Complexity of Melanoma: Risk Assessment and Screening

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1. Epidemiology of melanoma in Australia
2. Risk factors, risk assessment and screening
3. Melanoma clinical practice guidelines

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Most commonly diagnosed invasive cancers, by sex, est. 2017 incidence

Males			Females		
Site/type (ICD-10 codes)	**Cases**	**ASR**	**Site/type (ICD-10 codes)**	**Cases**	**ASR**
Prostate (C61)	16,665	115.2	Breast (C50)	17,586	124.2
Colorectal (C18–C20)	9,127	67.3	Colorectal (C18–C20)	7,555	49.4
Melanoma of the skin (C43)	8,392	62.1	Melanoma of the skin (C43)	5,549	39.0
Lung (C33–C34)	7,094	51.8	Lung (C33–C34)	5,340	34.6
Head and neck (C00–C14, C30–C32)	3,625	26.7	Uterus (C54–C55)	2,861	19.2
Lymphoma (C81–C86)	3,574	26.5	Lymphoma (C81–C86)	2,658	18.2
Leukaemia (C91–C95)	2,358	17.6	Thyroid (C73)	2,329	18.0
Bladder (C67)	2,267	16.7	Ovary (C56)	1,580	10.8
Kidney (C64)	2,256	16.6	Pancreas (C25)	1,548	9.7
Pancreas (C25)	1,722	12.6	Leukaemia (C91–C95)	1,517	10.4

Risk to age 85: 1 in 13 men 1 in 23 women

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Source: AIHW, Cancer in Australia 2017

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Melanoma in situ

- Complete data collected by state and territory cancer registries since 2004
- 12,679 cases of melanoma in situ in 2012 (excl. SA)
- **Higher incidence** than invasive melanoma

Rate per 100,000	Males	Females
In situ	66.4	46.3
Invasive	62.2	41.2

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Source: AIHW, Cancer in Australia 2017

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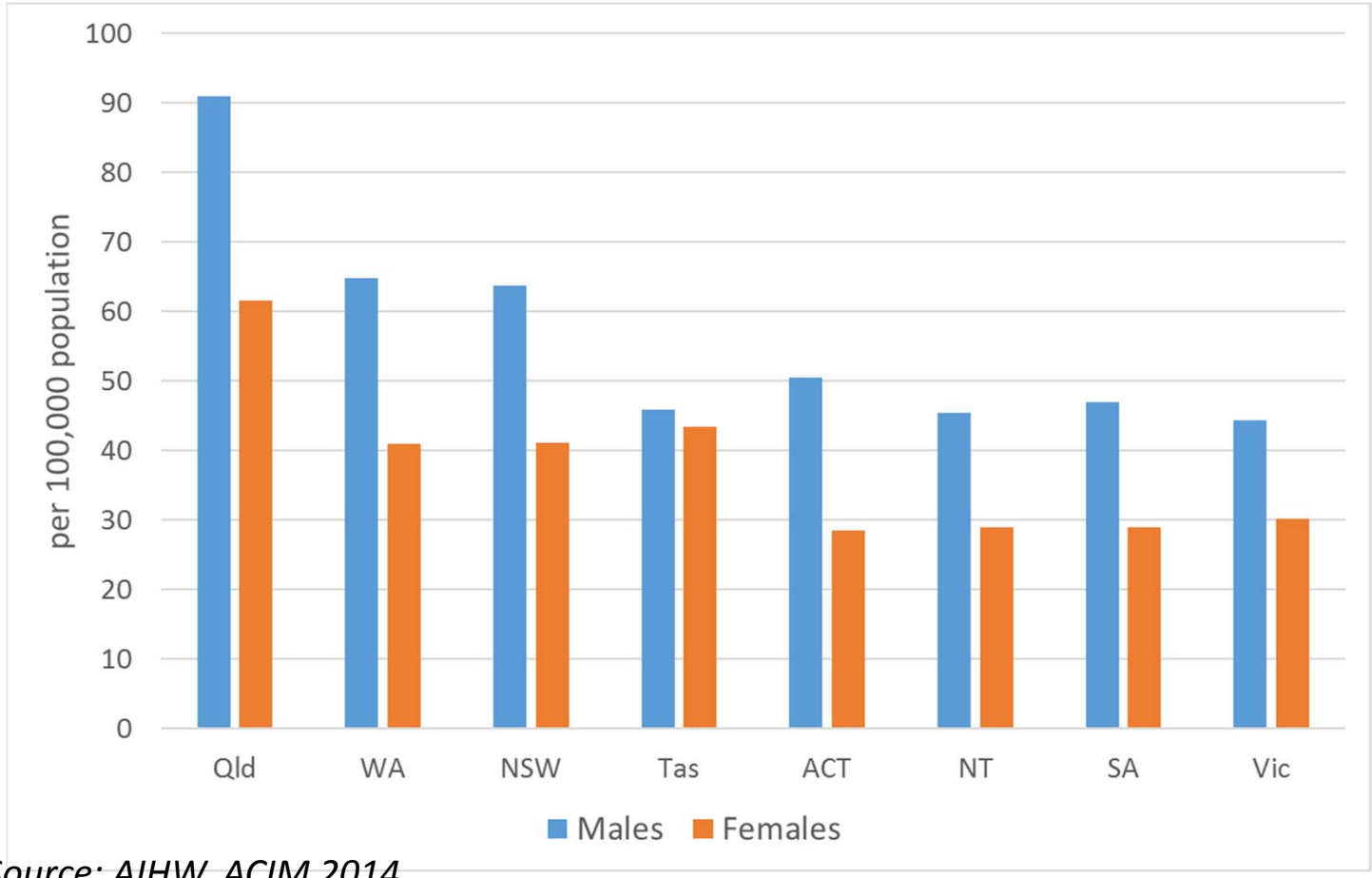
Age-standardised incidence rates, by state and territory, 2013



