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- **New Model Of Cancer Development: Low Vitamin D Levels May Have Role**

ScienceDaily (May 26, 2009) — In studying the preventive effects of vitamin D, researchers at the Moores Cancer Center at the University of California, San Diego, have proposed a new model of cancer development that hinges on a loss of cancer cells' ability to stick together. The model, dubbed DINOMIT, differs substantially from the current model of cancer development, which suggests genetic mutations as the earliest driving forces behind cancer.

"The first event in cancer is loss of communication among cells due to, among other things, low vitamin D and calcium levels," said epidemiologist Cedric Garland, DrPH, professor of family and preventive medicine at the UC San Diego School of Medicine, who led the work. "In this new model, we propose that this loss may play a key role in cancer by disrupting the communication between cells that is essential to healthy cell turnover, allowing more aggressive cancer cells to take over."

Reporting online May 22, 2009 in the *Annals of Epidemiology,* Garland suggests that such cellular disruption could account for the earliest stages of many cancers. He said that previous theories linking vitamin D to certain cancers have been tested and confirmed in more than 200 epidemiological studies, and understanding of its physiological basis stems from more than 2,500 laboratory studies.

"Competition and natural selection among disjoined cells within a tissue compartment, such as might occur in the breast's terminal ductal lobular unit, for example, are the engine of cancer," Garland said. "The DINOMIT model provides new avenues for preventing and improving the success of cancer treatment."

Garland went on to explain that each letter in DINOMIT stands for a different phase of cancer development. "D" stands for disjunction, or loss of intercellular communication; "I," for initiation, where genetic mutations begin to play a role; "N" for natural selection of the fastest-reproducing cancer cells; "O" for overgrowth of cells; "M" for metastasis, when cancer cells migrate to other tissues, where cancer can kill; "I" refers to involution, and "T" for transition, both dormant states that may occur in cancer and potentially be driven by replacing vitamin D.

While there is not yet definitive scientific proof, Garland suggests that much of the evolutionary process in cancer could be arrested at the outset by maintaining vitamin D adequacy. "Vitamin D may halt the first stage of the cancer process by re-establishing intercellular junctions in malignancies having an intact vitamin D receptor," he said.

According to Garland, other scientists have found that the cells adhere to one another in tissue with adequate vitamin D, acting as mature epithelial cells. Without enough vitamin D, they may

lose this stickiness along with their identity as differentiated cells, and revert to a stem cell-like state.

Garland said that diet and supplements can restore appropriate vitamin D levels, and perhaps help in preventing cancer development. "Vitamin D levels can be increased by modest supplementation with vitamin D3 in the range of 2000 IU/day," he noted.

The researchers noted that many studies show an apparent beneficial effect of vitamin D and calcium on cancer risk and survival of patients with breast, colorectal and prostate cancer. However, there are some studies that have not found such benefit, especially when taking smoking, alcohol and viruses into account. While more research needs to be done, Garland recommends that individuals should have their vitamin D level tested during an annual checkup.

Garland and his colleagues have published epidemiological studies about the potential preventive effects of vitamin D for some two decades. Last year, his team showed an association between deficiency in sunlight exposure, low vitamin D and breast cancer. In previous work, they showed associations between increased levels of vitamin D3 or markers of vitamin D and a lower risk for breast, colon, ovarian and kidney cancers.

Other authors on the study include Edward D. Gorham, Sharif B. Mohr and Frank C. Garland, UC San Diego.

- **Science News**

Vitamin D Found To Stimulate A Protein That Inhibits The Growth Of Breast Cancer Cells

ScienceDaily (Feb. 5, 2009) — Calcitrol, the active form of vitamin D, has been found to induce a tumor suppressing protein that can inhibit the growth of breast cancer cells, according to a study by researcher Sylvia Chistakos, Ph.D., of the UMDNJ-New Jersey Medical School.

Chistakos, a professor of biochemistry, has published extensively on the multiple roles of vitamin D, including inhibition of the growth of malignant cells found in breast cancer. Her current findings on the vitamin D induced protein that inhibits breast cancer growth are published in a recent issue of *The Journal of Biological Chemistry*.

Previous research had determined that increased serum levels of vitamin D are associated with an improved diagnosis in patients with breast cancer. Prior to the current study, little was known about the factors that determine the effect of calcitrol on inhibiting breast cancer growth, she said.

