

FAMILIAL MELANOMA STUDY

NEWS

Genetic Epidemiology Branch

Fall 2011

Table of Contents

The Genetics of Familial Melanoma: What Are We Learning?	page 1
Why Do Our Research Study Consent Forms Change So Often?	page 4
Vitamin D and Sun Exposure	page 5
Vitamin D: A Brief Overview	page 6
Updates on the Risk of Using Tanning Beds	page 8
Genetic Information and Nondiscrimination Act (GINA)	page 9
Some Updates About Sunscreens	page 9
Sun-Sensitizing Medications: A Brief Overview	page 11
Did You Know?	page 12
Contact Information	page 14
Glossary	page 15

Greetings from the Familial Melanoma Study Team

Our research team is truly grateful to you and your family for participating in this important study. We appreciate the time and energy you have spent completing the questionnaires, giving us access to your medical records, undergoing skin exams and photography, providing samples for our research, and letting us know about health and family updates. We hope that you will continue to assist us in this effort.

In this issue, we would like to update you about our recent study activities and the scientific findings that your participation makes possible. We have also included some other news items related to melanoma and sun safety. We hope that you will find the articles informative. Please let us know about topics or questions that you would like to see in future newsletters, or if you have any questions about any of the articles in

this issue. Our contact information is on page 14.

Each piece of information we receive from you brings us a little closer to understanding more of the complexities of familial melanoma. We are very interested in news about you and your family, everything from changes in address to information on births, deaths, mole biopsies, and new melanomas or other illnesses. We need your help to keep our records up to date! Please complete and send back the enclosed “Family Update Form,” or contact us by phone. We welcome your phone calls, letters, and e-mails.

Please accept our heartfelt “thank you”. Our research depends on the generous help of families like yours. Thank you very much!

The Genetics of Familial Melanoma: What Are We Learning?

A major goal of our Familial Melanoma Research Study is to learn more about why multiple individuals in some families develop melanoma. We know that melanoma results from extremely complex interactions of genetic and environmental (including lifestyle) factors. We do not yet know all of the genetic factors that contribute to risk, or how genes interact with environmental and lifestyle factors. Once we have a better understanding of the many factors and their interactions, we may be able to prevent, or at least reduce the risk of more melanomas.

Searching for Melanoma Susceptibility Genes in Families

In studies of families with three or more individuals who have melanoma, two major genes—called melanoma susceptibility genes—have been identified: *CDKN2A* and *CDK4*. Both of these genes affect when cells divide. When these genes are altered, some cells in the body can multiply and grow in an uncontrolled way. This uncontrolled growth can eventually develop into

melanoma. We are still working to understand how changes in these genes—called mutations—affect risk for melanoma.

In some families, alterations in *CDKN2A* or *CDK4* are associated with an increased risk of developing melanoma. However, alterations in these genes explain only a small portion of familial melanoma. Worldwide, between 8 to 40% of families with at least three individuals with melanoma have alterations in *CDKN2A*. Alterations in *CDK4* are quite rare. In the 16 years since the gene was identified, only about 15 families with alterations in *CDK4* have been reported worldwide.

In collaboration with members of the International Melanoma Genetics Consortium (GenoMEL), we have been searching for other major melanoma susceptibility genes. We are studying more than 450 families with multiple cases of melanoma from many areas of the world. So far, no additional major melanoma susceptibility genes have been found. We have a new opportunity, however, with newly developed technology, to more comprehensively search for alterations in genes.

Searching for Melanoma Susceptibility Genes in Populations

In addition to studies of families with multiple cases of melanoma, studies of populations can also help us learn more about genetic factors related to melanoma. First through population studies and later in family studies, a gene called *MC1R* (*melanocortin 1 receptor*) was linked to melanoma risk. *MC1R* belongs to a family of pigment genes that help determine skin, hair and eye color. Variations of the *MC1R* gene are often associated with fair skin, light eyes, and red hair, which are well-known risk factors for melanoma.

Compared to *CDKN2A* or *CDK4*, *MC1R* is associated with only modest increases in risk of melanoma. *MC1R* may be considered a “modifier gene” since it

modifies risk of melanoma in individuals with changes in *CDKN2A* or *CDK4*. In one study we found that individuals with mutations in both *CDKN2A* and *MC1R* had a higher risk of having multiple melanomas than individuals with just *CDKN2A* mutations.

• Genome-Wide Association Studies (GWAS)

During the last five years, we have been very actively involved in conducting genome-wide association studies (GWAS) [please see text box on page 3]. This research approach will help us identify common genetic variants associated with melanoma risk. These studies use fixed **genetic markers** across the **genome** to identify areas related to melanoma risk. Since the worldwide incidence of melanoma is highest in populations originally from Europe, most of the GWAS have been conducted in individuals of European ancestry. Our GWAS, as well as those by researchers who are not members of GenoMEL, have identified several areas of the genome that may affect a person’s risk of developing melanoma.

• Results of some major GWAS

Our GenoMEL collaborators and other researchers have identified six genetic

areas (**loci**) associated with melanoma risk in studies of about 6000 cases (individuals with melanoma) and over 46,000 controls (individuals without melanoma). The six areas were around the following genes: *MC1R*, *TYR*, *MTAP*, *ASIP*, *TYRP1* and *PLA2G6*. Variations in four of these genes are also associated with fair pigmentation traits, such as light eye, hair, and/or skin color. These findings suggest that genes that determine pigmentation may also contribute to the increased risk of melanoma associated with pigmentation.

An increased number of nevi (moles), particularly dysplastic nevi, is the strongest known risk factor for melanoma. Therefore, researchers also conducted a GWAS to identify genetic variants associated with an increased number of nevi. This GWAS was also performed in individuals with European ancestry. The researchers reported two areas associated with nevus (mole) counts: one near *MTAP*, a gene next to *CDKN2A*, and one near *PLA2G6*. When tested further, these variants appeared to increase melanoma risk, most likely because they were associated with high mole counts. These variants are related to number of moles (or nevi), but not to dysplastic nevi.