Source: AIHW, ACIM 2014

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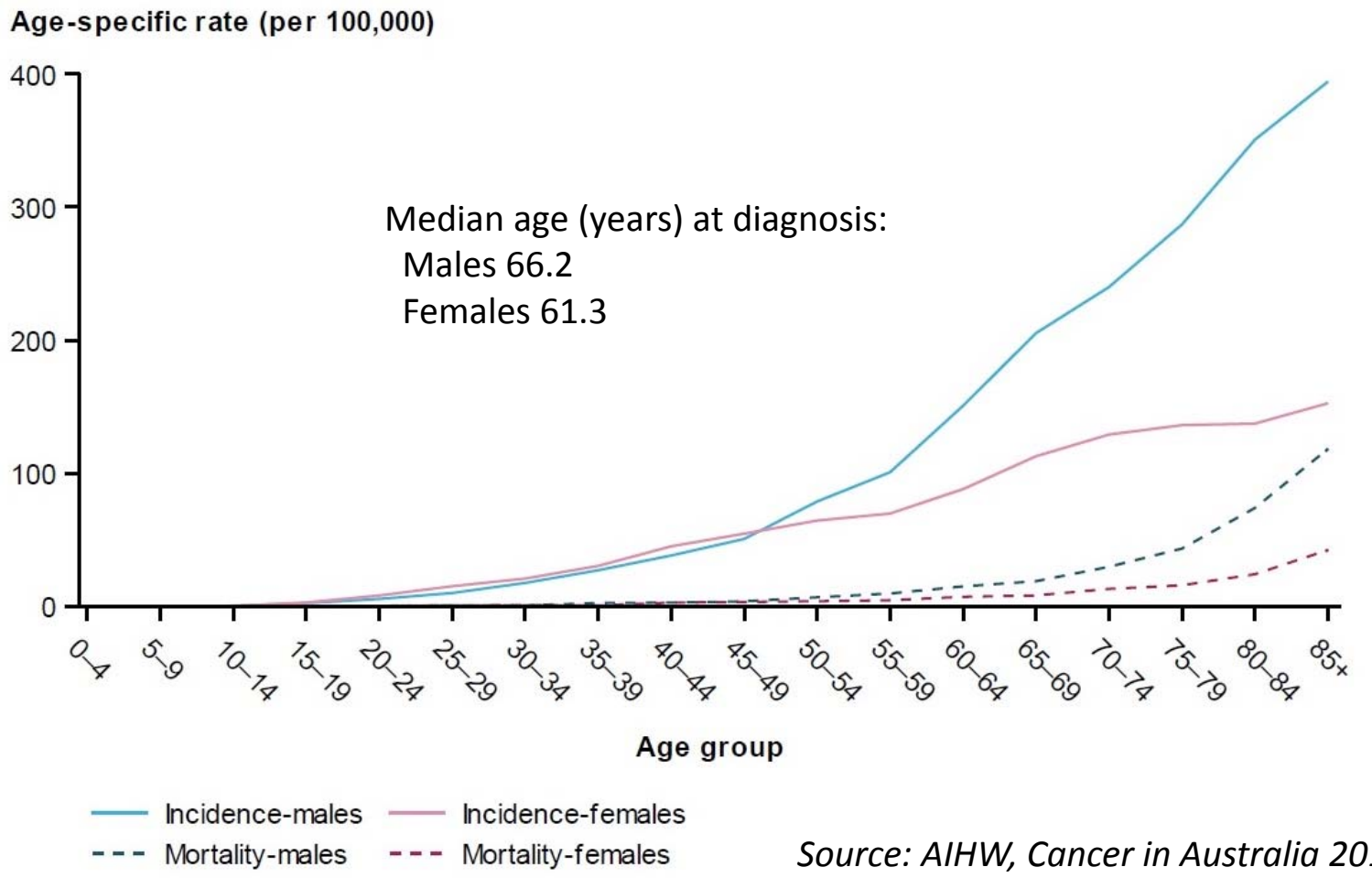
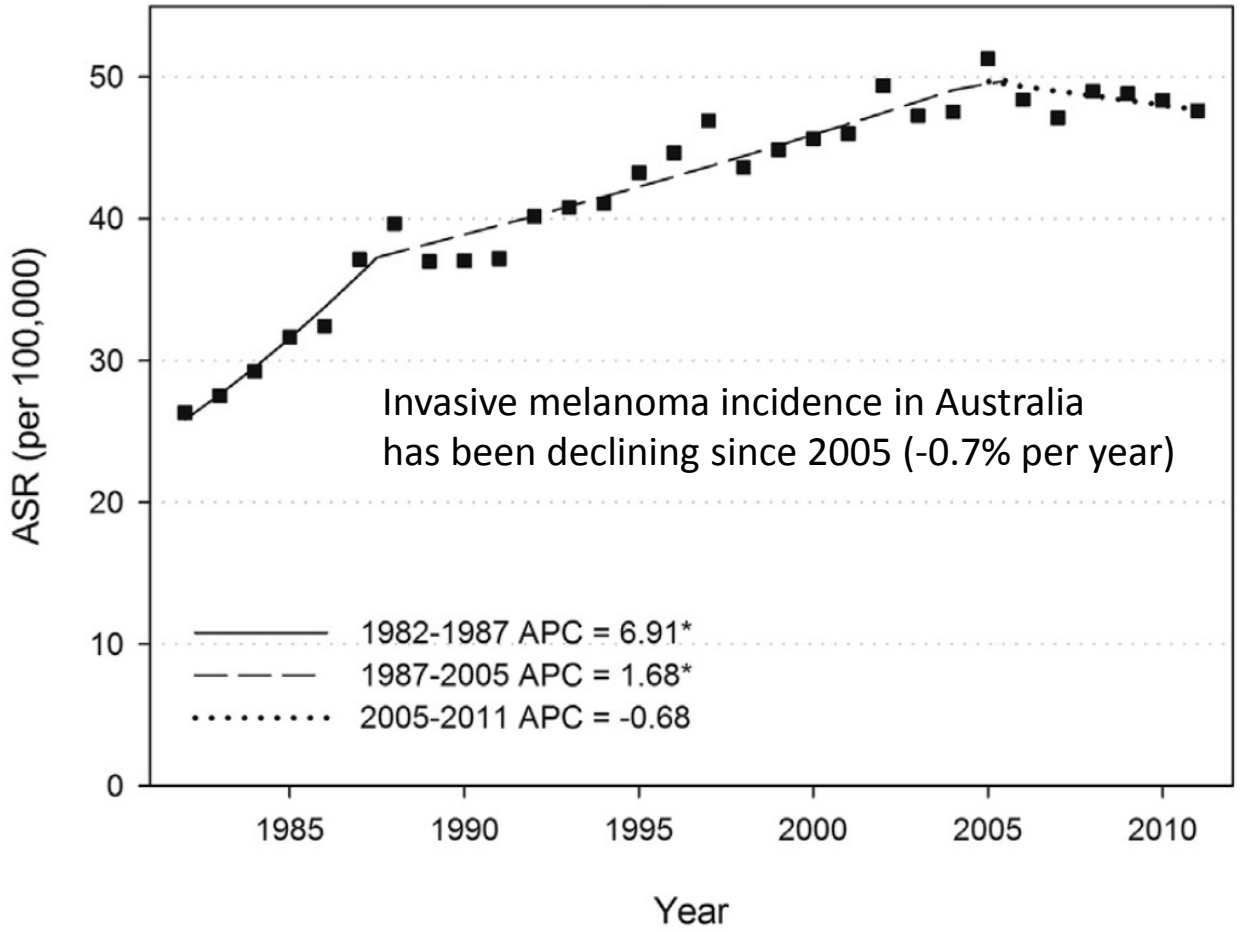
Incidence & mortality rates by age, invasive melanoma, 2014



