List of Skin Cancer Prevention Agents Grows

Evidence suggests a role for retinoids, statins, NSAIDs, and vitamins E, C, and D.

BY TIMOTHY F. KIRN
Sacramento Bureau

NAPLES, FLA. — Retinoids, NSAIDs, and perhaps statins lead the increasingly long list of possible skin cancer chemopreventive agents, James Spencer, M.D., said at the annual meeting of the Florida Society for Dermatology and Dermatologic Surgery.

In a wide-ranging discussion of the highly active field of cancer chemoprevention, Dr. Spencer made the following comments about the more notable, possible agents:

► **Retinoids.** Without a doubt, retinoids have been shown to prevent the development of skin cancer, said Dr. Spencer, the director of Mohs micrographic surgery at the Mt. Sinai Medical Center, New York. But they may never be an agent for the general, average patient.

Oral retinoids have been most thoroughly investigated in studies with solid organ transplant patients, who are extremely prone to the development of skin cancers.

In one study of Australian renal transplant patients followed for 20 years, 70% had developed skin cancers, and in a study that looked specifically at what caused death in heart transplant patients who had survived for 4 years, skin cancer was the cause of death in one-third of them.

Transplant-patient studies have been conducted with both etretinate and acitretin, with acitretin being the more commonly used drug now, at a dose of 30 mg/day. In a blinded trial in which 38 renal transplant patients received either drug or placebo for just 6 months, 11% of the acitretin-treated patients developed new squamous cell carcinomas vs. 47% of the placebo patients, and there was a 41% decline in keratotic skin lesions.

Unfortunately, transplant patients who take a retinoid have retinoid side effects, and it is not clear how low a dose they can be given to minimize those side effects, Dr. Spencer said. One trial of 10 mg/day was not effective.

Moreover, the evidence suggests that retinoids do not kill cancers, but simply halt their development during the drug's course. In one study of patients with xeroderma pigmentosum, isotretinoin significantly reduced the development of skin cancer, and it did so extremely rapidly, with a decrease in the incidence of skin cancer within 2 months of starting the drug. But the study also showed that the beneficial effect went away just as rapidly. Cancerous lesions began to reappear within 3 months of stopping the drug, too soon for it to be likely that the lesions were brand new malignancies that sprang up after the drug was stopped.

► **Vitamin D.** Vitamin D is being touted as having several health benefits, including cancer chemoprevention, and this is calling into question the wisdom of sunscreen use. The issue is being covered in the media, and the concept is being taken seriously enough by endocrinologists and oncologists that a recent paper (Cancer 2002;94:1864-75) actually tried to calculate how many excess deaths occur annually in the United States due to inadequate vitamin D. It estimated 21,000 excess deaths.

The major evidence for vitamin D chemoprevention comes from the epidemiologic observation that colon, breast, and prostate cancer incidences are lower in the lower latitudes and higher in the northern latitudes.

However, in the United States, that pattern is true in the East, but it is not so clearly apparent in the West, Dr. Spencer said.

The amount of vitamin D thought to be necessary to prevent cancer is very high, and some endocrinologists who advocate vitamin D are actually calling for amounts three times above the generally recommended minimum daily requirement. At the same time, it is known that too much vitamin D can have adverse health effects, including causing kidney stones, Dr. Spencer noted.

Because the evidence is so tentative, Dr. Spencer said he would advise patients who were worried about vitamin D not to give up sunscreen and instead take a supplement at a rational dose.

► **NSAIDs.** Ample evidence suggests that nonsteroidal anti-inflammatory drugs can prevent colon cancer, among other malignancies. A case-control study has suggested that they may protect against melanoma (Oncol. Rep. 2001;8:655-7).

Two large trials of NSAID prevention of skin cancer are underway, and they should be completed in the next year or so, Dr. Spencer said.

"This would be so simple, because you have NSAIDs in your medicine cabinet at home right now," he said.

► **Statins.** Epidemiologic evidence has suggested that statin use is associated with decreased risk of breast, advanced prostate, lung, esophageal, colon, and pancreatic cancers. Laboratory evidence suggests that statins have this effect because they interfere with two oncogenes, Ras and Rho. Those oncogenes are involved in most melanomas.

► **Vitamins E and C.** Trial results of the chemoprevention effect of vitamin E and vitamin C have not been positive. However, a recent trial of both vitamins together reported that the combination provided significant UV protection, increasing the minimal erythema dose by an average of about 50% in just a single week, Dr. Spencer said.

He noted that sunburn does not necessarily equate with skin cancer risk, but it is a surrogate often used.

► **Diet.** The evidence linking diet to cancer risk is confounding. For example, studies have suggested that a diet high in fat may be associated with an increased cancer risk, but also that saturated fat specifically may be protective.

The soy isoflavone genistein is a potent antioxidant and can block sunburn. However, it probably needs to be used in extremely high concentrations.

