What you really need to know about...

Photoprotection

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Real World Dermatology for PAs and NPs...
What you really need to know

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What you really need to know about Photoprotection

Disclosures:
J and J – A, H, I
Beiersdorf – C, H

What Causes Skin Cancer?

What Causes Melanoma?
The overwhelming majority caused by UV exposure

Photoprotection and Sunscreen

Protection

Melanoma is one of the few cancers that we know the cause – UV radiation exposure and where a simple behavioral change – UV minimization – lowers the risk of getting this cancer
Who is more likely to get Melanoma?
Why?
Who is more sensitive to UV radiation?

Melanoma vs. Latitude USA

UV and Melanoma Risk
Multiple studies show a latitudinal gradient
• United States
• Canada
• England
• Norway
• Scandinavia
• Australia
• New Zealand
• Conclusion:
  — Risk of developing MM directly related to amount of annual and lifetime UVB exposure

UV Radiation levels and MM incidence
Queensland Australia

UV Radiation levels and MM incidence
Queensland Australia

- Conclusion:
  - Risk of developing MM impacted by local climate on annual ambient UV radiation

15°S

20°S

25°S


Relationship between Latitude and Melanoma in Italy

- Sunlight is the major environmental risk factor for melanoma
- Descriptive studies have shown latitudinal variation in melanoma incidence
- Incidence increased in Italy by 17% for each degree of increase in latitude (was higher farther from the equator)

- Conclusion:
  - Risk of developing MM directly related to phenotypical sensitivity to UV radiation

Crocetti et al. ISRN Oncol. 2012

UV and Melanoma Risk

- The risk of getting melanoma decreases with increasing pigmentation
- In populations with strictly similar skin types there is a clear latitudinal gradient for melanoma
- Migration to more sunny countries ↑ melanoma risk
- UV induced pigmented nevi, and melanomas often arise in borders of nevi
- Sunburn episodes appear to increase the melanoma risk
- Conclusion:
  - UV is a directly related carcinogen for melanoma and phenotypical susceptibility is a factor


Do sunscreens protect against developing skin cancer?

The Facts...

Answering Our Patient’s Questions
Are sunscreens that effectively block UV radiation effective in lowering melanoma risk?

Reduced melanoma risk after regular sunscreen use

• 1,621 randomly selected residents of Nambour (Queensland) Australia, age 25 to 75 years, were randomly assigned to daily or discretionary sunscreen application to head and arms
• Treated for 5 years then followed for 10 years

Reduced melanoma risk after regular sunscreen use

• Sunlight is the major environmental risk factor for melanoma
• Examine if S-shaped curves describe the relationship between solar UV doses and MM incidence and the % of MM that can be directly related to UV exposure
• Analysis indicates that S-shaped associations describe the data well (P < 0.0001).
• Conclusion:
  — Between 89 and 95% of the annual CM cases are caused by solar UV exposure.
  — Avoidance of UV radiation will reduce the incidence of MM.

Green et al, J Clin Oncol, 2011


Sunscreen Usage and Melanoma Risk

All Melanomas

Sunscreen Usage and Melanoma Risk

Invasive MMs

Green et al, J Clin Oncol, 2011
Are ALL melanomas caused by UV exposure?

No, but the vast majority are!

Development of SPF

- Correlation of indoor solar simulator with natural sunlight
- Natural sunlight effects could be duplicated with solar simulator

Sayre et al, Arch Dermatol, 1978

How high an SPF is high enough?

SPF 50+ Status

- Sunscreens with SPF of 50 or more are available in some other developed countries, including New Zealand, the US and many European countries
- Australia and other countries have an SPF 50+ cap

SPF Cap 50+?

Pro

Con
**SPF Cap 50+?**

**Pro**
- Increased cost for higher SPF formulations
- Little marginal improvement in UVB protection for higher SPFs

**SPF Cap 50+?**

**Con**
- Higher SPFs have better protection at "real world" application concentrations

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**Underusage of Sunscreen**

Large variation in sunscreen application (many use less than recommended 2mg/cm²)

Users received a mean SPF of 20-50% of expected due to inadequate application

Underprotection due to inadequate application might explain why sunscreen use has been reported in some studies as a risk factor for melanoma

Stokes et al., Photodermatol Photoimmun Phoimeo. 1997

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**Impact of under application of sunscreen**

- SPF of sunscreens are tested using a thickness of 2 mg/cm²
- Investigations show that sunscreen under natural conditions is applied insufficiently with amounts about 0.39 to 1.0 mg/cm²
- Missing areas and UV radiation exposure before sunscreen application are other pitfalls that reduce the protective effect of sunscreens considerably