Source: AIHW, Cancer in Australia 2017

Annual percentage change using age-period-cohort models, 1982-2011



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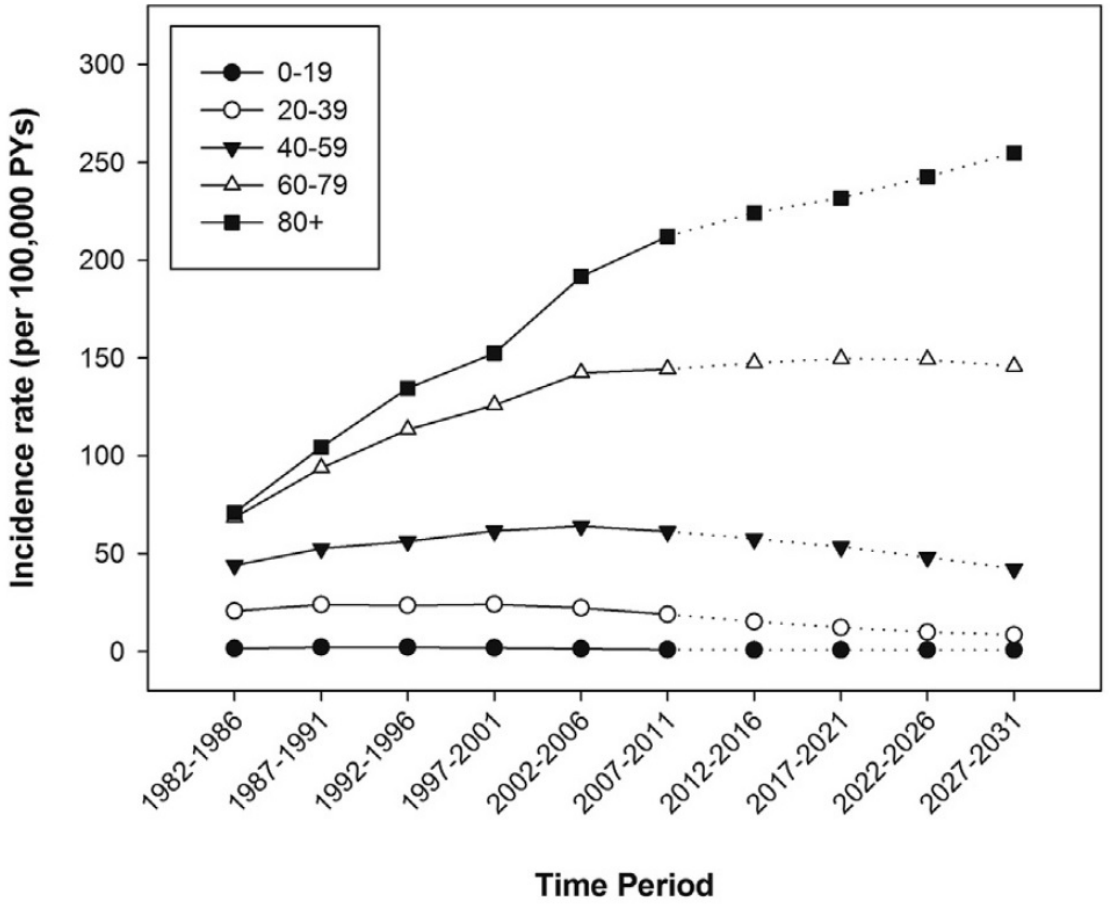
Whiteman et al. Journal of Investigative Dermatology (2016) 136, 1161e1171

Age-specific incidence rates, invasive melanoma, 1982-2011-2031



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Whiteman et al. Journal of Investigative Dermatology (2016) 136, 1161e1171

Melanoma survival

Gershenwald JE, et al. CA Cancer J Clin 2017;67:472-492.

