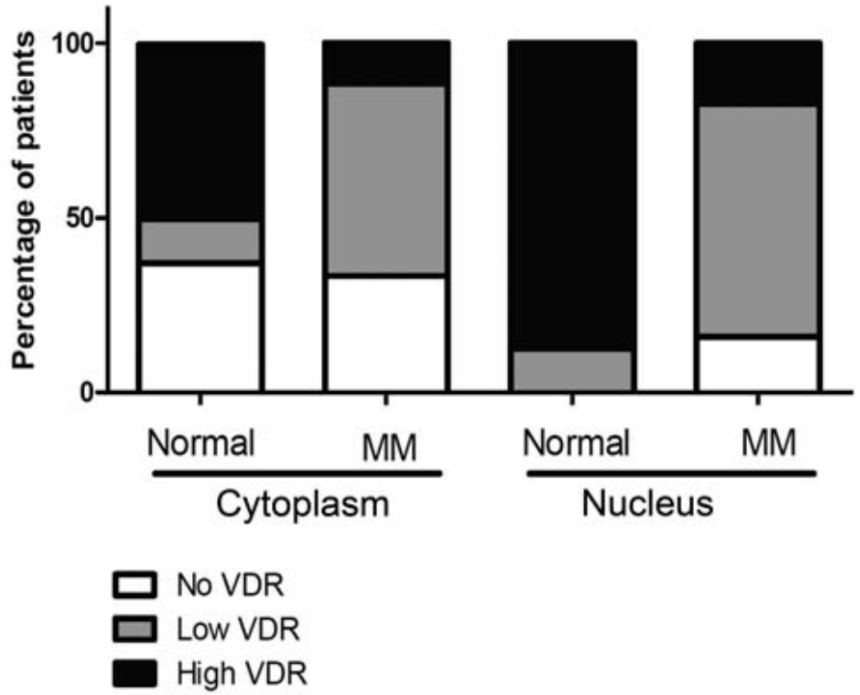
Fig. 1 *Probability of death by sun exposure habits in a competing risk scenario. Upper three graphs show death categorized into CVD, cancer and other (according to time in years since study inclusion). Bottom three graphs show relative contribution to death by sun exposure habits (according to time in years since study inclusion).*

ANTICANCER RESEARCH *34*: 2735-2744 (2014)

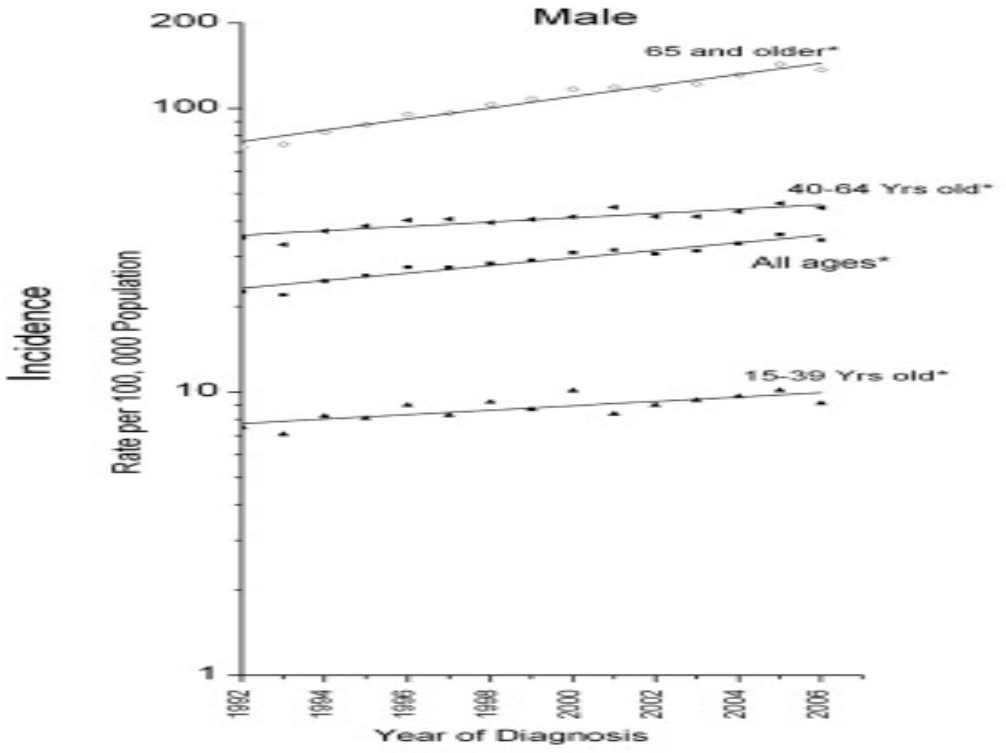
Decreased VDR Expression in Cutaneous Melanomas as Marker of Tumor Progression: New Data and Analyses

