Melanoma Multidisciplinary Symposium 2010

Prevention and the Molecular Aspects of Melanoma

Nancy E. Thomas
University of North Carolina
nthomas@med.unc.edu
Conflict of Interest

• Investigator for Plexxikon
Towards the control of melanoma

- Primary prevention
  - Causal factors
- Secondary prevention
  - Screening Prognosis
- Tertiary prevention
  - Therapeutic efficacy

Birth - Onset of melanoma - Diagnosis of melanoma - Death
Molecular Aspects

Germline (inherited)
- Rare mutations (primarily p16)
- Common polymorphisms (such as in MC1R --the ‘red hair’ gene)

Somatic (tumor)
- BRAF
- NRAS
- KIT
Strategies toward melanoma control

- **Birth**
  - Primary prevention
- **Onset of melanoma**
  - Secondary prevention
- **Diagnosis of melanoma**
  - Tertiary prevention
- **Death**
Multiple Pathways to Melanoma

"Chronic UV pathway"

Melanocyte or stem cell → Initiated cell

"Nevus pathway"

Many nevi → BRAF+

Few nevi

Few actinic keratoses

Unknown

Age

Childhood Adolescence Adulthood

"Nevus pathway" and "Chronic UV pathway" lead to different outcomes in the development of melanoma. Nevi and actinic keratoses are associated with these pathways, with nevi being more common in adolescence and actinic keratoses in adulthood. The BRAF+ mutation is a key factor in the progression of melanoma. Underlying factors such as UV exposure contribute to the different pathways and outcomes.

Whiteman et al. JID. 2010; 130

Thomas et al. Cancer Epidemiology and Biomarkers. 2007; 16
High levels of ambient sunlight are associated with high rates of melanoma.
UV INDEX FORECAST

Incidence of melanoma in Scotland and Queensland, by age

Early life ambient exposure is associated with high rates of melanoma
Migration studies

1800s

1900s

1800s
Migration studies

Native-born high exposure

"Forward" migration

Relative Risk

1.0

0.9

0.4

0.3

"Reverse" migration

Native-born low exposure

Birth

Death

Relative Risk

4.0

2.5

1.5

1.0
Early Sun Exposure
Genes, Environment, and Melanoma (GEM) Study

<table>
<thead>
<tr>
<th>Residence</th>
<th>Childhood in sunny climate</th>
<th>OR ~ 2</th>
</tr>
</thead>
</table>

Kricker et al. Cancer Causes Control, 2006
Sun behavior associated with increased risk of melanoma
Behavior Associated with Melanoma

GEM Study

- Holidays in sunnier climates
- Beach activities
- Sunburns

Kricker et al.  Cancer Causes Control, 2006
Artificial Tanning

• Any exposure to artificial tanning moderately but significantly increases the risk of melanoma

• Ever vs never exposed in a meta-analysis:
  – 1.25 (95%CI 1.05-1.49)

Multiple Pathways to Melanoma

“Chronic UV pathway”

Melanocyte or stem cell → Initiated cell → Few nevi → Few actinic keratoses

“Nevus pathway”

Melanocyte or stem cell → Many nevi → Few actinic keratoses

Unknown

Age

Childhood → Adolescence → Adulthood

Whiteman et al. JID. 2010; 130

Thomas et al. Cancer Epidemiology and Biomarkers. 2007; 16
Multiple Pathways to Melanoma

“Chronic UV pathway”

Melanocyte or stem cell → Initiated cell

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Many nevi → Few nevi → Few actinic keratoses

Unknown

NRAS+

GNAQ+

KIT+

Age

Childhood → Adolescence → Adulthood

Whiteman et al. JID. 2010; 130

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Strategies for melanoma control

Birth

Onset of melanoma

Diagnosis of melanoma

Death

Primary prevention

Secondary prevention

Tertiary prevention
Screening for melanoma?

Population Survivors
Population screening for melanoma?

Can we target those at highest risk for melanoma?

*Increased number of nevi, atypical nevi, fair traits, red hair, increased sun exposure*

Genetic?
Population screening for melanoma?

“A screening test is performed on an asymptomatic individual to determine that cancer might be present and that further evaluation, including a biopsy and staging, is necessary.”

