SOARING Rx

BY DR. DANIEL L. JOHNSON

Skin Cancer

Keeping the Sunny Side Up

Previous columns may be found at: http://www.tinyurl.com/drdanscolumns

We all have heard the message: sun exposure causes skin cancer and increases the risk of malignant melanoma.

Many of us remember the beloved Richard Johnson, who spent as many hours as possible under a canopy, who spent his last few years with a big notch in the top of his right ear, and gently reminded others to use sunscreen.

Many of us are anxious about exposure to UV light on the field and under our big canopies. What's the truth here? Should we all slather on SP-40, wear broad-brimmed hats and long sleeves, and buy charcoal-grey canopies?

No, we should not, for several reasons:

• We need the vitamin D sunlight creates more than we need to avoid sunlight. Vitamin D is very important to health, and avoiding sunlight shortens life and enhances the most common deadly diseases.

• Avoiding a blistering sunburn is the most important risk-reduction for skin cancer.

• Ultraviolet (UV) light is the problem, and can be avoided selectively. Use the iPhone or Android **dminder** app to manage sun exposure.

• The average person gets about 25% of their damaging light exposure before adulthood. The average SSA member is getting behind the adulthood power-curve, and has bigger health fish to fry than long-ago sunburns. (BUT: Glider pilots under 25, this is important for you.)

• Non-melanoma skin cancers, which kill hardly anybody, outnumber melanomas 100:1.

• Just because sunglasses or a canopy is dark doesn't mean it filters UV. Check with the manufacturer.

• Treatment is pretty easy for early lesions.

OK, that's the bottom line, for Bert Compton, and others who prefer to just read the intro. If you want the explanation and some of the nuances, read on.

Not Ignoring Skin Cancer

It's very convenient that our skin is on the surface, so it's easy to see tumors (yes, someone else has to check our caboose, preferably a discerning professional). I do believe that every older Caucasian should get naked in a doctor's office every year or two for an inspection. Everyone's head and neck should be checked. Men's other skin cancers are mostly on their upper trunk, women's mostly on their legs.

"Non-melanoma skin cancers" (basal cell and squamous carcinomas) are mostly reddish, nodular or crusty, and look irritated. It's good to catch these early, so that the good doctor doesn't have to carve a big divot out of your nose or lip in order to get rid of it. They're important because they're disfiguring.

Melanoma is rightly feared more, because it's the cause of most skin-cancer deaths, for it metastasizes enthusiastically.

Melanomas are actually a group of different cancers that can originate nearly anywhere in the body, not just in skin. The worst, of course, are those that develop in an internal organ and spread widely before discovery.

The frustrating thing about melanomas is that brown or black spots are exceedingly common, so even experienced doctors feel a little anxious about missing one. And when we find one, it can be quite a surprise.

For example, a middle-aged businessman came for a student pilot certificate. He mentioned that a brother had melanoma, which heightened our interest. I scrutinized every inch of his hide as I did the exam, and when checking his knee reflexes saw a pinhead-sized black spot on the side of his right leg just above the ankle. Five minutes later, it was in a jar. The pathology report confirmed that it was a melanoma and that he was likely cured. (Of that one.)

What Is Cancer?

Normal cells reproduce in a regulated way. Their movement and growth is limited by neighboring cells ("contact inhibition"). Normally motile cells migrate in response to specific hormonal signals. Every action or inaction is regulated, in response to the chemical milieu.

"Cancer" involves lost responsivity to intercellular controls of one or more of these functions. Cancer cells are *impaired*. Sometimes cells are impaired without damage that releases "cancer" characteristics – this is particularly relevant to *squamous* skin carcinoma, which is preceded by *actinic keratosis*. (*Actinic* refers to light, *keratin* is the crusty stuff atop our skin, and *osis* indicates it's abnormal. Light-damaged skin.) It's not "cancer" because the abnormal cells do not migrate into other tissues or invade their neighbors.

There are three classes of skin cancers. All are more common with increased UV exposure, the reason people are advised to be judicious with tanning beds and sunlight.