Petersen et al., Photodermatol Photoimmuno Photomed. 2014
Patients Under Apply Sunscreen

- Numerous studies have shown that consumers typically under apply product by 1/4 to 1/2 of what should be applied
- Data shows that consumers seldom re-apply after the initial application
- Not all body areas get comprehensive application and coverage

Patients Often Don’t Apply Recommended Amounts of Sunscreen

High-SPF Compensates for Under-Application of Sunscreen

- **OBJECTIVE:** To measure the actual SPF values of various sunscreens (SPF 30 to 100) applied in the reduced amounts typically used by consumers

Actual SPF at different application doses

<table>
<thead>
<tr>
<th>Application Density</th>
<th>SPF 30</th>
<th>SPF 50</th>
<th>SPF 70</th>
<th>SPF 100</th>
<th>SPF 50+</th>
<th>SPF 100+</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg/cm²</td>
<td>31.0</td>
<td>52.8</td>
<td>70.6</td>
<td>104.6</td>
<td>50.7</td>
<td>105.3</td>
</tr>
<tr>
<td>1.5 mg/cm²</td>
<td>21.8</td>
<td>41.3</td>
<td>54.4</td>
<td>79.3</td>
<td>38.6</td>
<td>75.0</td>
</tr>
<tr>
<td>1 mg/cm²</td>
<td>16.0</td>
<td>26.0</td>
<td>37.1</td>
<td>55.9</td>
<td>25.7</td>
<td>50.1</td>
</tr>
<tr>
<td>0.5 mg/cm²</td>
<td>8.8</td>
<td>13.9</td>
<td>19.3</td>
<td>27.1</td>
<td>12.6</td>
<td>22.4</td>
</tr>
</tbody>
</table>

Results

- There was a linear relationship between application density and the actual SPF
- **Sunscreens labeled SPF > 50 provided significant protection even when applied at “real world” typical application densities**

SPF Cap 50+?

**Con**

- Higher SPFs have better protection at “real world” application concentrations
- 50+... Is it 51 or 100?
**SPF Cap 50+?**

**Con**
- Higher SPF50s have better protection at “real world” application concentrations
- 50+… Is it 51 or 100?
- What will be the incentive to develop a better sunscreen if there is no way to reflect that on the label?

**Other factors that impact on protection**

**Why high SPF alone may not be enough**

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**SPF Not the complete answer...**

- Other issues:  
  - Application container

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**Children’s Sunscreen Application Thickness and the Influence of Age and Dispenser Type**

- Children applied sunscreen during 3 consecutive school weeks each week using a bottle, pump or roll-on
- Thickness of sunscreen application measured in mg/cm²
- Children applied significantly more sunscreen when using the pump (0.75 mg/cm²) and the squeeze bottle (0.57 mg/cm²) compared with the roll-on (0.22 mg/cm²)
- Conclusions:
  - Regardless of age, primary school children apply sunscreen at substantially less than 1mg/cm², similar to what has been observed among adults
  - Some sunscreen dispensers seem to facilitate thicker application than others

*Diaz et al, Arch Dermatol, 2012*

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**SPF Not the complete answer...**

- Other issues:  
  - Application container
  - Photostability

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**Photostable Broad Spectrum Sunscreens Are Superior for a given SPF**

- Photostable Sunscreen
- Nonphotostable Sunscreen

- Wavelength (nm)
- Absorbance
Photostability is most important AFTER the first MED

Both photostable and non-photostable have the same overall protection up to 15 MEDs, but protection after first MED is very different.

Longer Interval Sunscreen Protection Using Photostable UVA/UVB Protection

- No difference noted in subjects in terms of effectiveness in side with reapplication vs. side with no reapplication
- Conclusion:
  - Sunscreen in vivo test demonstrated effectiveness of photoprotection of 4 hours

Rigel et al, AAD 2006

What is the Best Sunscreen?
The best sunscreen is the one a patient will use regularly and as recommended

What is the Best Sunscreen?
The best sunscreen is the one a patient will use regularly and as recommended

SPF
Not the complete answer...

- Other issues:
  - Application container
  - Photostability
  - Cosmetic acceptability

Are current sunscreens safe?

Are current sunscreens safe?
Are Sunscreens Safe?