Some Genetic Variants Associated with Susceptibility to Melanoma Identified by Genome-Wide Association Studies

LOCUS	CHROMOSOME	ASSOCIATIONS
<i>TYP1</i>	9	Pigmentation and melanoma
<i>TYR</i>	11	Pigmentation and melanoma
<i>MC1R</i>	16	Pigmentation and melanoma
<i>ASIP</i>	20	Pigmentation and melanoma
<i>MTAP</i>	9	Number of nevi and melanoma
<i>PLA2G6</i>	22	Number of nevi and melanoma

- **What is the significance of these results?**

Genome-wide association studies in melanoma have identified genetic areas that appear to be associated with traits associated with melanoma, and with increased risk of developing melanoma. Additional work to better our understanding of how these genetic loci influence fair pigmentation traits, the occurrence of moles, and risk of melanoma could provide important clues about the causes of melanoma and possibly other cancers. The results of all

the GWAS in melanoma reported so far do not appear to have a large effect on risk. Therefore, we do not recommend that individuals or families be tested for these variants at this time. Future GWAS and other research approaches may help us further understand the role of genetic variations related to the risk of developing melanoma.

What are the next steps?

In this modern era of genetic research, GWAS is the first step toward discoveries that will one day improve clinical care.

At the moment, findings from GWAS need to be repeated and confirmed in additional groups of people. Additional studies are needed to pinpoint the genetic variants through resequencing (determining the order of the building blocks of DNA) and fine mapping. Then, in-depth research is necessary to help us understand the mechanisms of how the genetic variations increase melanoma risk. Many of these types of studies are being actively pursued.

Genome-Wide Association Studies (GWAS)

Genome-Wide Association Studies (GWAS) are contributing to our understanding of human diseases for which there is a genetic predisposition. GWAS is a powerful method to study complex common diseases in which many common genetic variations contribute to a person's risk. The disorders are considered "complex" since they are caused by interactions among multiple variant (or different) forms of genes and environmental factors.

Although the analysis and interpretation of these studies are quite complicated, the GWAS approach has already identified genetic variants related to several complex conditions such as Alzheimer's disease, diabetes, heart abnormalities, Parkinson disease, and certain types of common cancers such as prostate, breast, lung, bladder, and kidney cancers.

An in-depth understanding of the biology underlying the contribution of genetic variations may one day lead to new approaches for therapy or prevention of specific cancers and other diseases. Researchers

hope that future GWAS will identify more genetic variants associated with chronic diseases, as well as variations that affect a person's response to certain drugs and influence interactions between a person's genes and the environment.

Resources:

For more information about genome-wide association studies:

Genetics Home Reference. Help Me Understand Genetics presents basic information about genetics in clear language and provides links to online resources.

<http://ghr.nlm.nih.gov/handbook>

The NIH National Human Genome Research Institute provides a detailed explanation about genome-wide association studies.

<http://www.genome.gov/20019523>

Take home message: *The enormous challenge to further understand the causes of melanoma in families is continuing. We have made some progress, but much work remains. Although two major melanoma susceptibility genes and several other genetic variants have been identified, recommendations for clinical care remain unchanged at this time. We will provide periodic updates to keep you posted. Please know that your participation in our study has made this research possible. We could not conduct this type of research without the clinical examinations and specimens that you have so generously contributed to our research. We are persevering in our quest to gain more knowledge about the genetics of melanoma. Please let us know if you have any questions about any of these findings.*

Why Do Our Research Study Consent Forms Change So Often?

Some of you might have wondered why we ask you to sign a new copy of the consent form each time we see you in our clinic. There are several important reasons!

First, a little background.....

All research involving human subjects conducted by the NIH and all other research organizations must comply with certain legal and regulatory requirements. These requirements have been put in place to protect you, the study participant.

When we design a research study (called a protocol), it is reviewed by the NCI's Institutional Review Board (IRB). The IRB is made up of doctors, nurses, statisticians, social workers, ethicists, clergy and patient representatives. There are guidelines the NCI IRB must follow before approving the study. The IRB will only approve protocols that address medically important questions in a scientific and responsible manner. Every year, the IRB is required to monitor the progress of the study.

The study consent form.....

Simply put, the consent form states that participation in the study is voluntary, and it describes what participants can expect from participation. The form explains the study's purpose, research procedures, potential risks and benefits, protection of privacy and confidentiality, and the individual's rights as a research participant. After signing the consent, you are free to change your mind and decide not to participate further. This means that you are free to withdraw from the study at any time. You are also free to refuse to participate in any part of the study.

In the past few years, there have been several changes and additions to the Familial Melanoma Study consent forms. We change the consents to add in new information required by the IRB or when our study team plans new parts in the study. We ask you to sign these new documents to ensure you are fully informed about study participation.

What have been some of the recent changes?

- **Questions About Other Uses of Your Information**

"Optional Studies" allows you to choose how we use the specimens you donated (such as blood and cheek cells) and the data (information) you provided. The consent now contains several "Yes" or "No" questions about whether you allow or decline the use of your samples and questionnaire information for additional purposes. Although the IRB has required that we ask about using your data in studies of other diseases, our highest priority has been and will always be understanding melanoma. It is unlikely that we would use information or specimens for research on conditions not related to melanoma.

With your permission, we will store your blood and other tissue samples for future research. During the course of this study new research opportunities and technologies may emerge. We also ask whether we may contact you in the future to ask permission to use your specimen(s) in new research that was not included in the consent.

- **New Consent Form for Data Sharing**

We may contact some of you to request permission to share data from your samples with other scientists. Recent

technical advances make it possible for us to study larger and smaller pieces of genetic material in new ways. We are starting to use this technology to identify new genes related to melanoma by looking at the entire DNA sequence and structure. This is called genomic sequencing. We are also starting to use an abbreviated version of sequencing that evaluates only the regions of the genome that code for proteins (exome sequencing). The information from genomic or exomic sequencing is very complex. It may take years for us to fully understand its meaning. We hope information from this work will eventually reveal how genes contribute to the development of melanoma and associated tumors.