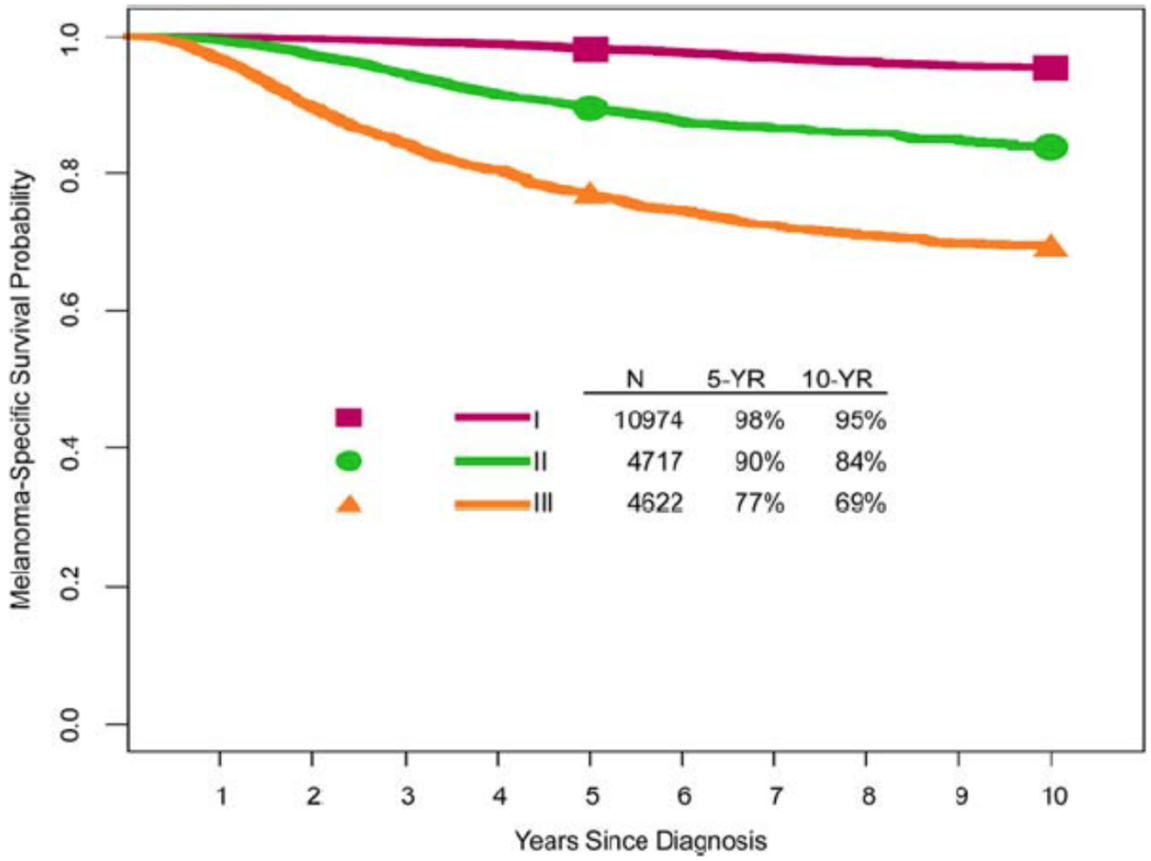

FIGURE 5. Kaplan-Meier Melanoma-Specific Survival Curves According to Stage in Patients With Stage I to III Melanoma From the Eighth Edition International Melanoma Database.

2. Risk factors, risk assessment and screening for melanoma

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Who is at high risk of melanoma?

- Demographic factors
  - age, sex, geographic location
- Skin and hair phenotype
  - number of naevi (common and atypical), fair skin, sun sensitivity, red and blonde hair colour,
- Personal or family history of melanoma or nmsc (keratinocyte cancers)
- Sun exposure
  - evidence of actinic skin damage
  - sunburn (especially in childhood)
  - intense intermittent sun exposure (especially in childhood)
  - previous sunbed use
- Genetic factors
  - CDKN2A (high penetrance mutation)
  - Common gene variants (in > 21 known genes)

Is occupational sun exposure a risk factor?

- Most studies have found null or inverse associations between occupational (more continuous pattern) sun exposure and melanoma risk
  - Meta-analysis of 24 studies: OR 0.91 (95% CI: 0.81–1.01) for high vs low continuous exposure (Caini et al, 2009)
  - Meta-analysis of 33 studies: 0.95 (95% CI: 0.87–1.04) (Gandini et al, 2005)
  - Aust. Melanoma Family Study: 1.22 0.82–1.81 (Vuong et al, 2014)

- May differ according to anatomical site or latitude
  - Head and neck at low latitudes: 1.7 (1.0–3.0) (Chang et al, 2009)
  - Usually sun exposed sites: 1.09 (0.96–1.24) (Caini et al, 2009)
  - Occasionally sun exposed: 0.90 (0.84–0.96) (Caini et al, 2009)
  - Greater association with chronic sun exposure at higher latitudes (Gandini et al, 2005)

Risk prediction model for predicting first invasive melanoma

Australian Melanoma Family Study; JAMA Dermatol. 2016 Aug 1;152(8):889-96

- Age
- Sex
- Hair colour
- Nevus (mole) density
- First-degree family history of melanoma
- Previous non-melanoma skin cancer
- Lifetime sunbed use

Internal validation
AUC 0.70 (95%CI, 0.67-0.73).
External validation ranged from 0.63 to 0.67 in 4 independent population-based studies

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Risk factors in final model for invasive or in situ melanoma, Qskin cohort JNCI March 2018

- Age
- Sex
- Ethnicity
- Private health insurance
- Tanning ability
- Number of moles at age 21 (none, few, some, many)
- Number of previous skin lesions destroyed
- Past history of excisions for skin cancer
- Number of skin checks by a doctor (past 3 years)
- Hair colour
- Family history of melanoma
- Sunscreen use (past-year)

AUC on internal validation
0.72, 95% CI: 0.69 to 0.75

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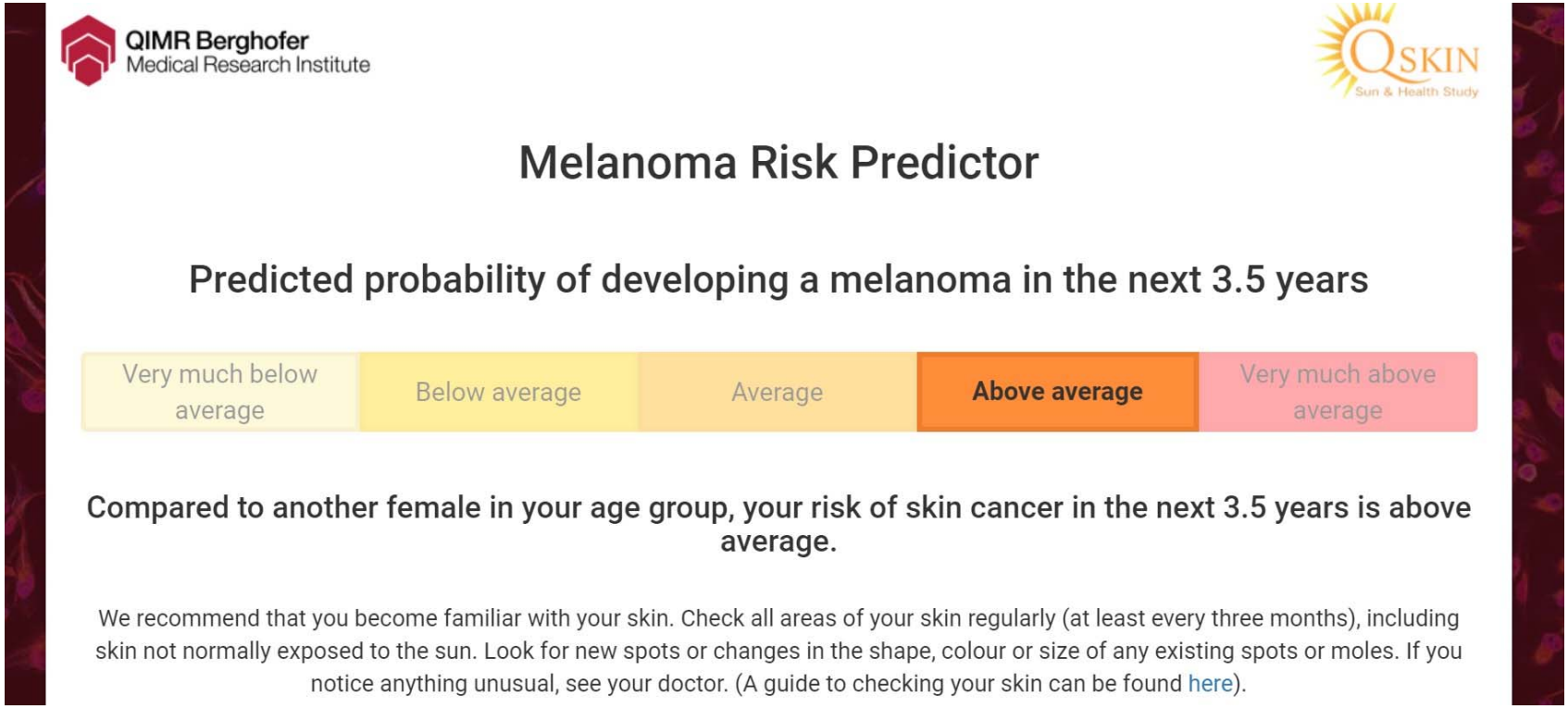
Google: QSkinMelanomaRisk