- Retinyl palmitate – cosmetic ingredient and antioxidant
  - 41% of sunscreens
  - Photo degraded → induces ROS
  - Photocarcinogenic
  - 10 year old FDA study of mice

- Oxybenzone – broad spectrum agent
  - Absorbed into skin
  - Carcinogen???
  - Causes "hormone disruption" (estrogenic activity)

Concerns not supported by available literature

Safety of Retinyl Palmitate in Sunscreens

- There is no published evidence to suggest that topical retinoids increase the risk of photocarcinogenesis.
- RP is regularly used in topical agents for >40 yrs.
- Retinoids are used for chemoprevention of skin cancers in individuals at high risk, such as transplant populations and patients with xeroderma pigmentosum, with no evidence for increased skin cancer risk.

Conclusions:
- Based on currently available data from studies, there is no convincing evidence to support the notion that RP in sunscreens is photocarcinogenic.
- In fact, clinical observations spanning over decades suggest that retinoids are helpful in skin cancer chemoprevention.
- Correcting this false impression is an important and necessary step to ensure that the public continues to use sunscreen as a component of photoprotective strategy.

Wang et al., JAAD, 2010

Safety of Oxybenzone

- Oxybenzone widely used in sunscreens
- Study suggested uterotrophic effects in immature rats after oral administration of oxybenzene
- Amount of topical application in humans to reach same levels of absorption computed

Wang et al., Arch Dermatol, 2011

Safety of Oxybenzone

Scenario 1: 100% body surface area (BSA) coverage at a standard dose of 2 mg/cm² would require 30 mL (10,950 mL/y with daily application).

Scenario 2: 100% BSA coverage at a dose of 1 mg/cm² would require 15 mL (5,475 mL/y).

Scenario 3: 25% BSA coverage at a dose of 1 mg/cm² would require 3.75 mL (1,369 mL/y).

Wang et al., Arch Dermatol, 2011

Years of Daily Sunscreen Application Required by an Average US Woman to Reach Systemic Levels of Oxybenzone per Unit of Body Mass Equivalent to Those Given to Immature Rats

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body surface area covered, %</td>
<td>100</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>Application dose, mg/cm²/d</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Application amount required, mL/d</td>
<td>30.00</td>
<td>15.00</td>
<td>3.75</td>
</tr>
<tr>
<td>Time required, y</td>
<td>34.6</td>
<td>63.3</td>
<td>277.0</td>
</tr>
</tbody>
</table>

Oral chemoprevention of skin cancer in mice by benzophenone sunscreens in drinking water

• 15 hairless mice (control and test groups) had skin tumors induced by a single dose of NOR-1 and 1 wk later application of TPA applied to skin tw for 20 weeks as tumor a promoter
• Benzophenone sunscreen agents were administered at 0.0025% to mice through drinking water starting 1 wk prior to and stopping 1 wk post tumor initiation
• Significant inhibition (p<0.001) of tumor incidence (50% and 60%, respectively) and tumor burden (papilloma inhibition/mouse, 50% and 70%) were observed when compared to the positive control group.
• Conclusions:
  – Skin cancer chemoprevention potential of orally-ingested benzophenone sunscreens in mice
  – Synergistic protection achievable by complementation of oral and topical sunscreen usage


Change in “traditional” formulation mix
US Sunscreen Sales Last Year

Spray sales exceed lotions for the first time

Sun Protection and Anti-oxidants

• Vitamin E
• Vitamin C
• Polyphenols (Green tea) epigallocatechin-3-gallate (EGCG)
• Genistein (soybeans)
• Resveratrol (grape skins, peanuts, and red wine)
• Lycopene (an isomer of beta carotene - red fruits and vegetables, such as tomatoes, watermelons)
• Combinations may be synergistic

Junkins-Hopkins et al. JAMA. 2010

Oral Polypodium Leucotomos extract

New Formulations...
**Polypodium leucotomos**

*Decreases UV induced skin damage*

- Investigated photoprotective effects of oral administration in 9 patients
- Measured erythema (MED) and biopsied skin and measured sunburn cells, pyrimidine dimers, dermal mast cell infiltration and Langerhans cells
- All of these measures were improved with the administration of polypodium

**Conclusion:**
- Effective systemic chemoprotective agent against UV radiation exposure skin damage

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**Polypodium leucotomos**

- Polypodium leucotomos is a natural fern leaf extract with antiinflammatory and antioxidant (AO) properties.
- The administration of oral P leucotomos to a group of high-risk patients with MM or DNS led to a significant reduction in sensitivity to UVR in all patients.
- Other studies have found that oral administration of 480 to 1200 mg daily of this extract can prevent polymorphous light eruption lesions in patients with PMLE
- Has been shown to reduce the known effects of UVR, including minimal erythema dose, minimal phototoxic dose, UV-induced epidermal proliferation, development of DNA damage, and the generation of ROS.