We have an additional new consent form to allow protected sharing of some genetic data with other scientists. Since the new technologies are quite expensive, not all investigators have access to them. NIH is developing rules for sharing data with other bona fide researchers. These rules will ensure privacy and confidentiality for you and the other participants in the study.

- **NIH Investigators' Explicit Assurances of Ethical Conduct**

All NIH consent forms must now include a new section called "Conflict of Interest". This section explains that the NIH Ethics Office reviews all NIH researchers at least every year for conflicts of interest. Avoiding financial and other conflicts of interest is important for NIH. Your trust and protection of you, the research participant, is vital to NIH's mission to improve public health.

If you have any questions about our study consent forms, please let us know.

Vitamin D and Sun Exposure

Vitamin D and sun exposure have been in the news a lot lately. Vitamin D is often called the “sunshine vitamin” because exposure to the ultraviolet (UV) component (specifically UVB) of sunshine stimulates its production in the skin.¹ Some articles have stated that many people in the U.S. and around the world have low levels of vitamin D. One controversial remedy suggested by some is deliberate exposure to the sun for a few minutes each week. Experts are hotly debating the balance of risks and benefits of unprotected sun exposure. For families at high-risk for melanoma, sun exposure is likely too risky. (For more information on vitamin D, please see “Vitamin D: A Brief Overview” on page 6.)

Ultraviolet Radiation – a Risk Factor for Skin Cancer

A major benefit of unprotected sun exposure is that UVB radiation from the sun stimulates human skin to produce active vitamin D. Vitamin D is important in maintaining bone health and has many other health benefits (please see next article). In addition to the sun, vitamin D is also available in dietary supplements (including multivitamins), milk products, and in oily fish.

For individuals in melanoma-prone families, unprotected sun exposure is particularly risky. It is well established that UVB rays are the major cause of sunburns and play a role in the development of both melanoma and non-melanoma skin cancers. Ultraviolet A (UVA) radiation penetrates skin more deeply than UVB. UVA may also play a role in the development of both melanoma and non-melanoma skin cancer. In addition, both UVA and UVB radiation cause other types of damage such as skin wrinkling and certain forms of cataracts in the eye. Both naturally-occurring UV radiation from the sun

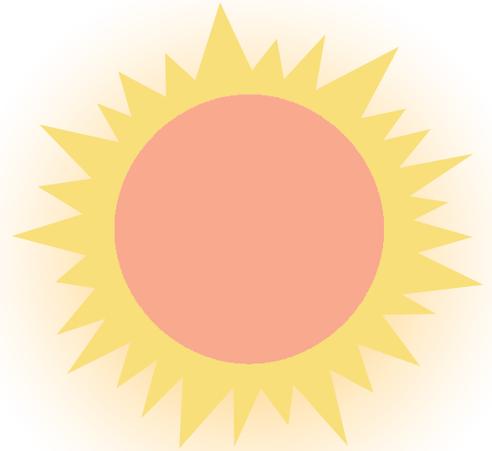
and artificial UV radiation from indoor tanning devices (e.g. tanning beds) damage skin cells. Over time, the damage accumulates and cells can grow abnormally or out of control, resulting in the development of premature aging of the skin and skin cancer.

On the basis of an increasing amount of scientific information from human, animal, and laboratory studies, the NIH National Toxicology Program (<http://ntp.niehs.nih.gov/>) and the International Agency for Research on Cancer (<http://www.iarc.fr/>) classified UV radiation from the sun and from indoor tanning devices as a carcinogen (any substance that causes cancer). (Please see article “Update on the Risk of Using Tanning Beds” on page 8.)

Currently, there is no known safe amount of unprotected sun exposure that maximizes vitamin D production without increasing the risk of skin cancer. In addition, there is no sound scientific data to support the use of artificial tanning devices to increase vitamin D levels.

Practice Sun Protection and Get Vitamin D Safely

Many skin cancer experts from clinical, laboratory, and epidemiology research and health policy settings have considered issues concerning vitamin D and sun exposure. During the last three years, both the American Academy of Dermatology (AAD) and the National Council on Skin Cancer Prevention (NCSCP) have updated their Position Statements to urge individuals to obtain vitamin D from nutritional sources and dietary supplements, and not from unprotected exposure to UV radiation from the sun or indoor tanning devices.

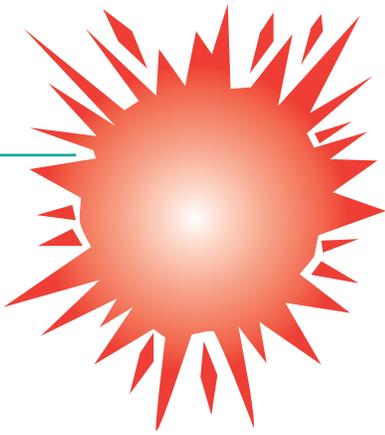


This approach is beneficial to maintaining a healthy vitamin D level, but it avoids the risks associated with UV exposure. The NCSCP’s statement reflects the recommendations of its members which include the AAD and more than 40 other organizations and government agencies such as the American Cancer Society, the Skin Cancer Foundation, the NIH, the Centers for Disease Control and Prevention, and the Environmental Protection Agency.

The position statements acknowledge that individuals who regularly and properly practice sun protection, such as through daily use of sunscreen on exposed skin or by wearing sun protective clothing, may be at risk for vitamin D insufficiency. Fortunately, people who practice sun protection can obtain a sufficient amount of vitamin D from a combination of diet and vitamin supplements. A higher dose of vitamin D may be necessary for these individuals and others with known risk factors for vitamin D insufficiency.

¹ UV light is made up of UV-A (longer wavelengths), and UV-B (shorter wavelengths).