GenoMEL
the Melanoma Genetics Consortium

Melanoma low-medium penetrance genes and their biological pathways:

- pigmentation (14)
- nevus (7)
- telomere, senescence, and other pathways (5)

Region/ Gene	Chromosome	Pigmentation	Nevi (moles)	Telomere, Senescence, other
PARP1	1			X
ARNT	1	X		
CYP1B1/ RMDN2	2	X	X	
CASP8	2			X
MITF	3	X	X	
TERT	5			X
SLC45A2	5	X		
CDKAL1	6	X		
AGR3	7	X		
CDKN2A	9		X	
RAD23B	9	X	X	
OBFC1	10			X
TYR	11	X		
CCND1	11	X	X	
ATM	11		X	
OCA2	15	X		
FTO	16			X
MC1R	16	X		
ASIP	20	X		
MX2	21	X		
PLA2G6	22	X	X	

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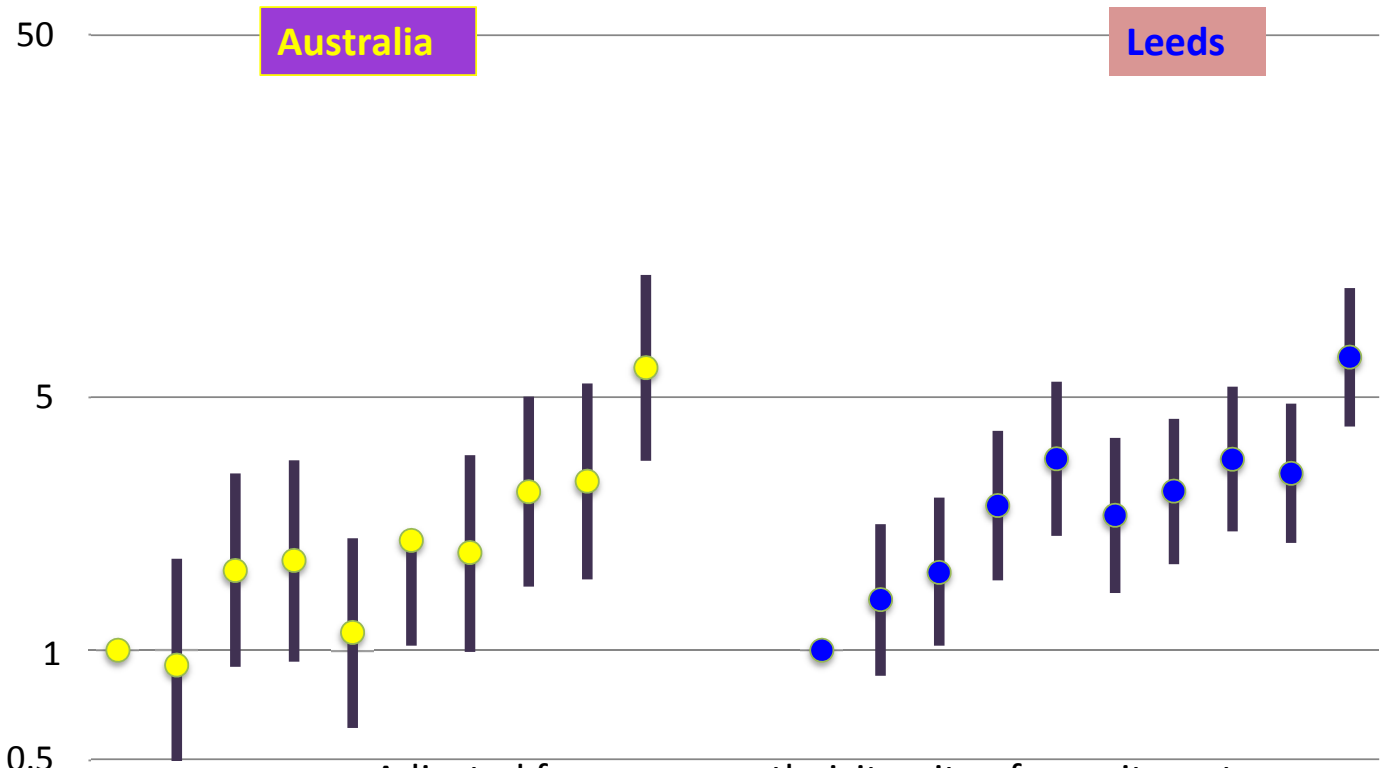
Association of polygenic risk score (deciles) with melanoma risk



Cust et al, Under review

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Incremental contribution of polygenic risk score to risk prediction

	AUC (95% CI)	Change in AUC from base model	P-value
Australia (N=1,035)			
Base model with traditional risk factors	0.72 (0.69, 0.75)		
+ All SNPs	0.74 (0.71, 0.77)	0.023	0.003
Leeds (N=1,460)			
Base model with traditional risk factors	0.65 (0.62, 0.68)		
+ All SNPs	0.68 (0.65, 0.71)	0.028	0.002

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Cust et al, Under review

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Predicting the development and timing of subsequent primary melanomas

- Age at first melanoma
- Sex
- History of non-melanoma skin cancer
- Family history of melanoma
- Skin colour
- Ability to tan
- Nevus (mole) count (none, few, some, many)
- *CDKN2A* pathogenic mutation
- Polygenic risk score (from SNPs)
- Sun exposure during leisure hours
- Anatomical site of first melanoma
- Histological subtype of first melanoma

Population-based GEM study. NSW melanoma patients, N=1,282. Enriched for multiple primaries. Median follow-up was 14 yrs