• *Malignant melanoma*. The melanomas are a group of cancers that develop from pigment-producing cells. Some occur internally, others occur in the skin, where light exposure is important. Only about 1% of skin cancers are melanomas. Melanomas beginning internally cannot be found before they metastasize.

• *Squamous cell carcinoma*. These develop from the cells of the most superficial layer of the skin. This type of cancer can develop anywhere there are "squamous" cells – the skin, the mucous membranes of the mouth and upper respiratory tract, and anal-genital area. In

the skin, risk is increased by UV, in the mouth and respiratory tract, by tobacco, and in the anal-genital area by venereal wart virus. About a third of skin cancers are squamous. These are the crusty ones. They may sometimes spread to lymph nodes in the region.

• *Basal cell carcinoma.* These develop from the underlying, *basal* layer of skin cells. These are typically round and raised, often eroded, with a scab at top center. About two-thirds of skin cancers are basals. They may ulcerate and invade locally, but don't metastasize.

In Australia, a sunny clime mostly populated by Caucasian immigrants, annually 1:50 persons is found to have basal cell carcinoma, 1:100 to have squamous cell carcinoma of the skin, and 1:2,000 to have melanoma of the skin.

The Importance of Sunlight

There's been a lot of publicity during the last few decades about the risk of skin cancer from sun exposure. There are also powerful social pressures to seek a brown skin color rather than white or black. This leads whites to sunburns – and leads blacks to avoid sun so as not to be too dark.

The result of this, and of living our lives indoors, is widespread vitamin D deficiency, with broad health consequences.

It turns out that sunlight is very important to general health. People who avoid sun exposure have shorter lives, and increased rates of death from hypertension, cardiovascular disease, and cancer of the colon, breast, and prostate, and have a higher risk of immune disease such as multiple sclerosis and rheumatoid arthritis.

The common thread is "sunshine vitamin D." 90% of our vitamin D is formed in the skin through sunlight. We all know that this is crucial for bone health. Its actions making for healthy bones are complicated and interesting. Vitamin D also has hormonal functions. In this role it's important in a healthy immune system. The immune system normally detects and eliminates cells that have been transformed into cancer cells, and does not attack our own normal cells. In animal models, vitamin D deficiency increases the risk of juvenile-onset diabetes, which is an autoimmune disease.

Vitamin D deficiency promotes hypertension, and by increasing parathyroid hormone levels, causes insulin resistance and thus promotes diabetes. Vitamin D lack increases major cardiovascular events by 50-80% depending on its severity. Using a tanning bed 3 times a week for 3 months almost doubles serum D levels and drops blood pressure 6 mm Hg.

The protective effect of less intense solar UV light clearly outweighs its effects toward skin cancer. A problem is that the young sometimes seek too much, for attraction, and after middle age, most people seek too little. Black women, in particular, often severely lack vitamin D.

Vitamin D and its precursors can only be absorbed effectively with adequate acid. Acid-reducing medications, used continually, result in vitamin D deficiency. Unfortunately, continual use of

these meds causes acid rebound when they are stopped, so they must be tapered gradually.

We older types will do well to take 1,000 IU daily of cholecalciferol, vitamin D3.

How Much Sunlight?

I was told years ago that 15 minutes of sunlight daily to the face, neck, and arms is enough to maintain Vitamin D levels. Other recommendations differ slightly, but these all run aground in the elderly on the fact that young people manufacture about 5 times as much vitamin D from a single sun exposure sufficient to make the skin red.

This implies, I think, that us old folks should spend some time in the sun and not feel guilty about it. No, we don't want sunburn, and us bald guys should wear a hat. But our skin cancer risk is related to the sunburns we had in our foolish youth, not to today's line duty at the gliderport, and few of us are on the 30-year plan any more.

More important, having a normal vitamin D level delays or inhibits those common diseases that kill us – diabetes, atherosclerosis, and cancer.

If you are young, **now** is the time to avoid sunburn, protect your eyes from UV, and to eat a vegetables-based diet with lean protein, avoiding refined sugar and cooked fats, especially animal fat. This helps old people, but transforms the health future of the young.

