Primary and Secondary Skin Cancer Prevention Efforts

Can they have an impact?

Darrell S. Rigel, MD MS
Clinical Professor of Dermatology
New York University Medical Center
New York, New York

Primary and Secondary Skin Cancer Prevention Efforts

DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Darrell S, Rigel, MD MS
Primary and Secondary Skin Cancer Prevention Efforts

Ferndale – A, H
Beiersdorf – A, H
Neutrogena – A, H, I

Primary vs Secondary Prevention

Primary = Protection  Secondary = Early Detection

Impact → Incidence  Impact → Mortality

Current Data on Melanoma in the U.S.

Melanoma cases are projected to increase in 2018 vs. 2017

Melanoma deaths are projected to decrease in 2018 vs. 2017

American Cancer Society, 2018

What can we conclude from this data?

Both types of prevention important, but…

✓ Secondary prevention efforts appear to be making an impact
✓ Primary prevention not as impactful

Primary Prevention Considerations
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

Green et al, J Clin Oncol, 2011

Reduced melanoma risk after regular sunscreen use

Sunscreen Usage and Melanoma Risk

All Melanomas

Invasive MMs

Sunscreen Usage and 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
- Only 11 new MMs in daily group vs. 22 (p=0.051)
- 2 Invasive MMs in daily group vs. 11
- Conclusions:
  - Melanoma risk significantly lowered by regular sunscreen use in adults

Green et al, J Clin Oncol, 2011

Skin cancers in Australia prevented by regular sunscreen use

- Estimated the proportion of skin cancers that would have occurred but were likely prevented by regular sunscreen use
- Regular sunscreen use prevented around 14,190 persons from developing SCCs (PF 9.3%) and 1,730 from Melanoma (PF 14%)
- Conclusions:
  - Prevailing levels of sunscreen use probably reduced skin cancer incidence by 10-15%
  - Sunscreen should be a component of a comprehensive sun protection strategy

Calculated the PF, the proportional difference between the observed number of melanomas arising under prevailing levels of 5% annual increase in sunscreen use for 10 years (50% increase)

Estimated that cumulatively to 2031, 231,053 fewer melanomas would arise in the U.S. white population (PF 11%)

Conclusions:
- Interventions to increase use of sunscreen would result in reductions in melanoma incidence
- Countries with a high incidence of melanoma should monitor levels of sunscreen use

How many melanomas might be prevented if more people applied sunscreen regularly?

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Does SPF>50 provide additional benefit?

High SPF formulation more effective during intense UV exposures

- SPF 85 formulation tested vs. SPF 50
- 56 subjects applied sunscreen to face while skiing at Vail, Colorado 1/13/08
- 1 application only at start of day
- Average hours exposed 5.0 hours
- Noon Sun 22 minutes = 1 MED
- 7/28 sunburned SPF 50 vs. 1/28 SPF 85 (p=0.02)
- Conclusion:
  - SPF 85 formulation more effective than SPF 50 in protecting from sunburn with a single application in a high UV test environment

Russak et al, JAAD 2010

METHODS

- 199 healthy men and women ≥18 years of age participated in a one day split face, randomized, double blind study in Vail, Colorado.
- The difference in sunburn protection provided by two currently available sunscreens (SPF 50+ and SPF 100+) was evaluated.
- Products were supplied in a kit containing two overwrapped tubes of sunscreen marked “right” and “left.” Each subject wore both sunscreens simultaneously, with product application randomized to either the right or left side of the face.
- Subjects utilized the sunscreens as they would normally during ski activities. Diaries were used to record sun exposure time and the frequency and timing of sunscreen re-applications.
- Subjects reported the next morning for clinical evaluation.

Williams et al, JAAD, 2018

RESULTS

Primary Endpoint

Williams et al, JAAD, 2018

RESULTS

Primary Endpoint

Williams et al, JAAD, 2018
Erythema progression was observed to be more than twice as severe on the SPF 50 vs SPF 100 protected side.

**RESULTS**

**Usage**

<table>
<thead>
<tr>
<th>Product</th>
<th>Average Product Application Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPF 50+</td>
<td>1.10 mg/cm²</td>
</tr>
<tr>
<td>SPF 100+</td>
<td>1.04 mg/cm²</td>
</tr>
</tbody>
</table>

No differences were observed in usage, application density, or reapplication frequency of the study products.

