Complexity of Melanoma: Risk Assessment and Screening

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The University of Sydney
1. Epidemiology of melanoma in Australia
2. Risk factors, risk assessment and screening
3. Melanoma clinical practice guidelines
Most commonly diagnosed invasive cancers, by sex, est. 2017 incidence

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

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

Source: AIHW, Cancer in Australia 2017
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

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>66.4</td>
<td>46.3</td>
</tr>
<tr>
<td>Invasive</td>
<td>62.2</td>
<td>41.2</td>
</tr>
</tbody>
</table>

*Source: AIHW, Cancer in Australia 2017*
Age-standardised incidence rates, by state and territory, 2013

Source: AIHW, ACIM 2014
Incidence & mortality rates by age, invasive melanoma, 2014

Median age (years) at diagnosis:
Males 66.2
Females 61.3

Source: AIHW, Cancer in Australia 2017
Annual percentage change using age-period-cohort models, 1982-2011

Invasive melanoma incidence in Australia has been declining since 2005 (-0.7% per year)
Age-specific incidence rates, invasive melanoma, 1982-2011-2031

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

2. Risk factors, risk assessment and screening for melanoma
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
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
Melanoma Risk Predictor

Predicted probability of developing a melanoma in the next 3.5 years

- Very much below average
- Below average
- Average
- Above average
- Very much above average

Compared to another female in your age group, your risk of skin cancer in the next 3.5 years is above average.

We recommend that you become familiar with your skin. Check all areas of your skin regularly (at least every three months), including skin not normally exposed to the sun. Look for new spots or changes in the shape, colour or size of any existing spots or moles. If you notice anything unusual, see your doctor. (A guide to checking your skin can be found here).
Melanoma low-medium penetrance genes and their biological pathways:
- pigmentation (14)
- nevus (7)
- telomere, senescence, and other pathways (5)

<table>
<thead>
<tr>
<th>Region/ Gene</th>
<th>Chromosome</th>
<th>Pigmentation</th>
<th>Nevi (moles)</th>
<th>Telomere, Senescence, other</th>
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<tr>
<td>PARP1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ARNT</td>
<td>1</td>
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<td></td>
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<tr>
<td>CYP1B1/RMDN2</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>CASP8</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>MITF</td>
<td>3</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>TERT</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SLC45A2</td>
<td>5</td>
<td>X</td>
<td></td>
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<tr>
<td>CDKAL1</td>
<td>6</td>
<td></td>
<td></td>
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<tr>
<td>AGR3</td>
<td>7</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>CDKN2A</td>
<td>9</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>RAD23B</td>
<td>9</td>
<td>X</td>
<td>X</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>CCND1</td>
<td>11</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ATM</td>
<td>11</td>
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<tr>
<td>OCA2</td>
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<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>FTO</td>
<td>16</td>
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<td></td>
<td></td>
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<tr>
<td>MC1R</td>
<td>16</td>
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</tr>
<tr>
<td>MX2</td>
<td>21</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>PLA2G6</td>
<td>22</td>
<td>X</td>
<td>X</td>
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</table>
Association of polygenic risk score (deciles) with melanoma risk

Cust et al, Under review
## Incremental contribution of polygenic risk score to risk prediction

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

*Cust et al, Under review*
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

Stratified by number of previous primary melanomas

*Cust et al, Manuscript in preparation*
Absolute risk of a 2nd primary melanoma (for people with 1)

1-year risk

5-year risk

10-year risk

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

1-year risk

5-year risk

10-year risk

Cust et al, Manuscript in preparation
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*
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)
Cost-Effectiveness of Skin Surveillance Through a Specialized Clinic for Patients at High Risk of Melanoma

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

<table>
<thead>
<tr>
<th></th>
<th>High Risk Clinic</th>
<th>Standard care</th>
<th>Difference (95% confidence interval)</th>
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</thead>
<tbody>
<tr>
<td>Mean cost per patient</td>
<td>$13,468</td>
<td>$20,295</td>
<td>$6,828 ($5,564-$8,092)</td>
</tr>
<tr>
<td>QALYs</td>
<td>7.87</td>
<td>7.56</td>
<td>0.31 (0.27-0.35)</td>
</tr>
</tbody>
</table>

= more effective and less costly
3. Melanoma clinical practice guidelines
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

UV Index

- **11+**  Extreme
- **8,9,10**  Very High
- **6,7**  High
- **3,4,5**  Moderate
- **1,2**  Low

Sun protection is generally not needed unless outside for extended periods.

5 ways to protect yourself

- Slip on sun-protective clothing
- Slop on SPF30+ sunscreen. Reapply every 2 hours
- Slap on a broad-brimmed hat
- Seek shade
- Slide on wrap-around sunglasses


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

- Cancer Council Australia, Cancer Guidelines wiki

**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

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