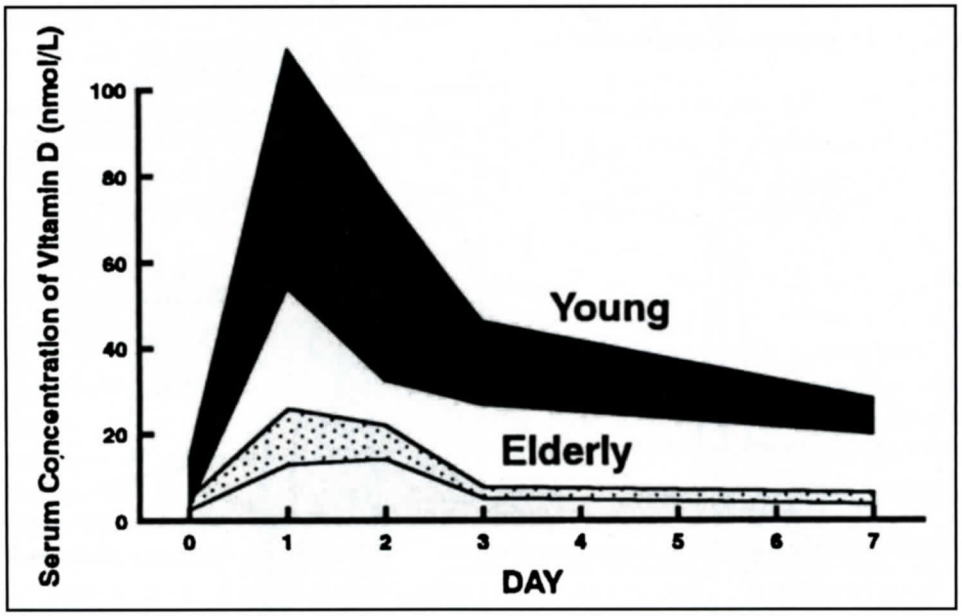
The Risks of Sunlight

UV exposure clearly increases skin cancers. In general, occupational exposure creates a modest risk. Sunbathing is not a vocation, and getting sunburned is not the right thing: having had a blistering sunburn 5 or more times in one's *life* causes the greatest risk of all three types of skin cancer.

I work in a farming area. The elderly and retired farmers (both male and female) seem all to have light-damaged skin (actinic keratosis) and we always scrutinize their sun-exposed areas no matter why they have come to see us. Typically, new cancers have been present for months, but aggressive ones can double in weeks. (If you have any rapidly-enlarging skin lesions, get a diagnosis promptly.)

These folks often have skin cancers, but none of them die of it. Like the rest of Westerners, they die mostly of atherosclerotic heart disease from eating the Western Diet, and sometimes of cancer.

Nearly every elderly Caucasian who's spent time in the sun has light-damaged skin. This can be pretty extensive in the semi-pro sunbather, like the woman in her seventies, in a bikini, wearing skin that looks three sizes too big. For most people, the sun-exposed areas are simply those parts normally not covered by clothing, which of course get much more sun exposure.



From MF Holick, 1994, McCollum Award Lecture, Am J Clin Nutr 1994;60:623. (Used by permission of Dr. Holick.)

What to Look for

Look first at your light-exposed skin: bald pate, ears & temples first, and also hands, forearms, upper chest, and back. Women, check your legs and thighs, too. Thanks to the Internet, you can easily find example illustrations by searching for images of these things.

Here's what you're looking for:

- *Actinic keratosis*, the pre-cancer change, is characterized by patchy redness with scaling that's flat. It feels rough but not bumpy.
- *Basal cell carcinoma* is bumpy. Typically it's a soft nodule, and when lit from the side with a strong light may seem to be clear inside. As it develops, usually a little crust forms at the top that never quite heals – usually blamed on shaving or scratching.
- These are worth quick attention when on the lips, eyelids, nose, or ears because their removal can be disfiguring. This is because the cancer cells tend to glide away from the nodule under the surface, so that a divot much larger than the nodule must be removed by the surgeon.
- *Squamous cell carcinomas* are scaly. An expanding scaly bump with a reddish base should probably be biopsied.
- A *wart* may be mistaken for skin cancer – this is OK, as warts can be treated with the anti-wart cream, *imiquimod.*
- *Seborrheic keratosis*, the classic "age spot," is sometimes mistaken for skin cancer. These are typically thick, waxy, and not irritated. They enlarge over years, not weeks or months.