**RESULTS**

The number of sunscreen reapplications was not observed to diminish the enhanced protection benefit of the SPF 100 product.

SPF 100 sunscreen was significantly more effective at protecting against sunburn in all examined skin types.

**CONCLUSIONS**

- The SPF 100+ sunscreen was significantly more effective in protecting against sunburn than the SPF 50+ sunscreen for all skin types evaluated.
- These findings demonstrate that there is a need for sunscreens labelled with SPF's greater than 50+ to provide consumers with better choices for sunburn protection.

**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

Polypodium leucotomos

Decreases UV induced skin damage


Williams et al., JAAD, 2018

Williams et al., JAAD, 2018

Williams et al., JAAD, 2018

Williams et al., JAAD, 2018

Williams et al., JAAD, 2018
**Polypodium leucotomos extract (PLE): a status report on clinical efficacy and safety**

- 25 studies found via Pubmed
  - 6 basic science studies
  - 19 human studies
- Dose range: 120-1080 mg
- No major adverse effects or long-term sequelae
- Mild-moderate side effects: 16/1016 patients (2%)
  - Most commonly reported gastrointestinal discomfort and pruritus
- Conclusions:
  - Current level of evidence suggests oral PLE can be prescribed confidently for long-term use

Wrinkelman et al. J Drugs Dermatol. 2015

**UV-induced Cyclobutane Pyrimidine Dimers**

UV-induced cyclobutane pyrimidine dimers (CPDs, T-T abnormal nucleotide binding) are a defect known as 6-pyrimidine-4-pyrimidone (6-4 PP). Both effects distort the helix, and alter replication. Photolyase identifies the defective DNA where the helix breaks by converting the dimers into monomeric bases. Normal transcription mechanisms by DNA polymerase then resume.


**After UVA Exposure Photolyase Identifies the Defective DNA**

After UVA exposure photolyase identifies the defective DNA where the helix breaks by converting the dimers into monomeric bases. Normal transcription mechanisms by DNA polymerase then resume.


**Potential Benefit of Photolyases when Exogenously Applied**

- Almost half of the thymidine dimers can be repaired
- Humans have other endogenous repair mechanisms such as T4N5 endonuclease, which are less efficient
- Exogenously applied photolyases have potential benefits

**Reduction of AKs and NMSCs**

Differences in the mean rate of production of AK and NMSC over a one year treatment time with sunscreen containing photolyases.

Photolyase containing sunscreens have the potential to reduce production of AKs and NMSCs.
Comparison Between High SPF Sunscreen vs Shade

- First study to evaluate sun protection efficacy of shade
  - Side-by-side comparison of sun protection efficacy of shade (beach umbrella) vs. SPF 100
  - Shade alone doesn’t provide sufficient sun protection
    - 78% of subjects in shade group showed erythema in one or more sites vs. only 25% in sunscreen group

Combination of behaviors provided the best protection

Promoting sunscreen use and sun-protective practices in NCAA athletes: Impact of educational intervention

- 846 NCAA Student athletes (SA) were surveyed about sunscreen use patterns before and after they, their coaches, and athletic trainers participated in the Stanford University Network for Sun Protection, Outreach, Research, and Teamwork (SUNSORT) educational program
  - After intervention, significant increases were observed in:
    - Sunscreen use 4 or more days per week by SAs (from 26% to 39% [P = .02]),
    - SAs spoken to by their coach about sun safety (from 26% to 57% [P = .0001]),
    - SA recognition of higher skin cancer risk (from 54% to 67% [P = .04]).

Promoting sunscreen use and sun-protective practices in NCAA athletes: Impact of educational intervention

- Conclusions:
  - Following educational intervention, NCAA athletes were more likely to use sunscreen, especially if encouraged by their coach
  - Coaches were more likely to encourage sunscreen use following participation in SUNSPORT
  - Study emphasizes that education directed to athletes, Athletic Trainers, and Coaches can improve sun-protective practices in Student Athletes.