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**Benefits of oral Polypodium Leucotomos extract in MM high-risk patients**

- 61 pts (25 familial and/or multiple MM, 20 sporadic MM and 16 with DNs without history of MM) were exposed to varying doses of artificial UVB radiation without and after oral administration of a total dose of 1080 mg of PL.
- Oral PL treatment significantly increased the MED mean in all groups

**Conclusions:**
- Oral PL leads to a significant reduction of sensitivity to UVR (p<0.05) in all patients in study

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**Are patients really “allergic” to sunscreens?**

- 1,527 with a concern about sunscreen allergy tested
- Only 4 patients had a positive reaction to a sunscreen chemical or to the product they were using.
- In addition, 8 of the patients who had no specific history of sunscreen allergy reacted to benzophenone-3.
- Other more common final diagnoses included ACD to excipients such as fragrances or preservatives and suspected photosensitive disorders

**Conclusion:**
- ACD to sunscreen was found to be very uncommon (0.8%).

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**Polypodium leucotomos extract (PLE): a status report on clinical efficacy and safety**

**25 studies showing safety and efficacy**

**Conclusion:**
- Current level of evidence suggests oral PLE can be prescribed confidently for long-term use

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**Answering Our Patient’s Questions**
Stability of sunscreens following exposure to extreme temperatures

- 9 commercially available sunscreens after an 8-hour exposure to a range of temperatures including −20°C, 4°C, 21°C, 30°C, and 60°C
- Phase separation and failure to rehomogenize on shaking
- Conclusions:
  - Extended exposures to high temperatures can degrade sunscreen


Do you really have to wait 15-20 minutes for sunscreen protection?

- Sunscreen testing protocols mandate drying times of 15-20 minutes before SPF testing can begin: mandatory labeling reflect this instruction
- UV Protection is actually instantaneous
- Water resistance MAY require more drying time

Re-application is Important

- Re-application after 2 hours is mandatory labeling by FDA
  - Based on JAAD paper, 2011, AAD comment to FDA
- Photostable sunscreens do not "wear out" and will continue to protect as long as they are on the skin
- Re-application is advisable to assure proper application level and to hit "missed spots," and after toweling or wiping off


Rules of Sunscreen Application

- Patients tend to “rub in” sunscreens — so you can’t see it anymore. Does “rubbing in” assure best protection? NO!
  - Best protection is achieved by having uniform film on the surface of the skin
  - For inorganic filters (ZnO, TiO2) it is even more important not to “rub” it till you can’t see it
  - For Spray products — spray the surface until it glistens “wet” and then gently spread to make sure all spots are covered
  - Best to spray in sheltered area so the sunscreen is not blown away

How to choose the right sunscreen to avoid getting burned

It turns out that the sunscreen sold by actress Jessica Alba’s eco-friendly baby product company Honest Co. might not do much to shield users from burns.

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How can people know whether a sunscreen actually works before slathering it on and risking burns? “You have to be an organic chemist to really understand what’s on the back of a sunscreen label,” says Darrell Rigal, a clinical professor of dermatology at New York University’s School of Medicine, who has researched the effects of sunlight on skin and runs a practice in New York City.
Protect your largest organ…

Your skin from the Sun

All-natural labels don't matter. “Every chemical, whether it’s natural or artificial, is a chemical,” Rigel says. “People could be allergic to natural things. I’m allergic to onions, just because it’s natural doesn’t make it any better.”

Look for the terms “broad spectrum” on the front of the bottle. That means the lotion protects against both ultraviolet A and ultraviolet B rays, both of which can hurt skin.

The sunscreen should say it is water-resistant for 30 minutes, but reapply it more often. People often apply sunscreen at the start of the day, but the product can wear off. Select lotions that last for at least 80 minutes. And try to reapply sunscreen at least every two hours to remain shielded against harmful rays, Rigel says.

Sprays can be less effective than lotions. When you spray sunscreen on, you are more likely to miss a spot. Apply two coats if you prefer not to get your hands greasy with a lotion.

Try out the lotion on the back of your hand at the store. The best sunscreen is the sunscreen you actually use. “If you don’t like the way it feels, you’re not going to use it,” Rigel says. “The most important thing to say about sunscreen is to use it.”

What you really need to know about…

Photoprotection

- Photoprotection important and lowers melanoma risk
- New labeling helpful but not the ”end all, be all”
- We don’t have answers to all of the questions and formulations can still be improved
- Formulations evolving in future with new agents and other ingredients
- The best sunscreen is the one that a person will use
- Have to improve getting the message to our pts