Vitamin D: A Brief Overview*



Adults who practice sun protection should ingest extra vitamin D-fortified foods and/or supplements



Vitamin D is a nutrient that is essential for optimal health. Its major function in the body is to regulate normal blood levels of calcium and phosphorus to form and maintain healthy bones and teeth. People who get too little vitamin D may develop soft, thin, and brittle bones. This condition is known as rickets in children and osteomalacia in adults. As they get older, millions of people (mostly women, but men too) develop, or are at risk of, osteoporosis, or decrease in density of the bones. Osteoporosis makes bones fragile and prone to fracture if one falls.

Although it has been known for many years that vitamin D plays a crucial role in forming and maintaining strong healthy bones and teeth, recent research indicates other important roles in maintaining health in the body. For example, muscles need vitamin D to work properly. Nerves use vitamin D to carry messages between the brain and every part of the body. The immune system needs vitamin D to fight

off invading bacteria and viruses. Vitamin D is found in cells throughout the body.

In late 2010, The National Academies' Institute of Medicine (IOM) (a national group of experts) released a major report about vitamin D. The report was based on testimony from scientists and the IOM's thorough review of the increasing body of scientific literature on vitamin D and its importance for health. The IOM report concluded that the evidence for vitamin D's role in bone health was strong. However, the evidence for other conditions was inconsistent, inconclusive and insufficient to inform nutritional requirements. For example, the group concluded that at this time, it's too early to say whether low or high vitamin D levels increase or decrease cancer risk. Several research studies are underway to attempt to more fully understand the many and complex mechanisms of action of vitamin D in children and adults.

How Much Vitamin D do I Need?

The amount of vitamin D you need each day depends on your age. Based on the IOM report, the recommended dose of vitamin D was increased for several age groups. The IOM's Food and Nutrition Board average daily recommended amounts are listed here.

According to the NIH Office of Dietary Supplements, "People who avoid the sun, who cover their bodies with sunscreen or clothing, or who live in the northern half of the U.S. during the winter months should include good sources of vitamin D in their diets or take a supplement."

Recommended Dietary Allowance International Units (IU)/Day	
Birth to 12 Months	400 IU
Children 1 to 13 Years	600 IU
Teens 14 to 18 Years	600 IU
Adults 19 to 70 Years	600 IU
Adults 71 Years and Older	800 IU
Pregnant and Breastfeeding Women	600 IU

Position Statements on Vitamin D

American Academy of Dermatology

<http://www.aad.org/>

search: "Vitamin D Position Statement"

National Council on Skin Cancer Prevention

<http://www.skincancerprevention.org/>

<http://www.skincancerprevention.org/skin-cancer/vitamin-d>

What are the Sources of Vitamin D?

There are three main sources of vitamin D: foods; vitamin D supplements; and vitamin D produced following sun exposure.

Foods: Very few foods naturally have vitamin D. Fortified foods provide most of the vitamin D in American diets.

Vitamin D supplements: Vitamin D is found in supplements in two different forms: D2 (ergocalciferol) and D3 (cholecalciferol). Both increase vitamin D in the blood.

Vitamin D produced by the body following sun exposure: Vitamin D is produced by our bodies when UVB rays from the sun penetrate unprotected skin. Despite the importance of the sun to vitamin D synthesis, it is prudent to limit exposure to sunlight and avoid using tanning beds and other artificial sources of UV radiation. (Please see Vitamin D and Sun Exposure article, page 5).

FOODS WITH NATURALLY OCCURRING VITAMIN D	FOODS FORTIFIED WITH VITAMIN D
<ul style="list-style-type: none"> • Fatty fish such as salmon, tuna, and mackerel are among the best sources. • Beef liver, cheese, and egg yolks provide small amounts. • Mushrooms provide some vitamin D. 	<ul style="list-style-type: none"> • Almost all of the U.S. milk supply is fortified with 400 IU of vitamin D per quart.[#] • Vitamin D is added to many breakfast cereals and to some brands of orange juice, yogurt, margarine, and soy beverages. Check the labels. • In some mushrooms that are newly available in stores, the vitamin D content is being boosted by exposing these mushrooms to ultraviolet light.

[#] Foods made from milk, like cheese and ice cream, are usually not fortified with vitamin D.

Can Vitamin D be Harmful?

Yes, when amounts in the blood become too high, vitamin D can be harmful. Signs of toxicity include nausea, vomiting, poor appetite, constipation, weakness, and weight loss. Because a major function of Vitamin D is to maintain normal blood levels of calcium, too much vitamin D can raise the calcium levels in

the blood. When the calcium levels are too high, confusion, disorientation, and problems with heart rhythm can occur. Excess vitamin D can also damage the kidneys.

The safe upper limit for vitamin D is 1,000 to 1,500 IU/day for infants, 2,500

to 3,000 IU/day for children 1-8 years, and 4,000 IU/day for children 9 years and older and for adults. Vitamin D toxicity almost always occurs from overuse of supplements.

Ask Your Doctor

Talk with your healthcare provider about the amount that is recommended for you. A blood test is available to determine the level of vitamin D. However, it's not yet clear what levels of vitamin D in the blood are best for good health. If you have concerns about your level of vitamin D, we recommend that you discuss them with your doctor.

* Modified and excerpted from NIH Office of Dietary Supplements
<http://ods.od.nih.gov/>

Where Can I Find Out More About Vitamin D?

- NIH Office of Dietary Supplements

Vitamin D QuickFacts

<http://ods.od.nih.gov/factsheets/VitaminD-QuickFacts/>

- NIH National Library of Medicine
<http://www.nlm.nih.gov/medlineplus/>

Update on the Risk of Using Tanning Beds

The scientific evidence concerning the serious risks of using artificial tanning devices continues to mount. This article focuses on some important new information.