Secondary Prevention Considerations

A B C D’s of Melanoma

Developed in 1985 by our Group at New York University to provide the clinician with a framework for enhancing the detection of early melanoma

Friedman et al., CA, 1985
**ABCD Rule for MM Diagnosis**

- ABCD rule improved diagnostic skills
- Sensitivity and specificity improved
- Conclusion:
  - Level of Diagnosis improved for dermatologists and non-dermatologists

Whited et al, JAMA, 1998

**Using Technology to Enhance Early Detection**

- 783 MM pts who were diagnosed between 1996 and 2012 were included.
- Associations between who first noticed the melanoma (ie, self-detected, relatives, health care workers, or dermatologists), epidemiology, clinical presentation, histology, and patient outcomes were analyzed.
- Patients with self-detected MMs had a poorer prognosis than those with MMs that were detected by dermatologists.
- Conclusions:
  - Dermatologists make a difference in their impact on early detection.
    - Patients with MMs that were self-detected by women had better prognoses than those that were self-detected by men, especially for patients >70 years of age.
    - This group might therefore be a logical target for melanoma detection education.

Aviles-Izquierdo et al, JAAD, 2016

**MM screening by means of complete skin examinations for all patients in a derm practice reduces MM thickness at diagnosis**

- Chart review of melanoma detection was conducted over a 10-year period in a Central New York private practice employing 1 board-certified dermatologist and 2 physician extenders.
- Over 45% of all MMs detected were diagnosed as an incidental finding unrelated to the patient's chief complaint.
- Moreover, the average depth of invasion in dermatologist-detected MMs was 0.21 mm, which was statistically less than when the patient's lesion was their chief complaint, with an average depth of 0.49 mm.
- In selecting for invasive melanomas, those Dermatologist diagnosed were <1 mm in depth compared with those being a patient's chief complaint were typically >1 mm in depth.
- Conclusions:
  - Full skin examination for all patients, regardless of their chief complaint, increases melanoma detection, decreases overall thickness of melanoma at diagnosis, and decreases patient morbidity and mortality.

Chinwakar et al, JAAD, 2014
Impact of dermatology eConsults on access to care and skin cancer screening in underserved populations

- Retrospective cohort study of 2385 dermatology referrals from primary care from June 2014 through November 2015
- Before implementation of electronic eConsults, access to dermatology was limited:
  - Only 139 (11%) of 1258 referrals resulted in a confirmed appointment with a median wait time of 77 days.
  - Post implementation, 499 of 1127 consults (44%) were sent electronically, and of those, 16% required a face-to-face visit with a median wait time of 28 days. Ten malignancies were identified via eConsults.

- Conclusions:
  - eConsults increase access to dermatologic care and reduce wait times for patients receiving medical care at community health centers.
  - Teledermatology could increase access to skin cancer screening and treatment for medically disadvantaged populations.

Naka et al, JAAD, 2018

Intervention to promote early detection of melanoma in women undergoing mammography

- Pilot study designed to promote early detection of melanoma among women undergoing mammography
- Self skin examination (SSE) materials placed in changing rooms
- Out of 560 women undergoing mammography, 68% noticed SSE information on their own, 78% who noticed the information thought that it applied to them, and 68% identified at least one risk factor for melanoma in their personal history
- 20% of subjects performed SSE in the changing room, 13% noticed a concerning mole, and 60% who noted a concerning lesion stated intent to f/u with a dermatologist


Randomized trial of intervention to improve early detection of melanoma by pts with a history of melanoma and their partners

- 856 pts with history of melanoma and their partners randomized to control group (99 pts) or 30-minute intervention to train self skin examination (SSE) either in person (159 pts), using a pamphlet (165 pts), or using an app on a tablet (71 pts)
- Main outcome: SSE performance
- Secondary outcome: Detection of new or recurrent melanoma by pt/partner or physician
- Tertiary outcome: Number of unscheduled appointments for concerning lesions
- Results: Pts in intervention arms had increased SSEs persisting to 2 years f/u and identified more melanomas than control group without an increase in unscheduled pt visits

Robinson et al. JAMA Dermatol, 2016

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- Pts in intervention arms had increased SSEs persisting to 2 years f/u and identified more melanomas than control group without an increase in unscheduled pt visits

Conclusions:
- Pts and partners can reliably perform SSE after participating in a structured skills training program with reinforcement every 4 months
- Accurate SSE by those at risk may enhance early detection of melanoma and relieve some of the burden on health services

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UV radiation-related behaviors among young people after a diagnosis of MM or BCC

- Online survey of UV-related behaviors in 50 young skin cancer survivors and evaluated predictors for these behaviors
- Those who worried about skin cancer were 3x more likely to not sunburn and to engage in multiple protective behaviors
- Riskier UV-related behaviors were statically more likely in:
  - Younger survivors
  - Those with NMSC
  - Those who did not worry about skin cancer