Brawley and Kramer, J Clin Oncol, 2005

1. Disease must be common and serious
2. Disease must have a ‘pre-clinical’ stage
3. Effective treatment must be available
4. Benefits must outweigh harms

5. A reliable screening test…?
Genetic Testing?

Screen common polymorphisms?
Development of a risk estimate?

Inherited polymorphisms in:
• Melanocortin-1 receptor gene
• Nucleotide excision repair genes

Millikan et al., Carcinogenesis 2006, 27
Kanetsky et al. Cancer Research 2006; 66
## ‘Genetic testing’ for melanoma risk?

<table>
<thead>
<tr>
<th>Gene / locus</th>
<th>Phenotype</th>
<th>Genotype OR</th>
<th>PAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC1R</td>
<td>Hair colour, freckling</td>
<td>~1.5-2</td>
<td>0.10</td>
</tr>
<tr>
<td>ASIP / 20q11.22</td>
<td>Hair colour, freckling</td>
<td>~1.4-1.8</td>
<td>0.04</td>
</tr>
<tr>
<td>TYR</td>
<td>Pigmentation, freckling</td>
<td>~1.2</td>
<td>0.05</td>
</tr>
<tr>
<td>TYRP1</td>
<td>Pigmentation</td>
<td>~1.1</td>
<td>0.10</td>
</tr>
<tr>
<td>MTAP</td>
<td>Nevi</td>
<td>~1.3</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Screening as a survival challenge

760,000 US adults living with a diagnosis of melanoma.

Who is at risk for a second primary melanoma?
Risk of Second Primary

MSKCC followed 4,484 first primary melanoma patients

- Additional primary melanomas in their lifetime \(\sim 3 \text{ to } 5\%\)
- First 5 years \(\sim 10\%\)
- First 5 years with positive family history or dysplastic nevi \(\sim 20\%\)

Ferrone et al. JAMA, 294, 2005, p 1647
Screening for Melanoma

Baseline pictures

Dermoscopy

Confocal
Line Up Monitor with Patient
Compare Moles
No Precursor Mole

Invasive Melanoma

Thomas & Groben, JAAD, 2004
No Precursor Mole
New Pigmented Lesion

b. Unaided view

c. Dermoscopy
Melanoma
(Breslow depth 0.28 mm)

Unaided view

Dermoscopy
Strategies for melanoma control

- Primary prevention
- Secondary prevention
- Tertiary prevention

Birth → Onset of melanoma → Diagnosis of melanoma → Death
DNA alterations in melanoma and targeted therapy
Mutually Exclusive in Melanoma

- **BRAF+**
- **NRAS+**
- **BRAF- NRAS-** (wildtype)
- **KIT** (mucosal, acral)
- **GNAQ** (rare)
- **Unknown**

Davies et al. Nature 2002
Bastian et al. JCO, 2006
Van Raamsdonk et al. Nature 2009
GNAQ- Mutant

Heterotrimeric G protein a-subunit
- Blue nevi (50-80%)
- Nevus of Ota (46%)
- Uveal melanoma (46%)
- CNS melanocytosis (37%)
- CNS melanoma (25%)

Molecular testing for tumor mutations

Slide review

Melanoma

Other

Dissection

Extract DNA

Amplify exons known to harbor mutations

Sequence

Pathologist interpretation

- Dissection
- Extract DNA
- Amplify exons known to harbor mutations
- Sequence
- Pathologist interpretation

- Melanoma
- Other

- Slide review

- Melanoma

- Other
KIT-mutant melanomas

A number of clinical case reports show impressive responses to imatinib mesylate (Gleevec)

Multicenter trials initiated

Holdi et al., JCO, 2008
Carvajal, JCO 27, 2009
BRAF-mutant melanomas

New classes of compounds with high selectivity for V600E BRAF over wildtype

Science. 2009 Dec 18;326(5960):1619. [Flaherty et al. JCO 27 (suppl.)15s 2009]
Towards melanoma control

- **Primary prevention**
- **Secondary prevention**
- **Tertiary prevention**

- **Molecular Aspects**
  - Targeted prevention
  - Targeted screening
  - Targeted therapy