Tanning Beds Classified as a Carcinogen

In the Spring 2008 Familial Melanoma Study newsletter, we reported that the International Agency for Research on Cancer (IARC) expert panel of scientists had stated tanning bed use before the age of 35 increased the risk of both melanoma and squamous cell skin cancer. Because of this elevated risk, the IARC panel recommended that minors' and young adults' access to artificial tanning facilities should be restricted.

In June 2009, IARC reconvened its group of experts to review the latest research on UV radiation. The panel revised their classification for naturally occurring (from the sun) and artificially produced (from tanning devices) UV radiation from 'probable' to 'known' human carcinogen. Furthermore, the experts noted that risk of melanoma is increased by 75% when use of tanning devices starts before age 30. In addition, an increased risk of melanoma of the eye is associated with the use of tanning devices such as tanning beds and sunlamps.

http://www.iarc.fr/en/media-centre/iarcnews/2009/sunbeds_uvradiation.php

Skin Health Study Results Strongly Link Tanning Bed Use to Increased Risk of Melanoma

A recent study confirmed that using indoor tanning devices increases the

chances of developing melanoma. The Skin Health Study was conducted in Minnesota and included more than 2,200 adults 25 to 59 years old. Approximately half of the participants (more than 1,100) had melanoma, which was diagnosed between July 2004 and December 2007. The other group of the participants (more than 1,100 people) did not have melanoma.

Since this study was designed to help answer more definitively whether tanning bed use is linked to skin cancer, detailed information on the participants' tanning habits was collected. For example, the researchers collected data on tanning bed use, including number of years used, age at which use began, and the specific types of tanning devices used. Participants also provided information about their use of sunscreens and whether or not they had a family history of melanoma.

The results of the study provide strong evidence that indoor tanning is a risk factor for melanoma. The major findings showed that:

- People who had ever used an indoor tanning device were about 75% more likely to have developed melanoma than people who had never used them.
- The risk of melanoma was highest among those who used indoor tanning devices most frequently.
- Frequent users were approximately 3 times more likely to develop melanoma than those who had never used them. Their chance of developing melanoma increased by as much as 200% when indoor tanning usage exceeded 50 hours, 100 sessions, or 10 years.



- The risk of melanoma was elevated regardless of the type of tanning device that was used.

The results are also significant because they are the first to show a clear dose-response relationship. This means that the more an individual used a tanning bed, the higher was his or her chance (risk) of developing melanoma.

Conclusions: This study is the most solid research to date showing tanning bed use is associated with melanoma. We can conclude from this research that a person's risk of developing melanoma is associated more with how often he or she uses tanning devices, rather than the age at which he or she began tanning. The risk rises with frequency of use, regardless of age, being female or male, or which type of tanning device is used.

Take home message: *On the basis of these findings, it is important that everyone, but especially all individuals of any age who are at increased risk of developing melanoma or other skin cancers, avoid using tanning beds or sunlamps*

Federal Tan Tax

On July 1, 2010, a 10% federal tax on the cost of using indoor tanning bed facilities took effect. This tax was passed as part of the Patient Protection and Affordable Healthcare Act, the health-care overhaul in March, 2010. Frequently referred to as the "tanning tax", the tax applies to electronic products designed for tanning that use one or more ultraviolet lamps with wavelengths between 200 and 400 nanometers. Other sunless tanning options such as spray tans and tanning lotions are not taxed.

GINA – Genetic Information Nondiscrimination Act of 2008: A Brief Overview

The Genetic Information Nondiscrimination Act is a Federal law that prevents discrimination by health insurers and employers based on genetic information. “Genetic information” includes family medical history and information regarding individuals’ and family members’ genetic tests and genetic services, including genetic counseling and participation in clinical trials.

GINA, along with other Federal laws, prohibits health insurers from requesting or requiring genetic information from an individual or their family members, or using such information to make decisions about coverage, rates or preexisting conditions. Employers are not allowed to use genetic information for hiring, firing, or any decisions about the terms of employment, including health or disability benefits.

The specific sections of GINA that apply to health insurance coverage took effect for individual insurance plans in May 2009, and for all group health insurance plans in May 2010. The employment discrimination sections took effect in November 2009. These sections regulate the use of genetic information regardless of when genetic information was obtained or collected. The provisions of the law restrict how health insurers or employers may use the information once the sections of the law became active.

Why GINA?

Each person’s DNA contains thousands of differences from the standard, so-called

‘reference’ sequences. These differences may increase or decrease a person’s chance of disease (for example, heart disease, diabetes, or cancer). Increased risk from DNA differences does not mean a person will develop a disease, and GINA prohibits this genetic information from being used against an individual in a health insurance or employment context. As genetic testing becomes more common, information about a person’s DNA may be used by his or her doctor to help prevent or detect certain diseases, or to develop individualized treatment plans. Today, there are many research studies including, of course, our familial melanoma study that may involve genetic testing. Privacy protection ensures scientific progress without the fear of discrimination based on genetic information.

We want you to understand that the type of genetic testing we do as part of our familial melanoma study is for research. We are searching for melanoma susceptibility genes, and evaluating the functions of the genes and their interactions with other genes and also other factors. We do not believe that the results of this testing will affect our recommendations for you or your family’s health care. Research genetic testing is different than clinical genetic testing. Clinical genetic testing is performed by your doctor to improve clinical care. Therefore, specimens collected for clinical genetic testing must follow strict procedures to ensure the identity of the sample and allow for counseling prior to and after collection of the specimen. The

test must be performed at a laboratory regulated by the Clinical Laboratory Improvement Amendments (CLIA: <http://www.cms.gov/clia/>).

What GINA doesn’t do

- GINA’s provisions do not protect you from genetic discrimination related to life insurance, disability insurance, or long-term care insurance.
- Generally, GINA does not apply to employers with fewer than 15 employees. People who are, or will be employed by small businesses receive none of the GINA protections that prohibit discrimination in employment on the basis of genetic information.

This brief summary provides only some background on GINA and how it might impact your family. Your state may have additional laws to protect genetic information. GINA provides a baseline level of protection and works in conjunction with state laws to protect people.