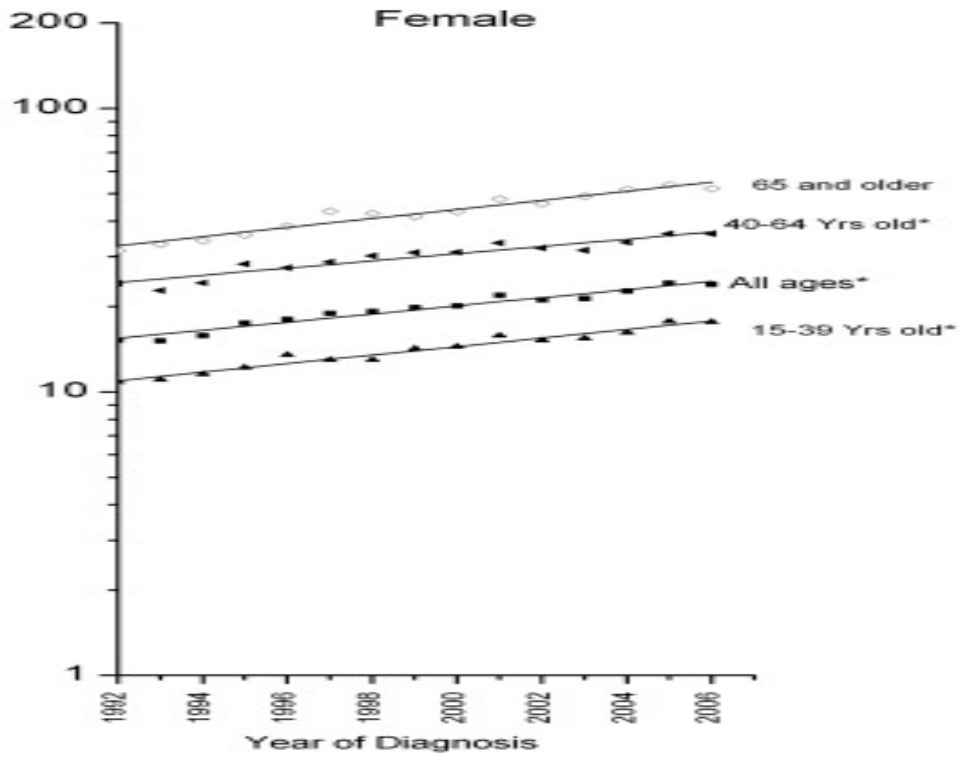
ANNA A. BROŻYNA[1], WOJCIECH JÓŹWICKI[1] and ANDRZEJ T. SLOMINSKI[2,3]