During the study, Christakos and co-author Puneet Dhawan, Ph.D., examined the protein involved in the action that can reduce the growth of vitamin D in breast cancer cells. “These results provide an important process in which the active form of vitamin D may work to reduce growth of breast cancer cells,” said Christakos. “These studies provide a basis for the design of new anticancer agents that can target the protein as a candidate for breast cancer treatment.”

- **Science News**

Human Lung Tumors Destroy Anti-cancer Hormone Vitamin D

ScienceDaily (Apr. 24, 2009) — Human lung tumors have the ability to eliminate Vitamin D, a hormone with anti-cancer activity, a new study from the University of Pittsburgh Cancer Institute (UPCI) suggests.

"High levels of Vitamin D help the body produce proteins with anti-tumor activity," explained principal investigator Pamela Hershberger, Ph.D., a research assistant professor in UPCI's Department of Pharmacology and Chemical Biology. "We've discovered that lung cancer cells make an enzyme called CYP24, which counteracts the positive effects of Vitamin D. To better study it, we developed the first radioactive-free assay that measures the amount of Vitamin D in tissues and blood."

According to Dr. Hershberger, this test is sensitive enough to have clinical potential. "We hope this new assay will help identify the best approaches to maintain therapeutic levels of Vitamin D in tissues," she said.

Lung cancer is the leading cause of cancer death in the United States in both men and women, killing 160,000 people annually, and remains one of the most difficult cancers to treat. The five-year survival rate remains low, and better treatments are much needed. According to Dr. Hershberger, it is possible that one day Vitamin D could be used as a chemopreventive agent to improve patient outcomes.

Results of the study, Abstract Number 2402, are being presented at the 100th annual meeting of the American Association for Cancer Research (AACR), April 18 to 22, in Denver.

This study was supported by UPCI's Lung Cancer Specialized Program of Research Excellence.

- **Science News**

Vitamin D Deficiency In Infants And Nursing Mothers Carries Long-term Disease Risks

ScienceDaily (Dec. 29, 2008) — Once believed to be important only for bone health, vitamin D is now seen as having a critical function in maintaining the immune system throughout life. The newly recognized disease risks associated with vitamin D deficiency are clearly documented in a new report.

Vitamin D deficiency is common across populations and particularly among people with darker skin. Nutritional rickets among nursing infants whose mothers have insufficient levels of vitamin D is an increasingly common, yet preventable disorder.

Carol Wagner, MD, Sarah Taylor, MD, and Bruce Hollis, PhD, from the Department of Pediatrics, Medical University of South Carolina (Charleston), emphasize the need for clinical studies to determine the dose of vitamin D needed to achieve adequate vitamin D levels in breastfeeding mothers and their infants without toxicity.

The authors point out that vitamin D is now viewed not simply as a vitamin with a role in promoting bone health, but as a complex hormone that helps to regulate immune system function. Long-term vitamin D deficiency has been linked to immune disorders such as multiple sclerosis, rheumatoid arthritis, type I diabetes, and cancer.

"Vitamin D is a hormone not a vitamin and it is not just for kids anymore," writes Ruth A. Lawrence, MD, Editor-in-Chief of Breastfeeding Medicine, from the Department of Pediatrics, University of Rochester School of Medicine and Dentistry, in an accompanying editorial. "Perhaps the most startling information is that adults are commonly deficit in modern society. Vitamin D is now recognized as a pivotal hormone in the human immune system, a role far beyond the prevention of rickets, as pointed out in the article by Wagner et al in this month's issue of Breastfeeding Medicine."

- **Science News**

New Guidelines Double Amount Of Recommended Vitamin D For Young

ScienceDaily (Oct. 14, 2008) — The American Academy of Pediatrics (AAP) is doubling the amount of vitamin D it recommends for infants, children and adolescents. The new clinical report, "Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents," recommends all children receive 400 IU a day of vitamin D, beginning in the first few days of life.

The previous recommendation, issued in 2003, called for 200 IU per day beginning in the first two months of life.

The change in recommendation comes after reviewing new clinical trials on vitamin D and the historical precedence of safely giving 400 IU per day to the pediatric population. Clinical data show that 400 units of vitamin D a day will not only prevent rickets, but treat it. This bone-softening disease is preventable with adequate vitamin D, but dietary sources of vitamin D are limited, and it is difficult to determine a safe amount of sunlight exposure to synthesize vitamin D in a given individual. Rickets continues to be reported in the United States in infants and adolescents. The greatest risk for rickets is in exclusively breastfed infants who are not supplemented with 400 IU of vitamin D a day.