For more information online:

- NIH National Human Genome Research Institute
<http://www.genome.gov/10002328>
- Information compiled by the Genetic Alliance, the Genetics and Public Policy Center at the Johns Hopkins University, and the National Coalition for Health Professional Education in Genetics
<http://www.ginahelp.org/>

Some Updates About Sunscreens

The articles in this section focus on some news and other important information about sunscreens.

FDA Issues New Sunscreen Labeling Rules

On June 14, 2011, the FDA announced

new standards for testing the effectiveness of sunscreen products, including how well sunscreens decrease the amount of both UVA and UVB. Labels are required to accurately reflect these test results. Look for sunscreens that are “Broad Spectrum” and a minimum of “SPF 15”. We suggest SPF 30. These sunscreen products

provide protection against both UVA and UVB radiation, which can cause sunburn, skin cancer, and premature skin aging.

The new regulations will take effect by the summer of 2012. The changes are designed to help consumers decide how to buy and use sunscreens, and

allow them to more effectively protect themselves and their families from the sun’s harmful rays. Check the FDA website for the more information about sunscreens and sun safety tips: (<http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingOver-the-CounterMedicines/ucm239463.htm>).

Regular Sunscreen Use May Reduce the Risk of Developing Melanoma

Results of a study published earlier this year provide important new evidence regarding the protective role of sunscreens. The researchers reported that adults who use sunscreen regularly reduce their risk of developing melanoma by at least 50%. The study was conducted in Australia and involved more than 1,600 adults aged 25 to 75 years old.

Researchers randomly assigned the study participants to either one of two groups for use of sunscreen for five years. The first group was assigned to daily application of broad-spectrum sunscreen with a sun protection factor of 15 or more to the head, neck, arms, and hands. The second group was assigned to use of sunscreen according to a person’s usual level of sunscreen use, which for some included no use at all. The participants were then followed for 10 years.

The major findings showed that:

- Individuals in the daily sunscreen use group developed significantly fewer new “invasive” (those that penetrate the top layer of skin) melanomas than did the participants in the usual sunscreen use group.
- Extending the follow-up to 15 years revealed an additional protective effect for the daily use group: 73% fewer individuals developed invasive melanomas compared to those in the usual sunscreen use group.

Conclusions: This study is important because it is thought to be the first randomized trial to examine the use of sunscreen in preventing melanoma. The results of this study are consistent with the knowledge that excessive sun exposure causes melanoma.

Sunburn Protection Factor (SPF) – What Does It Really Mean? **

Sunburn protection factor (SPF) is a measure of how much of the sun’s energy (UV radiation) is required to produce sunburn on protected skin (i.e., in the presence of sunscreen) relative to the amount of UV radiation required to produce sunburn on unprotected skin. As the SPF value increases, sun protection increases.

There is a popular misconception about SPF and amount of time of sun exposure. For example, many consumers believe that, if they normally get sunburn in one hour, then an SPF 15 sunscreen allows them to stay in the sun 15 hours (i.e., 15 times longer) without getting sunburn. This is false. SPF is not directly related to time of sun exposure but to amount of sun exposure. Although the amount of UV radiation is related to time spent

in the sun, there are other factors that impact the amount of UV radiation. For example, the intensity of the sun’s energy contributes to the amount you receive through your skin. The following exposures may result in the same amount of UV radiation:

- one hour at 9:00 a.m.
- 15 minutes at 1:00 p.m.

Generally, it takes less time to be exposed to the same amount of UV radiation at midday compared to early morning or late evening. The sun is more intense at midday, relative to the other times. The sun’s intensity is also related to geographic location. Greater amounts of UV radiation occur in the southern states of the U.S., as compared to the north or northeast. Because clouds absorb some UV radiation, the sun’s intensity is generally greater on clear days than cloudy days, but substantial UV passes through the clouds.

In addition to the sun’s intensity, other factors influence the amount of UV radiation to which a person is exposed. For example:

Skin type	<ul style="list-style-type: none"> • Fair-skinned persons are likely to absorb more UV radiation than dark-skinned persons under the same conditions.
Amount of sunscreen applied	<ul style="list-style-type: none"> • More sunscreen results in less UV radiation being absorbed.
Frequency of reapplication	<ul style="list-style-type: none"> • Because sunscreens wear off and become less effective with time, the frequency with which they are reapplied is critical to limiting absorption of UV radiation. • The reapplication frequency is also impacted by the activities that consumers are involved in. For example, consumers who swim while wearing sunscreen need to reapply the sunscreen more frequently because water may wash the sunscreen from the body. In addition, high levels of physical activity require more frequent reapplication because the activity may physically rub off the sunscreen and heavy sweating may wash off the sunscreen. • In general, more frequent reapplication is associated with decreased absorption of UV radiation.

** [Modified and excerpted from <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm106351.htm>]

Summary: Because of the various factors that impact the amount of UV radiation, SPF does not reflect time in the sun. In other words, SPF does not inform consumers about the time that can be spent in the sun without getting sunburn. Rather, SPF is a relative measure of the amount of sunburn protection provided by sunscreens. The SPF allows consumers to compare the level of sunburn protection provided by different sunscreens.

Everyone should remember to protect themselves from overexposure to the sun by following the three main ways of sun protection:

- Avoid midday sun exposure (10am – 4pm) whenever possible
- Wear protective clothing, hats and sunglasses
- Use sunscreens



Sun-Sensitizing Medications: A Brief Overview

Many medications (drugs), even common ones, can cause a person's skin to become more sensitive to the sun (photosensitivity). Photosensitivity occurs when the interaction of a medication and ultraviolet (UV) light causes inflammation of the skin. Photosensitivity reactions can usually be divided into two types—phototoxic and photoallergic reactions. Some medications can cause both types of reactions. These reactions are usually caused by UV light from sunlight and/or artificial UV sources such as tanning beds. Both types of UV light, UV-A (longer wavelengths), and UV-B (shorter wavelengths), can trigger the reactions.