Many people have big freckly spots, *lentigines,* that are benign. (Singular: *lentigo.*) Because they are dark, people – and doctors – rightly worry that a melanoma might be overlooked in a field of lentigines.

What we look for is *change* in a lentigo: new notching at the edge, new bumpiness, or "patriotic colors" – new red, white, or blue tinge. Any of these changes warrants removal.

Extirpation of Skin Cancers

In cosmetically delicate areas, the best removal technique of non-melanoma cancers is *microscopically controlled surgery*, originated in 1938 by Dr. Frederic Mohs to ensure complete removal with minimal

tissue loss, followed by "plastic" repair. (Search for "Frederic Mohs" to read the fascinating history of its evolution.) This technique has evolved to be less tedious, and has become widely practiced only in this century.

In my neck of the woods, this procedure results in costs and fees of $5,000 per lesion or more.

Removal of Suspected Melanomas

Dark lesions that might be melanomas must be removed differently. While shaving through a red bump is perfectly fine for diagnosis of a basal or squamous carcinoma, the ability of melanoma to metastasize is feared, so we never cut across one. Instead, we do an "excisional biopsy," with a safety zone to the sides and below the lesion so that, if it turns out to be a melanoma, we already have clear margins, which are important to a good prognosis.

Treatment without Surgery

Actinic keratosis is often treated by superficially freezing lesions with liquid nitrogen. There are three topical creams that are used to treat squamous or basal cell carcinoma (if superficial) and actinic keratosis. These are *fluorouracil* (fluorinated *uracil*), *imiquimod* ("i-MIK-wi-mod"), and *ingenol*. Other techniques are available, less often used.

My own practice is to remove the cancers surgically and treat actinic keratosis topically. This is pragmatic – the doctor and the patient generally want to get rid of the problem expeditiously and efficiently, and surgical costs are well covered for insured Medicare patients.

Topical treatments are not curative for the majority of malignant lesions. The smaller, the more successful is treatment. Two-year recurrence rates run about 50% for skin cancers, with wide variation related mostly to lesion size. Lesions 1 cm or larger are clearly best suited to surgery, though a week of 5-FU can reveal hidden borders and guide the knife.

It's common to freeze any lesion with liquid nitrogen. Water frozen in cells forms spicules of ice as it thaws, disrupting cell walls. This hurts. The lesion forms a blister or scab. To the extent that abnormal cells are destroyed, the lesion may not recur. I use this with obviously benign lesions, where recurrence is merely an inconvenience. The healed scar is usually pale, a concern for folks with pigmented skin.

It isn't possible to know whether the nitrogen frostbite nails pre-malignant or malignant cells. For actinic keratosis I prefer topical therapy because the drug seeks out and selectively destroys cells beyond the visible skin lesions. Fluorouracil, imiquimod, and ingenol act in quite different ways.

Fluorouracil for Skin Cancer

Here's a simple version. Uracil is one essential DNA component. If a fluorine atom is attached to uracil at the 5-carbon, it is incorporated into new DNA by reproducing cells, destroying them. Spreading fluorouracil on skin avoids its internal toxicity. Normal skin cells rest quietly for a couple of weeks, then swiftly and efficiently divide in a few hours. Malignant and pre-malignant cells re-

produce badly but continually.

Thus, resting normal cells do not take up much 5-fluorouracil (5-FU), while abnormal cells continually take up this poison and are selectively killed. We minimize the damage to normal cells by using it for just a few weeks. The standard directions are to apply 5-FU cream twice daily for 3 weeks, until the lesions are blistered or raw, then give it a rest, let the skin heal, and take a tour of the battlefield later.

Once an elderly retired farmer with very severe actinic skin damage misunderstood my instructions and applied it for six weeks. I felt terrible when he came back for review, looking like a pizza-face. But a month later, he had a beautifully clear complexion, all lesions and even most wrinkles completely gone.