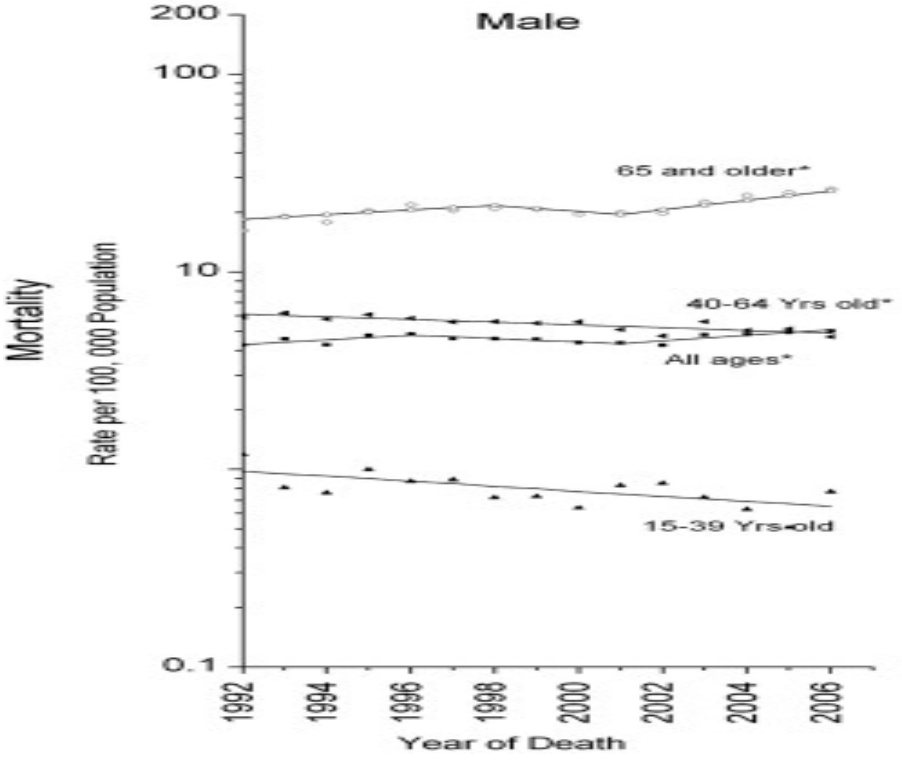
[1]Department of Tumor Pathology and Pathomorphology, Oncology Centre, Prof. Franciszek Łukaszczyk Memorial Hospital, The Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland; [2]Department of Pathology and Laboratory Medicine, and [3]Division of Dermatology, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN, U.S.A.

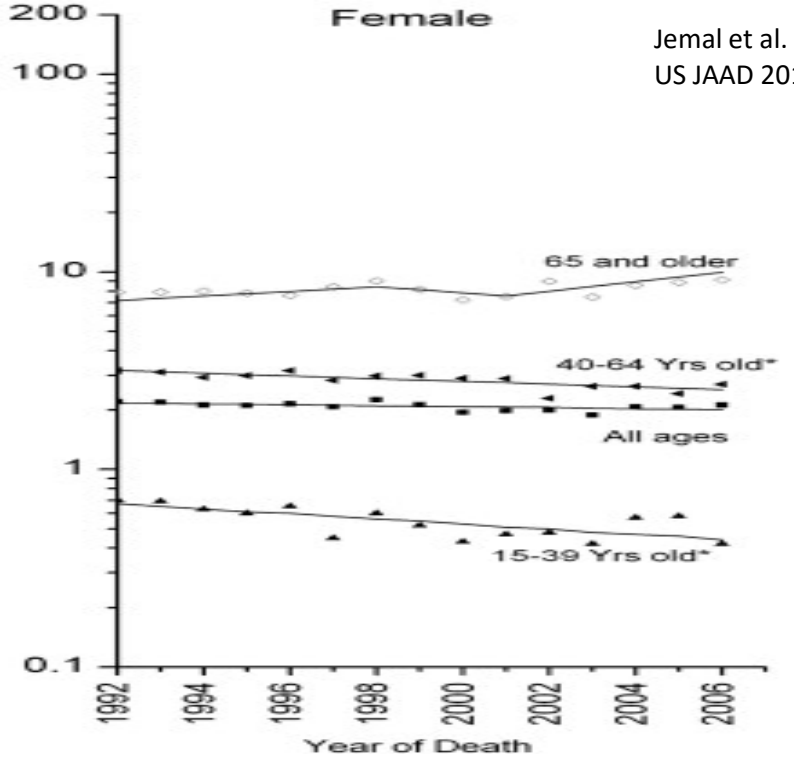


Distribution of cytoplasmic and nuclear VDR levels in normal skin and MM.