Phototoxic reactions

Phototoxic reactions are much more common than photoallergic reactions. Exposure to UV light, usually UV-A, causes sunburn-like damage in the skin of individuals taking certain medications. UV-B light and, rarely, visible (non-ultraviolet) light can also cause this type of reaction. Skin redness, swelling, and even blistering can occur in areas exposed to UV light only. After the drug is discontinued and no longer circulating in the body, the skin condition usually resolves.

Photoallergic reactions

Photoallergic reactions are less common. UV light can cause a chemical change

in the structure of certain medications circulating in the body. As a result, the body may mount an allergic response to the new substance. This response can lead to inflammation usually affecting the areas of the skin that were exposed to the sun. Many of the drugs that can cause photoallergic reactions are applied topically to the skin, such as creams, gels, or ointments. Symptoms may not appear for several days after taking a medication for the first time. However, when a medication has been taken before, the reaction can occur within 1-2 days. Symptoms usually consist of itching and redness of the skin, with an eczema-like rash (dry, scaly) that can spread beyond exposed areas if severe. These rashes can last longer than those caused by phototoxic reactions. Once they go away, the rashes may recur when a person is exposed again to UV light, even after the drug has been cleared by normal metabolism in the body.

Examples of some of the more common types of medications that are associated with sun sensitivity are:

- Acne medications
- Antibiotics
- Antihistamines
- Cancer chemotherapy drugs

- Cardiac drugs
- Oral diabetic drugs
- Diuretics
- Hormones (oral contraceptives, menopause replacement hormones)
- Malaria medications
- Pain medications (e.g. non-steroidal anti-inflammatory drugs)
- Photodynamic therapy (combination of a photosensitizing drug with a specific type of light to kill cancer cells)
- Psychiatric medications

If you have any questions or concerns about any medications you are taking, we suggest that you discuss them with your doctor and/or pharmacist.

Information about specific medications that may cause phototoxic and/or photoallergic reactions can be found at (http://www.medicinenet.com/sun-sensitive_drugs_photosensitivity_to_drugs/article.htm).

Did you know?

Experimental Treatments Improve Survival in Advanced Melanoma

Much research has been underway to find better treatments for patients with melanoma. Some encouraging news about new experimental treatments that improve survival of advanced melanoma was reported last year. Indeed, these therapies are considered the most promising new treatments for advanced melanoma that have become available during the last 30 years. The advances were possible because of a better understanding of the biology of the disease and the genetics of melanoma tumors.

The results were from clinical trials treating a small number of patients whose advanced melanoma had progressed on other treatments. The trials used a newer treatment approach called “targeted therapy”. Targeted therapies are aimed at interrupting important pathways (often signaling pathways) in cancer cells. The most successful targeted therapies are those aimed at proteins that are changed in cancer cells, but not in normal cells. These therapies use medications/drugs or other substances to target faulty genes or proteins that contribute to cancer growth and development. Targeted therapies are already available for some types of cancers, such as Gleevec® for chronic myelogenous leukemia.

One of the experimental treatments for melanoma used the drug ipilimumab (ih-pih-LIH-myoo-mab). Ipilimumab targets the body’s immune system. The drug stimulates the immune system to attack and kill melanoma cells in a new way. In late March 2011, the FDA approved Yervoy® (the brand name for ipilimumab), making it the first commercially available medicine proven to extend survival in metastatic melanoma.

The other experimental treatment that showed promise was the drug PLX4032. The drug targets a common genetic

change that occurs in many melanoma tumors. The drug blocks or inhibits growth-promoting signals in melanoma tumors that have a specific genetic change in the gene called “*BRAF*”.

With the exception of Yervoy®, targeted therapies are still experimental, which means that they are only available for patients enrolled on clinical trials. Although the therapies are not curative, the results are quite promising and represent an important step forward in treating metastatic melanoma. Important next research steps are identifying the individuals most likely to benefit from these (and other new drugs under development) and combining these new drugs with other drugs to maximize their benefits. The best treatment for melanoma remains preventing melanoma from developing or detecting melanomas at a very early stage when minimal surgery is curative.

You Might Want to Create Your Own Personal Medical Record

Many physicians and healthcare organizations routinely destroy medical records, including medication history, pathology reports, x-ray results, physician notes and other important health-related documents. This information might be helpful in the future as your life changes or health issues occur. The websites below have information on what is recommended for a personal medical record and for suggestions on how to collect that information. Start your personal medical record today!

Medline Plus, NIH National Library of Medicine
<http://www.nlm.nih.gov/medlineplus/personalmedicalrecords.html>

NIH Privacy Rule and Use of Personal Health Information for Research
<http://privacyruleandresearch.nih.gov/patients.asp>

American Health Information Management Association
http://www.mypbr.com/StartaPHR/quick_guide.aspx

The federal Health Insurance Portability and Accountability Act (HIPAA) provides a national standard for the privacy of health information but does not specify a set time for medical records to be kept. Many states have laws or regulations specifying a set period of time that medical records must be kept. To find out the laws or regulations for your state, the following website may be helpful.
http://library.ahima.org/xpedio/groups/public/documents/ahima/bok1_012547.pdf

Talking Glossary of Genetic Terms

The NIH National Human Genome Institute has extensive educational resources on its web site (<http://www.genome.gov/>). One site that may be of interest to you or someone in your family is the talking glossary of genetic terms (<http://www.genome.gov/glossary/>). It is designed to help learners at any level better understand genetic terms. The site is guided by national science standards, and the terms are explained by NIH scientists.

FDA Website on Safety Information for New Drugs and Biologics

The Food and Drug Administration (FDA) launched a website where patients and healthcare professionals can find safety information about recently-approved drugs and biologics. On its Postmarketing Drug Safety evaluations site (<http://www.fda.gov/Drugs/danceComplianceRegulatoryInformation/Surveillance/ucm204091.htm>), the FDA plans to include what it has learned about the safety of a new drug or biologic, such as a vaccine, 18 months after approval, or after 10,000 patients have used it, whichever comes later.