The benefit of 5-FU is that it destroys cells that are not yet visible. It is used for small squamous and basal carcinomas, being applied more aggressively to such lesions.

Imiquimod for Skin Cancer

Imiquimod was developed as a treatment for genital warts, a viral tumor, some varieties of which are premalignant. It turns out to be effective for warts on hands and feet, and somewhat effective for a variety of skin cancers. (Including melanoma, but surgical excision of melanomas is crucial for proper management.)

Imiquimod acts by enhancing the immune response against abnormal cells in the area to which it is applied. You'll want to know it's an agonist of the cell-wall Toll-Like Receptor 7, enhancing immune-cell recognition of pathogen-associated molecular patterns present in cell walls. In other words, it just works.

The main advantage of imiquimod is that it's less corrosive than 5-FU. The standard regimen for actinic keratosis is twice-weekly bedtime application for 16 weeks, and for basal cell carcinoma 5x weekly for 6 weeks. It's more expensive than 5-FU; neither is cheap (cash price of each is often upward of $300, depending on the amount and vendor).

Ingenol

A British plant with milky sap, euphorbia peplus (petty spurge in the UK, radium weed in Australia), has been used in traditional medicine to remove skin tumors. The sap is applied to lesions for a short time to remove them.

This was formally studied in 2011, when it was shown that applying the sap to nonmelanoma skin cancers daily for three days completely resolved the majority of skin lesion after 15 months. This is as effective as 5-FU and imiquimod, but with very brief application.

Since 2012, a purified extract of the active principle, *ingenol*, has been available in the US. There are two strengths, a weaker one (0.015%) for the face, stronger (0.05%) for elsewhere. It's applied daily for 2 or 3 days, after which an open sore develops that usually is healed in a month.

It's expensive: the facial gel is more than $700, the "elsewhere gel" more than $1,000.

My Own Preference

I like to do a biopsy to prove whether a lesion is skin cancer (I'm not always right, and prefer to know the truth), and I am more comfortable with surgical removal, with proof that no tumor remains behind. Most of the people that I've seen are not very enthusiastic about treating malignant lesions with cream to produce an open sore for several weeks. The idea tends to inspire the "Can you refer me to a better doctor?" question.

No topical therapy is reliably curative for any skin cancer, usually failing with "invasive" lesions and having high success rates with shallow, small lesions. Few people are willing to tolerate the open sore these produce for the many weeks required for thorough treatment. So it's an option for diligent folks who can hide the lesion until it's healed.

References

The Vitamin D Solution. Michael F. Holick, PhD MD. Hudson Street Press, New York, 2010.

A lay summary of Vitamin D need and benefits by the leading expert: http://tinyurl.com/nafucno

dminder: an app for Android and iTunes devices that uses your location on earth to calculate how much vitamin D you can make and includes a timer to avoid sunburn.

http://dminder.ontometrics.com/

"Actinic Keratosis: A Review of Therapeutic Options," Joshua M. Berlin. *Dermatology Nurses' Assn. Journal*, V6, No.1, Jan/Feb 2014, pgs 11-14.

DOI: 10.1097/JDN.0000000000000015 A fine, succinct summary of treatments – To request .pdf from the author: http://tinyurl.com/qg2tkeu

For an online history of Mohs surgery: http://tinyurl.com/Mohs-surgery

For imiquimod technicalities, fellow geeks can start with http://tinyurl.com/TLR-receptors – "Toll-like Receptors and Their Crosstalk with Other Innate Receptors in Infection and Immunity," Kawai T and Akira S, *Immunity*, V34, No.5, 27 May 2011, pgs 637–650.

Acknowledgments

I've forgotten who suggested that I write on skin cancer. In thanking him I confess that it seemed boring at first: I deal with this continually, and I prefer to write these essays on things that I want to learn.

But exploring the fringes of my knowledge unearthed many delightful things in the "how-it-works" department, a tiny sample of which there's room for here.

Thanks to Dr. Michael Holick, the world's vitamin D pioneer, for use of his illustration on aging skin's vitamin D synthesis retardation.

Thanks to you for reading. It's why I write.