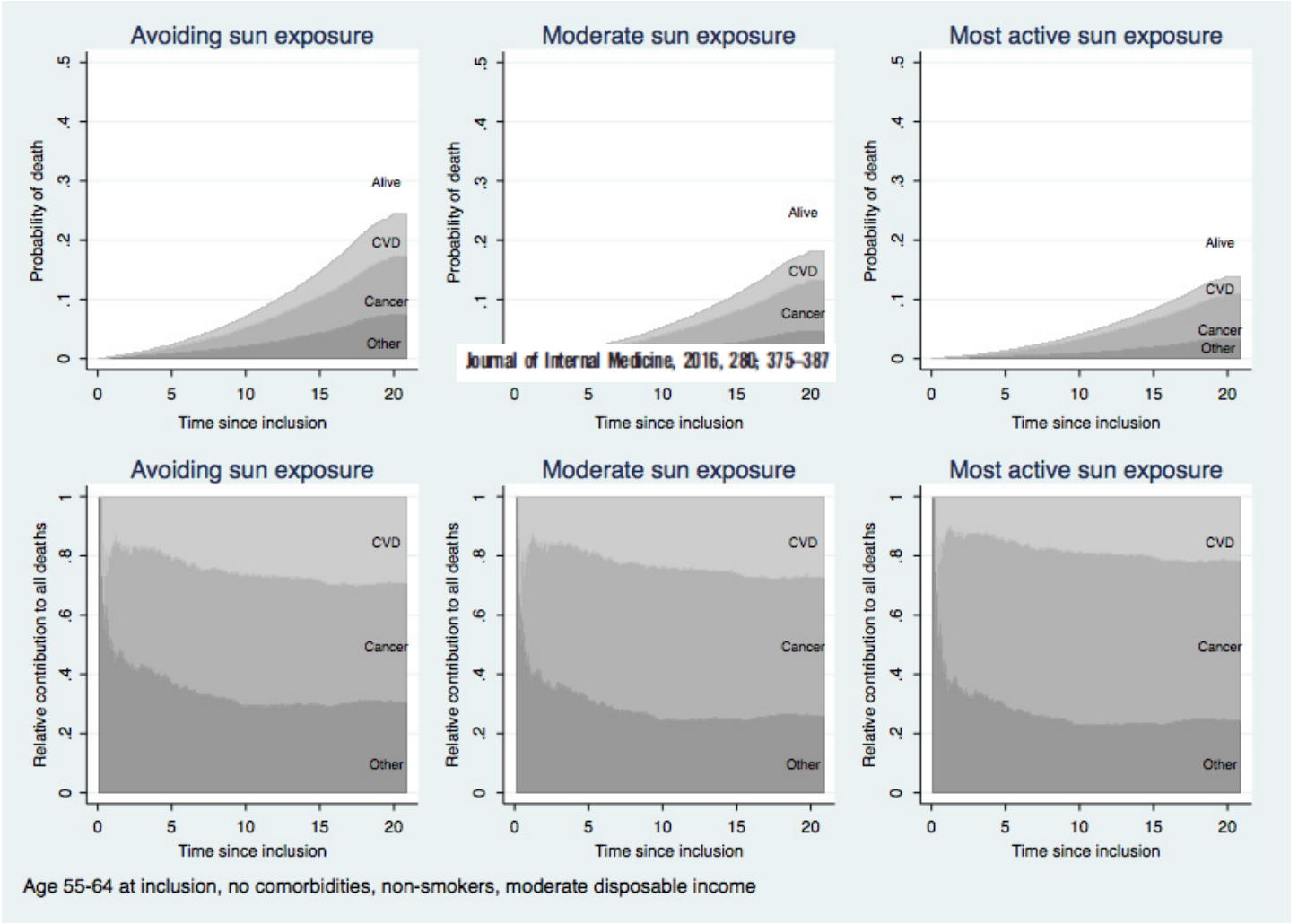




Jemal et al. MM in the US JAAD 2012

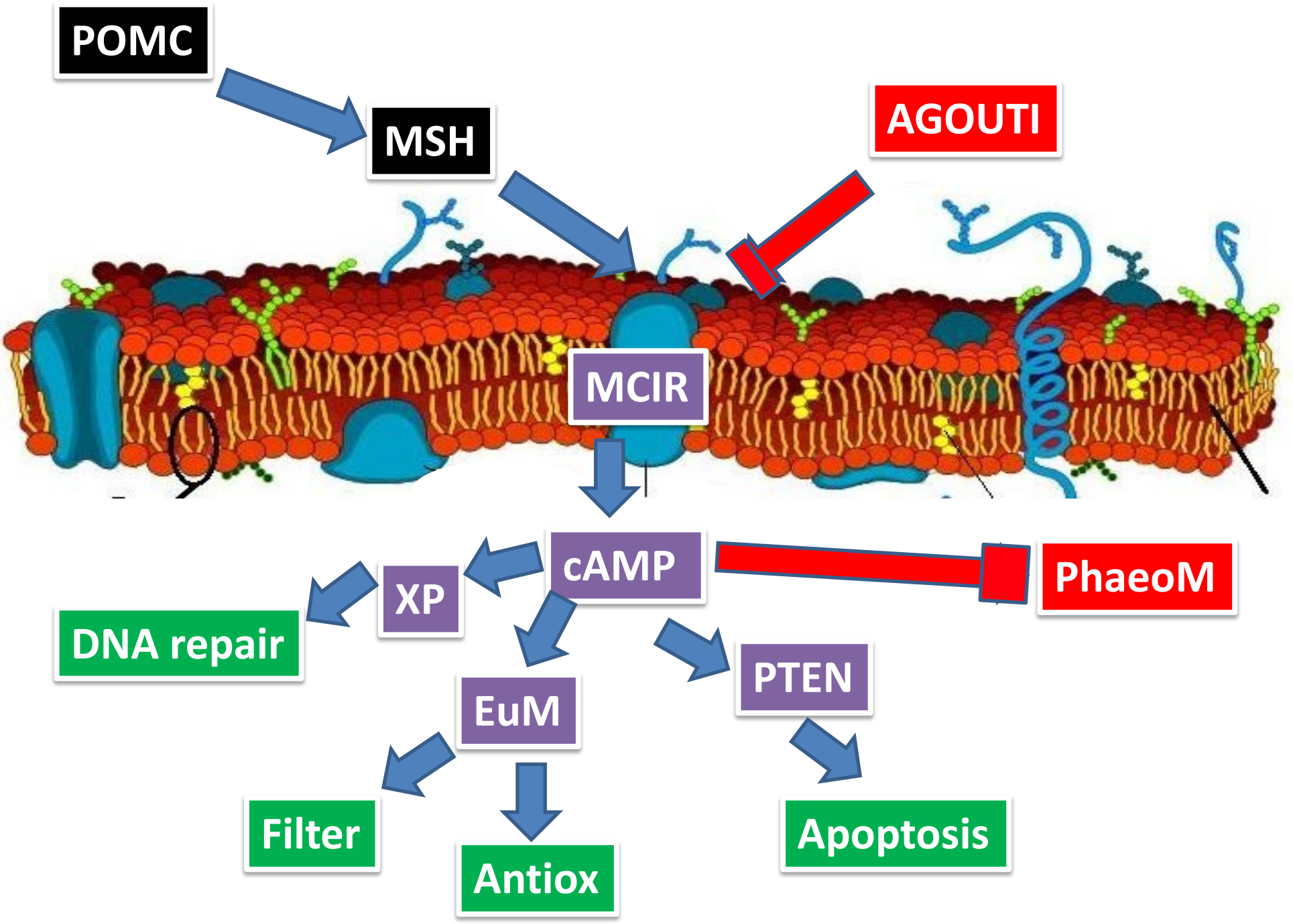
Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the Melanoma in Southern Sweden cohort

P. G. Lindqvist[1], E. Epstein[2], K. Nielsen[3], M. Landin-Olsson[4], C. Ingvar[5] & H. Olsson[6]



Journal of Internal Medicine, 2016, 280; 375–387

Fig. 1 *Probability of death by sun exposure habits in a competing risk scenario. Upper three graphs show death categorized into CVD, cancer and other (according to time in years since study inclusion). Bottom three graphs show relative contribution to death by sun exposure habits (according to time in years since study inclusion).*



PCB e inquinanti organo clorurati

- Association with plasma levels of PCB congeners and organochlorine pesticide residues: OR= 7.02 (95% CI: 2.30- 21.43)