Internet Resources for Skin Cancer and Prevention Information*

U.S. WEBSITES

American Cancer Society (ACS)	www.cancer.org search “sun safety”
Cancer.net (formerly People Living With Cancer)	www.cancer.net search “melanoma”
Centers for Disease Control and Prevention	www.cdc.gov search “skin cancer”
Environmental Protection Agency (EPA) Sunwise Program	www.epa.gov/sunwise
Food and Drug Administration	www.fda.gov search “sun safety”
National Cancer Institute	www.cancer.gov search “melanoma”
National Comprehensive Cancer Network Melanoma Guidelines for Patients	www.nccn.com/images/patient-guidelines/pdf/melanoma.pdf
Skin Cancer Foundation (SCF)	www.skincancer.org

INTERNATIONAL WEBSITES

Australian SunSmart	www.sunsmart.com.au
David Cornfield Melanoma Fund Canada’s Channel “Dear 16-year-old Me” melanoma awareness video	www.youtube.com/watch?v=_4jgUcxMezM&feature=share
Melanoma Genetics Consortium (GenoMEL)	www.genomel.org choose “patient information” tab
Cancer Research UK SunSmart	http://cancerresearchuk.org/sunsmart
Irish Cancer Society	www.cancer.ie search “sunsmart”
World Health Organization	www.who.int/en search “INTERSUN”

*We are providing links to other Internet sites for informational purposes and for your convenience. Please note the following:

- When you select a link to an external Web site, you are leaving the NCI Web site and you are subject to the privacy and security policies of the owners/sponsors of the external site;
- NCI does not endorse organizations that sponsor linked external Web sites. In addition, NCI does not endorse products or services that such organizations may offer. Furthermore, NCI does not control or guarantee the currency, accuracy, relevance, or completeness of information found on linked, external Web sites.
- NCI is not responsible for transmissions users may receive from linked, external Web sites.
- NCI does not guarantee that linked, external Web sites comply with Section 508 (Accessibility Requirements) of the Rehabilitation Act.

Melanoma is largely preventable. With early detection and prompt treatment, it is almost always curable.

Familial Melanoma Study Enrollment

Do you know someone who may be interested in enrolling in our familial melanoma study? Families with at least three relatives with melanoma are eligible. Family members—or their doctors or other health care providers can call **Stephanie Steinbart**, our referral team nurse at 1-800-518-8474, or email her at stephaniesteinbart@westat.com. More detailed information about this study is listed on the following NIH Websites:

NIH Clinical Center Clinical Studies
 (http://clinicalstudies.info.nih.gov/cgi/wais/bold032001.pl?A_02-C-0211.html@melanoma)

NCI Clinical Trials
 (<http://www.cancer.gov/clinicaltrials/search/view?cdrid=256916&protocolsearchid=9673940&version=patient>)

NCI Genetic Epidemiology Branch
 (<http://dceg.cancer.gov/geb>)

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 Bethesda, MD 20892-7236
 1-800-518-8474 (toll free)
 1-301-496-4375

New!

Familial Melanoma Study newsletter by email...

If you would like to receive this newsletter by email, please check the "Yes for email" box on the Update Form. Be sure to provide your email address.
 Thank you!

Glossary – Words to Know*

We have provided a list of definitions of some of the genetic and medical terms that will make this newsletter easier to understand.

Chromosome – an organized package of DNA found in the nucleus of the cell. Humans have 23 pairs of chromosomes—22 pairs of numbered chromosomes, and one pair of sex chromosomes, X and Y. Each parent contributes one chromosome to each pair so that offspring get half of their chromosomes from their mother and half from their father.

DNA – the chemical name for molecules inside cells that carry genetic instructions and pass it from one generation to the next.

Dysplastic nevi – are atypical nevi (moles) that are more likely than ordinary moles to develop into melanoma. However, most dysplastic nevi do not develop into melanoma. Dysplastic nevi are usually bigger than 5 millimeters (a pencil eraser) and have a flat or partially flat surface. They often have an irregular shape and an indistinct edge that fades into the surrounding skin, and often contain a mixture of colors from pink to dark brown. Dysplastic nevi occur in many melanoma-prone families.

Genetic marker – an identifiable segment of DNA (e.g. single nucleotide polymorphisms or SNPs) with enough variation between individuals that its inheritance and co-inheritance with different forms of a given gene can be traced. Genetic markers are used in linkage analysis or in genome-wide association studies.

Genetics – the study of inheritance, or the way traits are passed down from one generation to another. Genes carry the instructions for making proteins, which in turn direct the activities of cells and functions of the body that influence traits such as hair and eye color.

Genome – the entire set of genetic instructions in a cell.

Genome-wide association study – (GWAS) studies are a way for scientists to identify genes involved in human disease. This method searches the genome for small variations, called single nucleotide polymorphisms or SNPs (pronounced “snips”), that occur more frequently in people with a particular disease than in people without the disease.

Genomics – a newer term that describes the study of all the genes in a person, as well as interactions of those genes with each other and with that person’s environment.

Linkage analysis – a gene-hunting technique that traces patterns of disease in large, high-risk families, in an attempt to locate a disease-causing gene alteration.

Locus – a locus is the specific physical location of a gene or other DNA sequence on a chromosome, like a genetic street address. The plural of locus is “loci”.

Mapping – the process of making a representative diagram cataloging the genes and other features of a chromosome and showing their relative locations.

Osteomalacia – the softening and thinning of the bones due to a lack of vitamin D or a problem with the body’s ability to break down and use this vitamin. Osteomalacia causes bone pain and muscle weakness.

Osteoporosis – the most common type of bone disease. Osteoporosis occurs when the body fails to form enough new bone, when too much old bone is reabsorbed by the body, or both.

* (Sources: Modified from NIH and CDC)



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