Stratified by number of previous primary melanomas

Cust et al, Manuscript in preparation

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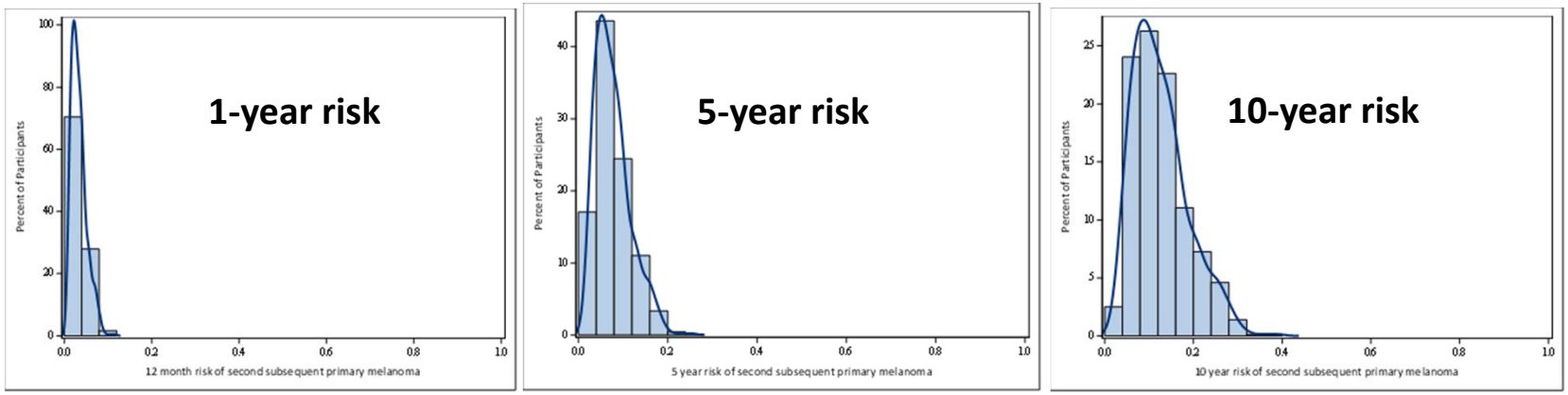
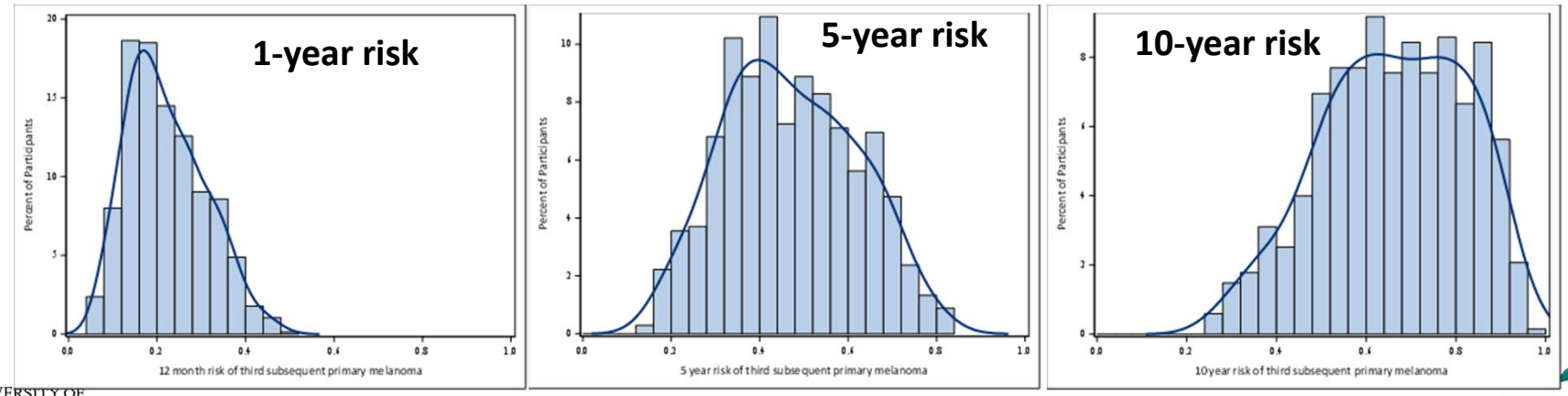
Absolute risk of a 2nd primary melanoma (for people with 1)



Absolute risk of a 3rd primary melanoma (for people with 2)



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Cust et al, Manuscript in preparation

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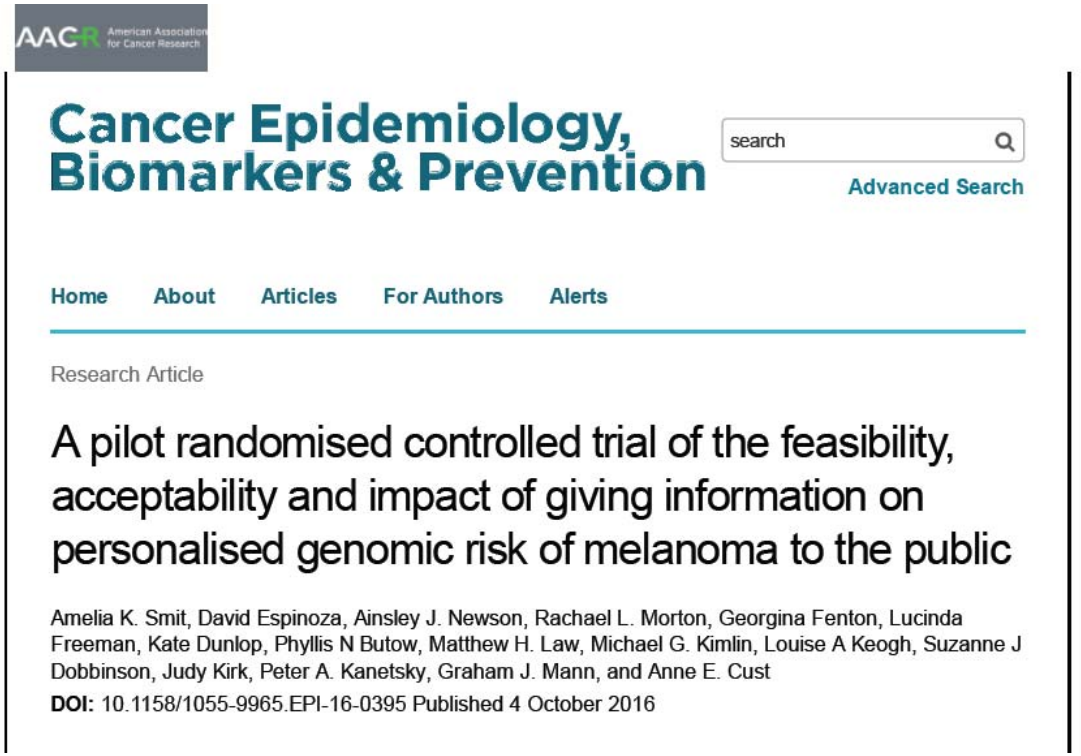
Intervention studies