"It's a very promising, potential medication, however, in real life I would say buyer beware," Dr. Spencer said.

► **Melanin.** An Australian company has a patent on an injectable, depot form of melanocyte-stimulating hormone, developed at the University of Arizona, Tucson, that induces a true tan (Melanotan, Epitan Ltd.). The product could prove to be a convenient way to have sun protection, since patients would need a shot only once every few months to have a tan.

However, it could have downsides as well, Dr. Spencer noted. The product could reinforce the idea that tanned skin looks attractive, and that could encourage tanning behavior. Also, it is not known how the hormone might affect existing melanomas.

► ***Polypodium leucotomos.*** In vitro studies suggest that this extract of a South American fern may be an antioxidant and have antitumor activity.

In one nine-subject study, a single dose significantly increased the minimal erythema dose of the subjects and reduced the levels of histologic markers of malignancy-associated sun damage within a few hours.

"It is not a sunscreen, so the UV light still gets in. For our endocrinology colleagues who are worried about vitamin D, it seems to me this may allow UV-induced, vitamin D production while lowering the UV damage," Dr. Spencer said. ■

Family History and Age Increase Risk of Skin Cancers in Women

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

ST. LOUIS — Family history is a strong risk factor for melanoma in women, while age appears to be the biggest risk for the development of basal cell carcinoma, Abrar Qureshi, M.D., said at the annual meeting of the Society for Investigative Dermatology.

Dr. Qureshi of Harvard University, Boston, used data from the ongoing Nurses' Health Study to examine independent risk factors for melanoma, squamous cell carcinoma, and basal cell carcinoma. His study examined incident cases of skin cancer among 113,333 women who were followed from 1984 to 2000.

Basal cell carcinoma was the most common cancer in the group, with 7,854 cases. There were 870 cases of squamous cell carcinoma and 370 cases of melanoma.

Based on a preliminary analysis of the data, Dr. Qureshi concluded that age was the biggest risk factor for basal cell carcinoma. Looking at age-specific incidence rates, between ages 55 and 59 years, the incidence rate was about 700 cases per 100,000 person-years, but after age 65, the rate rose to above 2,000. "You can see, it's quite different above age 65," Dr. Qureshi said at the meeting.

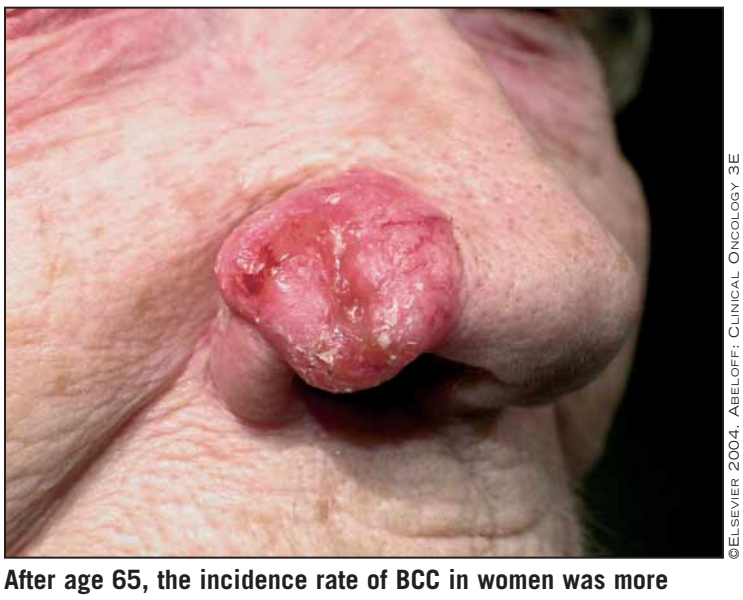
The incidence rate for melanoma was 44 cases per 100,000 person-years, and the rate of squamous cell carcinoma was 104 cases per 100,000 person-years. Age did not significantly alter the rate of melanoma; there was a slight elevation in the rate of squamous cell carcinoma after 55 years of age.

The strongest risk factor for melanoma was high mole count on one upper extremity (3.5 times increased risk). A family history of a first-degree relative with melanoma and little or no ability to tan increased the risk of melanoma in women by a factor of 2.5. A susceptibility to burn was associated with a 70% increase in the risk of melanoma.

For squamous cell carcinoma, the strongest risk factor was little or no ability to tan and susceptibility to burn (twice the risk). Family history of melanoma was associated with a 1.5 times increased risk of squamous cell carcinoma.

Although the strongest risk factor for basal cell carcinoma in women was age, they had a doubling of risk associated with susceptibility to burn, a 70% higher risk for little or no ability to tan, and a 50% higher risk for a high mole count. Women who had a first-degree relative with melanoma were found to have a 50% higher risk of basal cell carcinoma.

Further multivariate analyses are ongoing, Dr. Qureshi said. ■



After age 65, the incidence rate of BCC in women was more than 2,000 cases per 100,000 person-years.