uicc
global cancer control

IJC
International Journal of Cancer

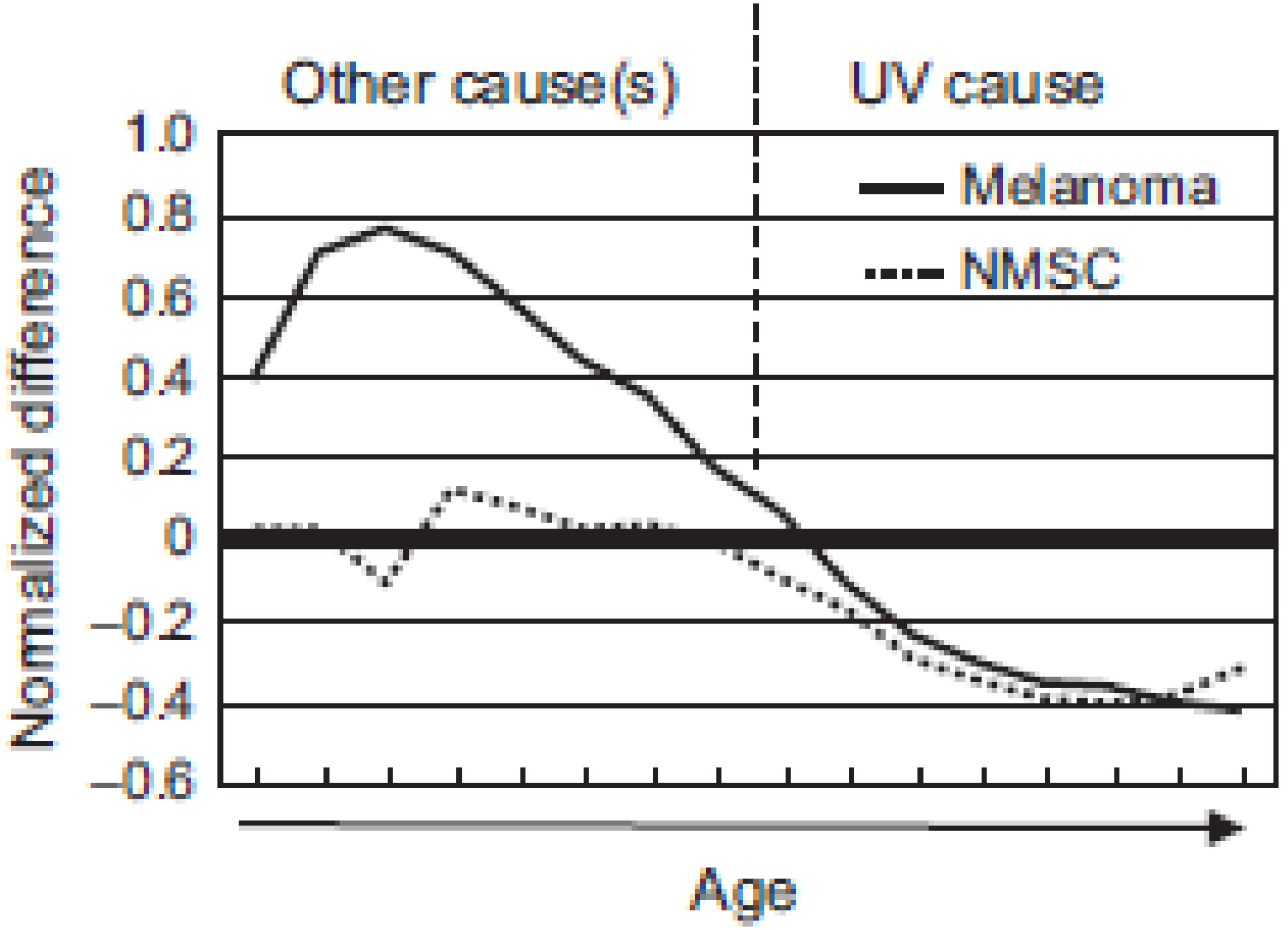
Plasma levels of polychlorinated biphenyls and risk of cutaneous malignant melanoma: a preliminary study

Richard P. Gallagher[1,2,3], Amy C. MacArthur[4], Tim K. Lee[1,3,5], Jean-Philippe Weber[6], Alain Leblanc[6], J. Mark Elwood[1], Marilyn Borugian[1,2], Zenaida Abanto[1] and John J. Spinelli[1,2]

UVA vs UVB (at equally erythemogenic doses) cancerogenesis in *Monodelphis domestica* *(Gray Short-tailed Opossum)*. *(Ley 1997)*

	UVA	UVB	p
SSC	4%	71%	<0.001
CMM	22%	31%	>0.05

The bimodal etiology of melanoma. Melanomas in young population may have other causes than UV radiation while melanomas in older population may have a predominantly UV cause (Liu 2012)