- Vuong et al. (Family Practice, 2018, in Press) *Personalised melanoma risk assessments and tailored prevention advice: a pragmatic randomised controlled trial in Australian general practice*



AACR American Association for Cancer Research

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Research Article

A pilot randomised controlled trial of the feasibility, acceptability and impact of giving information on personalised genomic risk of melanoma to the public

Amelia K. Smit, David Espinoza, Ainsley J. Newson, Rachael L. Morton, Georgina Fenton, Lucinda Freeman, Kate Dunlop, Phyllis N Butow, Matthew H. Law, Michael G. Kimlin, Louise A Keogh, Suzanne J Dobbinson, Judy Kirk, Peter A. Kanetsky, Graham J. Mann, and Anne E. Cust

DOI: 10.1158/1055-9965.EPI-16-0395 Published 4 October 2016

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Evidence for screening

- The available research evidence has generally been ruled as insufficient to recommend for or against population skin cancer screening. (*Wernli KJ, et al. JAMA 2016: Screening for Skin Cancer in Adults. Updated Evidence Report and Systematic Review for the US Preventive Services Task Force*)
- Population-based observational studies show that skin examination (self-conducted or by a doctor) is associated with diagnosis of melanoma at an earlier stage and reduced mortality
- No randomised controlled trials showing definitive effects on mortality
- "Future research on skin cancer screening should focus on evaluating the effectiveness of targeted screening in those considered to be at higher risk for skin cancer" (2016, US Preventive Services Task Force)

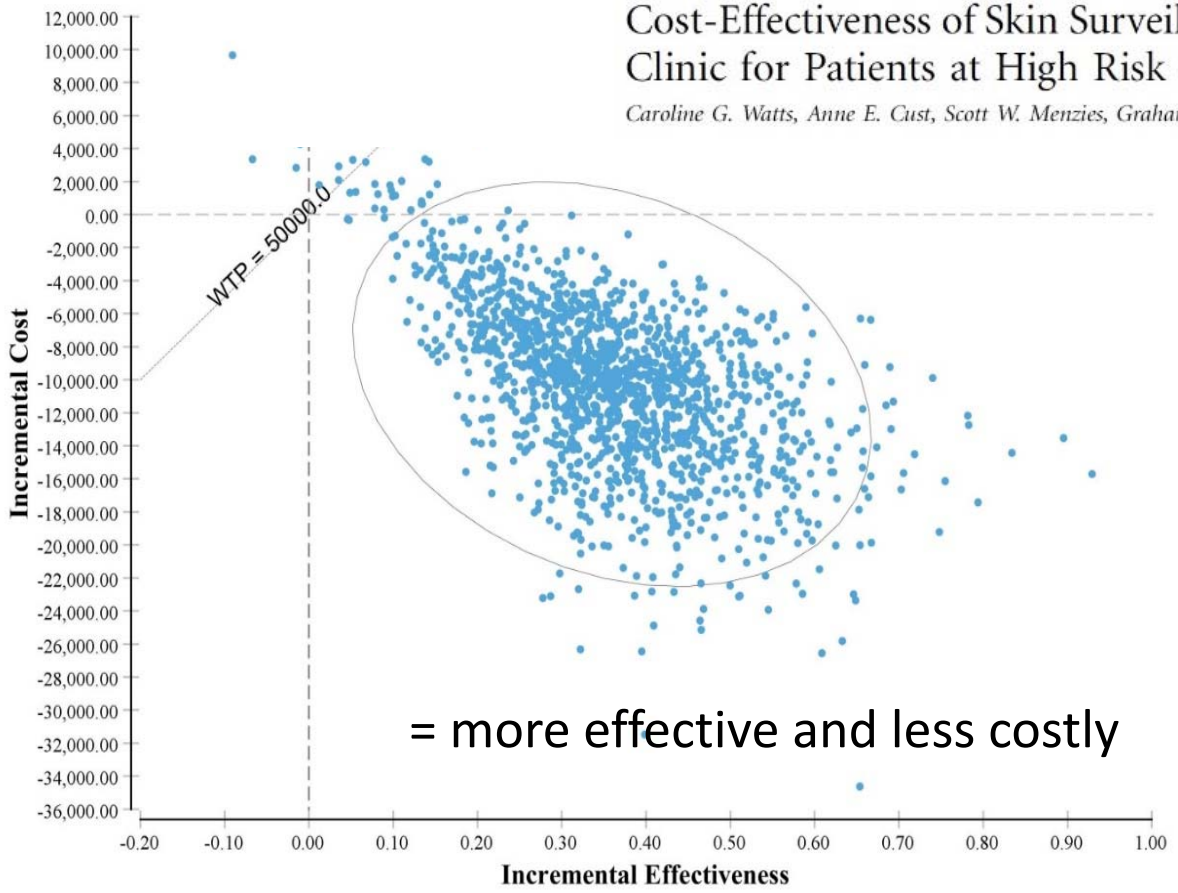
VOLUME 35 · NUMBER 1 · JANUARY 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cost-Effectiveness of Skin Surveillance Through a Specialized Clinic for Patients at High Risk of Melanoma

Caroline G. Watts, Anne E. Cust, Scott W. Menzies, Graham J. Mann, and Rachael L. Morton



= more effective and less costly

	High Risk Clinic	Standard care	Difference (95% confidence interval)
Mean cost per patient	$13,468	$20,295	$6,828 ($5,564-$8,092)
QALYs	7.87	7.56	0.31 (0.27-0.35)