Conclusion:
- Need to target these individuals for skin cancer risk reduction

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Enhancing the Effectiveness of Prevention Programs...
**Reasons for Using and Failing to Use Sunscreen**

Comparison Among Whites, Hispanics, and Asian/Pacific Islanders in Southern California

- "I often forget" was the most common reason for failing to use sunscreen.
- The second most common was that "it is too greasy."
- Approximately one-third of whites and more than 43% of Asian/Pacific Islanders, but only 16% of Hispanics, indicated that sunscreen use is "too much trouble."
- 26% of Asians indicated that sunscreen is too messy, and 29% of Hispanics checked that they do not use sunscreen because they have dark skin.

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**Association of UV Index and Sunscreen Use Among US White High School Students**

- White male students, as the mean UV index increased, the adjusted odds of never wearing sunscreen increased (OR = 1.15 p < .01) and the adjusted odds of most of the time or always wearing sunscreen decreased (OR = 0.85 p < .01).
- There was no association between sunscreen use and mean UV index among White female students.
- Conclusions:
  - Need for renewed public health efforts among school, clinical, and public health professionals to promote sunscreen use as part of a comprehensive approach to prevent skin cancer.

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**Melanoma risk-takers: fathers and sons**

- Individuals (N = 1172) with sun exposure were divided into:
  - Risk-takers (N = 442) who did not view sun protection as important
  - Those who used sun protection (N = 730).
- Risk-takers were significantly more often male (62% vs. 44%, P < 0.01), had a lower level of education (40% vs. 26%, P < 0.01), lower incomes and were more often smokers (42% vs. 31%, P < 0.01).
- Sun-protection measures for children of risk-takers were less stringent than those who used sun protection: Frequent use of sunscreen (77% vs. 86%, P < 0.01)
- Conclusions:
  - Sun risk-takers are characterized by a lesser understanding of sun-protection measures and behaviors and this impacts on their children
  - Educational opportunities exist

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**Special Considerations to Enhance the Impact of Prevention**

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**SUNSCREEN IN SCHOOLS**

CBS News 2017
Compliance of tanning salons with state legislation limiting youth access to tanning beds

- Cross-sectional telephone survey of 427 tanning salons in 42 states (and Washington, D.C.) with indoor tanning legislation restricting use in minors (10 salons randomly selected from each state/territory)
- Callers posed as minors attempting to schedule a tanning appointment
- Overall non-compliance documented in 159/427 salons (37.2%)
- Factors associated with non-compliance:
  - Rural location
  - Location in southern U.S.
  - Independently owned salons
  - States with younger age groups being regulated
  - States with >1 tanning regulation

Factors associated with non-compliance:

- Rural location
- Location in southern U.S.
- Independently owned salons
- States with younger age groups being regulated
- States with >1 tanning regulation

Conclusions

- Compliance with state legislation limiting tanning bed access by minors is poor, especially in rural, southern areas
- Additional efforts are needed to enforce these regulations

Assessment of Levels of UVA Protection in Automobile Windshields and Side Windows

- UVA levels inside windshields and side windows in 29 automobiles (1990-2014) from 15 automobile manufacturers were measured.

Do you need to wear sunscreen while in a car?

- UVA levels inside windshields and side windows in 29 automobiles (1990-2014) from 15 automobile manufacturers were measured.
Do you need to wear sunscreen while in a car?

- 2011 Lexus Rx350: 96% UVA blocked
- 2011 Mercedes-Benz E350: 97% UVA blocked
- 2014 VW Golf: 94% UVA blocked
- 2013 BMW 320i: 82% UVA blocked

Assessment of Levels of UVA Protection in Automobile Windshields and Side Windows

- UVA levels inside windshields and side windows in 29 automobiles (1990-2014) from 15 automobile manufacturers were measured.
- Average percentage of front-windshield UV-A blockage was 96% (range 95%-98%) and the side-window blockage, which was 71% (range 44%-96%).

Conclusions:
- These results may in part explain the reported increased rates of cataract in left eyes and left-sided facial skin cancer.
- Automakers may wish to consider increasing the degree of UV-A protection in the side windows of automobiles.