Adequate vitamin D throughout childhood may reduce the risk of osteoporosis. In adults, new evidence suggests that vitamin D plays a role in the immune system and may help prevent infections, autoimmune diseases, cancer and diabetes.

"We are doubling the recommended amount of vitamin D children need each day because evidence has shown this could have life-long health benefits," said Frank Greer, MD, FAAP, chair of the AAP Committee on Nutrition and co-author of the report. “Supplementation is important because most children will not get enough vitamin D through diet alone.”

"Breastfeeding is the best source of nutrition for infants. However, because of vitamin D deficiencies in the maternal diet, which affect the vitamin D in a mother’s milk, it is important that breastfed infants receive supplements of vitamin D,” said Carol Wagner, MD, FAAP, member of the AAP Section on Breastfeeding Executive Committee and co-author of the report. “Until it is

determined what the vitamin D requirements of the lactating mother-infant dyad are, we must ensure that the breastfeeding infant receives an adequate supply of vitamin D through a supplement of 400 IU per day."

The new recommendations include:

> Breastfed and partially breastfed infants should be supplemented with 400 IU a day of vitamin D beginning in the first few days of life.
>
> All non-breastfed infants, as well as older children, who are consuming less than one quart per day of vitamin D-fortified formula or milk, should receive a vitamin D supplement of 400 IU a day.
>
> Adolescents who do not obtain 400 IU of vitamin D per day through foods should receive a supplement containing that amount.
>
> Children with increased risk of vitamin D deficiency, such as those taking certain medications, may need higher doses of vitamin D.

Given the growing evidence that adequate vitamin D status during pregnancy is important for fetal development, the AAP also recommends that providers who care for pregnant women consider measuring vitamin D levels in this population.

- **Science News**

Vitamin D Deficiency Common In Patients With IBD, Chronic Liver Disease

ScienceDaily (Oct. 13, 2008) — New research presented at the 73rd Annual Scientific Meeting of the American College of Gastroenterology in Orlando found patients with inflammatory bowel disease or chronic liver disease were at increased risk of developing Vitamin D deficiencies. Two separate studies highlight the importance of regular Vitamin D checkups in the evaluation of patients with certain digestive diseases.

For IBD Patients, Vitamin D Deficiency Associated with Lower Quality of Life and Higher Disease Activity

Researchers at the Medical College of Wisconsin investigated whether Vitamin D deficiency in patients with IBD is associated with a lower quality of life or higher disease activity independent of other known risk factors and medication use.

Disease activity and quality of life were assessed using validated questionnaires, which were administered at every clinic visit. The researchers also looked at the prevalence and seasonality of Vitamin D deficiency in this inflammatory bowel disease population, as well as its association with IBD-related hospitalizations, surgeries and medication use.

This retrospective cohort study conducted by Dr. Alex Ulitsky and his colleagues analyzed vitamin D levels of 504 inflammatory bowel disease patients. They recorded the patients' lowest Vitamin D measurements and date when each low measurement was taken.

Dr. Ulitsky and his team found almost 50 percent of the patients were Vitamin D deficient at some point, with 11 percent being severely deficient. Vitamin D deficiency was not significantly associated with being hospitalized for IBD or having IBD-related surgeries. However, in both Crohn's disease (CD) and ulcerative colitis (UC) patients, vitamin D deficiency was independently associated with having increased disease activity scores compared to those with normal levels of Vitamin D. Vitamin D deficient CD patients, but not UC patients, had worse quality of life when compared to patients who were not Vitamin D deficient.

According to Dr. Ulitsky, "All IBD patients, irrespective of their disease, disease location or nature should have their Vitamin D levels checked regularly and corrected aggressively when insufficiency is found."

- **Vitamin D Deficiency Prevalent in Patients with Chronic Liver Disease**

Researchers from the University of Tennessee in Memphis measured the vitamin D levels of 118 chronic liver disease patients. Researchers found 92.4 percent of chronic liver patients had some degree of vitamin D deficiency and at least one third were severely deficient. Severe vitamin D deficiency was more common among cirrhotics.

"Since deficiency is common among these patients, Vitamin D replacement may hopefully prevent osteoporosis and other bone complications related to end stage liver disease," said lead researcher Dr. Satheesh P. Nair.