3. Melanoma clinical practice guidelines

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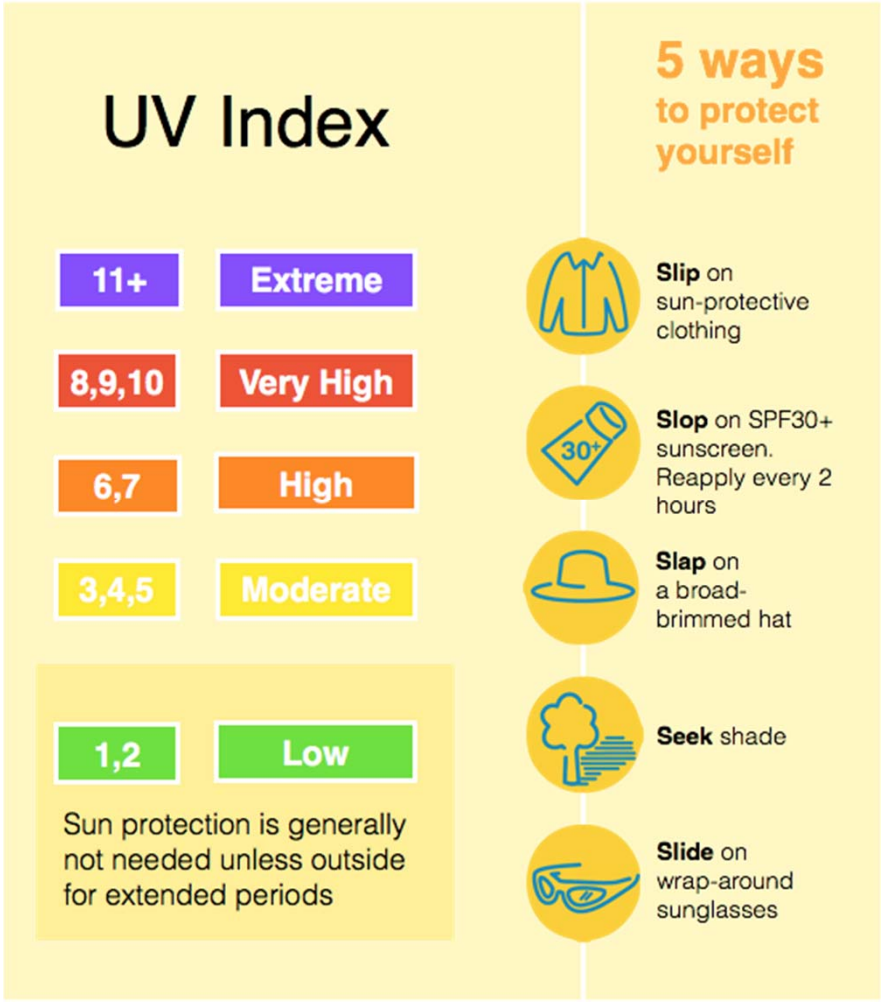
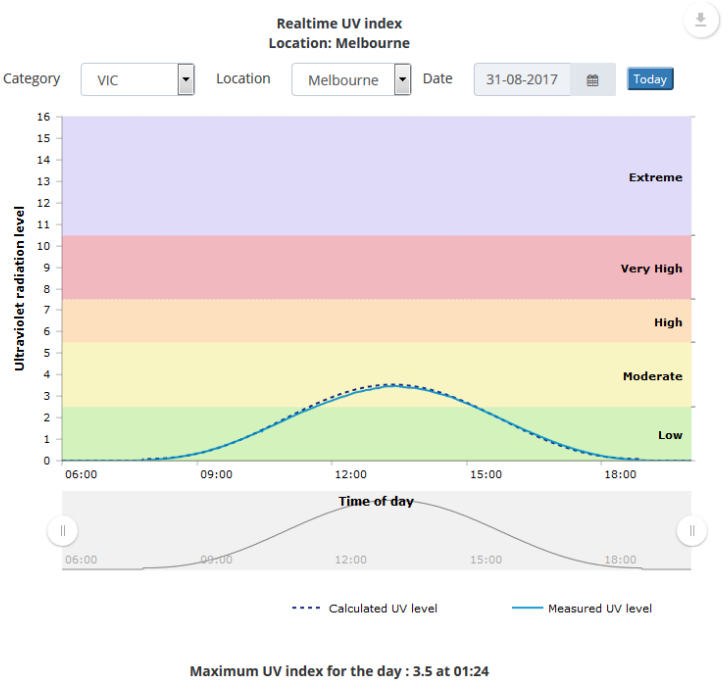
RACGP Guidelines (9th edition, 2016)

- Average risk (medium/dark skin colour and no other risk factors):
  - Primary preventive advice
- Increased risk (fair skin, family history, UV damage):
  - Primary preventive advice and opportunistic examination of skin
- High risk (previous history of melanoma, >5 atypical naevi)
  - Preventive advice, examination of skin (with or without photography) every 6-12 months and advice on self-examination

Primary preventive advice





http://www.bom.gov.au/uv/index.shtml

http://www.sunsmart.com.au/skin-cancer/health-professionals

https://wiki.cancer.org.au/policy/Position_statement_-_Risks_and_benefits_of_sun_exposure (Position statement - Sun exposure and vitamin D - risks and benefits)

Clinical practice guidelines for the diagnosis and management of melanoma, 2018

- Cancer Council Australia, Cancer Guidelines wiki

https://wiki.cancer.org.au/australia/Guidelines:Melanoma

Risk assessment

- Assess all patients for future risk of melanoma, using validated risk factors and a model that integrates personal risk factors into an overall index of risk (Grade B recommendation)
- Clinical genetic testing for CDKN2A mutations and genetic counselling should be considered in individuals with a strong family history of melanoma (3 or more cases related in the first- or second-degree) where predictive features are present, such as multiple primary melanoma, early age of onset, or pancreatic cancer.

Clinical practice guidelines for the diagnosis and management of melanoma, 2018

Screening and surveillance

- Individuals at very high risk of melanoma and their partner or carer should be educated to recognise and document lesions suspicious of melanoma. These individuals should be checked regularly by a clinician with six-monthly full skin examination supported by total body photography and dermoscopy (Grade C recommendation)

Clinical practice guidelines for the diagnosis and management of melanoma, 2018

Diagnosis

- Clinicians who are performing skin examinations for the purpose of detecting skin cancer should be trained in and use dermoscopy (Grade A)
- The optimal biopsy approach for a suspicious pigmented lesion is complete excision with a 2 mm clinical margin and upper subcutis (Grade C)
- Punch biopsy should not be utilised for the routine diagnosis of suspected melanoma because this technique is associated with high rates of histopathological incorrect false negative diagnosis (Grade C)
- Sentinel lymph node biopsy should be considered for all patients with melanoma greater than 1 mm in thickness and for patients with melanoma greater than 0.75 mm with other high risk pathological features to provide optimal staging and prognostic information and to maximise management options for patients who are node positive (Grade B).

Conclusion

- Primary prevention efforts have been successful in reducing incidence of invasive melanoma among younger generations
- Increasing numbers of new melanoma cases because of ageing population and high age-specific rates in the elderly
- Increasing incidence of melanoma in situ
- Advances in risk assessment methods and early detection of melanoma
- Ongoing research into optimal screening and surveillance strategies
- Familiarise yourself with the new melanoma guidelines

Acknowledgements

Sydney Catalyst
Primary Care Collaboration Cancer Clinical Trials Group
PC4
Aust. & NZ Melanoma Trials Group
Clinical Oncology Society of Australia
NHMRC
Cancer Institute NSW

Many colleagues from many disciplines across Australia and internationally, including Investigators from GenoMEL, GEM, Australian Melanoma Family Study, and NHMRC Centre of Research Excellence in Melanoma

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