Identifying Knowledge and Practice Gaps and Providing the Education and Motivation to Close Them

Consumer knowledge of sunscreen labeling terminology

- Original survey study measuring understanding of three key terms on sunscreen labels addressed by the 2011 FDA Final Rule on Sunscreen
  - SPF
  - Broad-spectrum
  - Water-resistant
- Survey administered to 317 consecutive pts seen in a general dermatology office
- Results stratified by personal history of skin cancer (59 with skin cancer hx, 258 with no hx of skin cancer)
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- Results stratified by personal history of skin cancer (59 with skin cancer hx, 258 with no hx of skin cancer)
- Conclusions
  - FDA efforts to make sunscreen labeling more useful to the consumer have been largely unsuccessful...likely impacting on the proper use of sunscreen
  - Knowledge appears to be equally poor in those with a personal hx of skin cancer vs. those without
  - Public education initiative needed to instruct consumers how they can apply understanding of this terminology in order to better select sunscreens

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**Trends in US sunscreen formulations: Impact of increasing spray usage**

- If current trends continue, sprays will soon overtake lotions as the primary sunscreen formulation.
- Given this fact, dermatologists and manufacturers need to work together to establish guidelines for optimal application and usage of spray sunscreens to achieve the maximal skin cancer prevention benefit.

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**Oral green tea catechins do not provide photoprotection from direct DNA damage induced by higher dose solar simulated radiation**

- Double-blind, randomized, placebo-controlled trial in healthy white adults (13 male, 37 female; Skin types I and II) who received 1080 mg GTC (equivalent to 5 cups/day) with 100 mg vitamin C (n = 25) vs placebo maltodextrin (n = 25) daily for 12 weeks
- No difference between active and placebo groups in number of CPD-positive cells in UVR-irradiated epidermis at 24 hours
- Evaluation of a moderate (2MED) UVR dose and further time points similarly found no effect of supplement on CPD
- Conclusions:
  - Oral green tea catechins did not lower UV induced DNA CPD formation.

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**Sun behavior after dx of cutaneous MM**

- 24 pts recently dx’ed with MM, 29 pts diagnosed >1yr ago vs. 51 controls matched for age, sex, occupation and skin type
- Sun exposure diaries daily maintained and subjects wore personal electronic UVR dosimeters
- UVR dose of recently dx’ed patients was 1/3 lower; and the number of days using sunscreen was 2x that of matched controls
- In pts dx’ed more than 1 year earlier, the UVR dose on days with body exposure was 1/3 higher and the number of days using sunscreen was 1/2 that of recently dx’ed pts
- Conclusions:
  - Patients with CMM limited their UVR dose on days with body exposure, and by using sunscreen further reduced UVR reaching the skin, although only immediately after diagnosis
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*Idorn et al, Br J Dermatol, 2013*

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**Sun behavior after dx of cutaneous MM**
- 21 MM pts matched with 21 controls matched for age, sex, occupation and skin type
- Sun exposure diaries daily maintained and subjects wore personal electronic UVR dosimeters
- UVR dose was lower at time of diagnosis but increased over 3 years above controls for Daily UVR dose per year, days with sun exposure and holidays with sun exposure.
- In pts 2nd year of follow up, the UVR dose on days with body exposure was higher than prior to diagnosis
- Conclusions:
  - Patients with CMM do not maintain long term cautious sun behavior

*Idorn et al, JAMA Dermatol . 2014*

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**What do our colleagues think?**

**Dermatologists’ Perceptions Recommendations and Usage of Sunscreen**

**Dermatologists’ Views**
- 97% 100% 99% 99%
- Sunscreens safe
- Oxybenzone safe
- Retinyl palmitate safe
- High SPF safety margin
- Recommend SPF50+

*Farberg et al, JAMA Dermatol, 2016*

**Dermatologists’ Beliefs**
- 96% 91% 87% 83%
- SPFs level
- Broad spectrum
- Feel/elegance
- Photostability

*Farberg et al, JAMA Dermatol, 2016*
Despite Decades of Science, Education, Prevention Compliance is Low

- Only 39.1% of American households purchase sunscreen.
- Only 30% of women and >15% of men use sunscreen on face and exposed skin.

Can Primary and Secondary Prevention Make a Difference?

Summary

1. Understanding the difference between primary and secondary prevention issues
2. Assess the knowledge and practice gaps
3. Develop targeted public education programs
4. Given the long latency from intervention to change in incidence and mortality rates, develop metrics to measure shorter term effectiveness to guide future efforts