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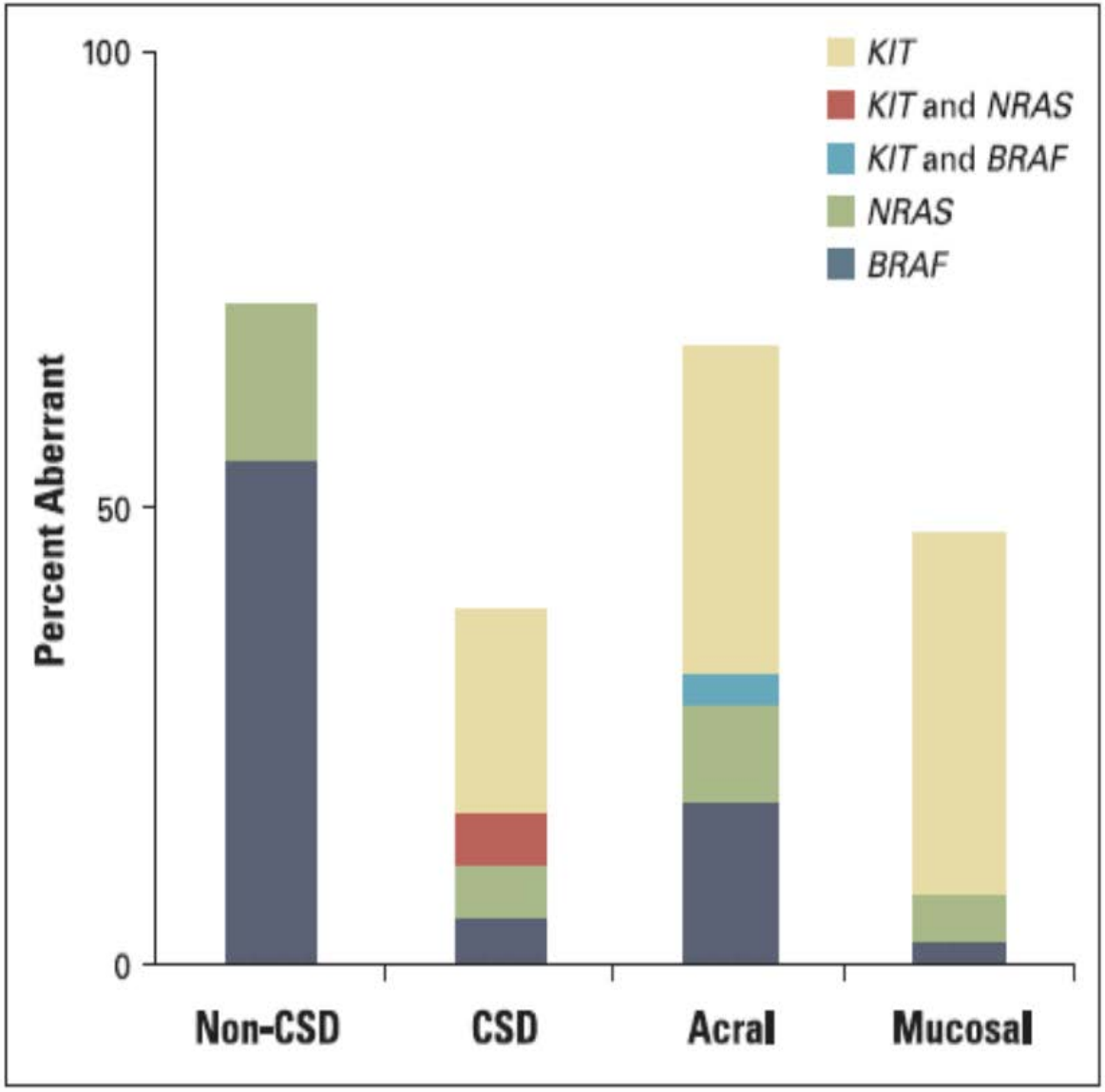
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Somatic Activation of KIT in Distinct Subtypes of Melanoma

John A. Curtin, Klaus Busam, Daniel Pinkel, and Boris C. Bastian



ALBINI E MM

- Review di 124 tumori da 89 pazienti albini residenti all' equatore.
- 70 SCC
- 63 BCC
- 1 MM (acrolentigginoso)

Kiprono SK, 2014.