The study included 43 hepatitis C patients with cirrhosis; 57 hepatitis C patients without cirrhosis; 18 cirrhosis patients without hepatitis C. The severity of vitamin D deficiency was divided into three groups: mild (between 20-32 ng/ml), moderate (between 7-20 ng/ml), and severe (less than 7 ng/ml).

- **Importance of Vitamin D and Bone Health**

Vitamin D, a fat-soluble vitamin, helps the body absorb calcium and plays a crucial role in the growth and maintenance of strong, healthy bones. A lack of vitamin D causes calcium-depleted bone, which can weaken the bones and increase the risk of fractures resulting from osteoporosis.

A diet rich in vitamin D, such as fish, eggs, fortified milk, and cod liver oil, is essential to maintaining good bone health.

- **Science News**

'Let The Sunshine In' To Protect Your Heart This Winter

ScienceDaily (Nov. 26, 2008) — The temperature might not be the only thing plummeting this winter. Many people also will experience a decrease in their vitamin D levels, which can play a role in heart disease, according to a new review article in Circulation.

Vitamin D deficiency results in part from reduced exposure to sunlight, which is common during cold weather months when days are shorter and more time is spent indoors.

"Chronic vitamin D deficiency may be a culprit in heart disease, high blood pressure and metabolic syndrome," said Sue Penckofer, PhD, RN, study author and professor, Marcella Niehoff School of Nursing, Loyola University Chicago.

The review article cited a number of studies that linked vitamin D deficiency to heart disease. These studies found rates of severe disease or death may be 30 to 50 percent higher among sun-deprived individuals with heart disease.

Penckofer and colleagues concluded that diet alone is not sufficient to manage vitamin D levels. Treatment options to correct this level, such as vitamin D2 or D3, may decrease the risk of severe disease or death from cardiovascular disorders. The preferred range in the body is 30 - 60 ng/mL of 25(OH) vitamin D.

"Most physicians do not routinely test for vitamin D deficiency," said Penckofer. "However, most experts would agree that adults at risk for heart disease and others who experience fatigue joint pain or depression should have their vitamin D levels measured."

Study authors also included Glen W. Sizemore, MD, emeritus professor of Medicine, Division of Endocrinology and Metabolism, Loyola University Chicago Stritch School of Medicine, and Diane E. Wallis, MD, Midwest Heart Specialists, Downers Grove, Ill.

- **Science News**

A Ray Of Sunshine In The Fight Against Cancer: Vitamin D May Help

ScienceDaily (Feb. 16, 2008) — It sounds too good to be true … a little inexpensive pill that could block the development of some cancers, strengthen bones, prevent multiple sclerosis and alleviate winter depression.

But it's not science fiction. The "new aspirin" could be Vitamin D. Just as we discovered that aspirin can guard against heart disease, Vitamin D could become a useful weapon in the fight against MS, osteoporosis, mild depression and one of the most devastating diseases of our time – cancer.

"As time has gone by, Vitamin D has raised its head as a sort of ambrosia for cancers," says Dr. Louise Parker, an epidemiologist and a world expert in the environmental exposures that can lead to cancer. Or, in the case of Vitamin D, the lack of exposure.

"One of the most important sources of Vitamin D is from the sun and through your skin," says Dr. Parker.

"Many parts of Canada don't get much sun in the winter. We've also been telling people to cover up and use sunscreen to prevent skin cancer. Sunscreen actually impairs your (skin's ability) to make Vitamin D."

So the Canadian Cancer Society recommends that during the winter, Canadians take at least 1,000 units a day of Vitamin D, dubbed "the sunshine vitamin."

Dr. Parker says 1,000 units a day is well beyond what you can obtain from your diet. Vitamin D is a bit of a rare vitamin, appearing only in fatty fish, cod liver oil and egg yolks. Even if you were to sunbathe in southern climates, you would not take in 1,000 units.

“If you were to lie naked on a beach in the Bahamas, and I don’t recommend that because of skin cancer, you cannot get up to the equivalent of 1,000 units of Vitamin D a day,” says Dr. Parker.

She notes Vitamin D as a factor is turning up in study after study. It turns out people with lung and colon cancer are Vitamin D deficient. And it helps the body absorb calcium. In a study examining whether women who took Vitamin D had a lower risk of osteoporosis, it was found the women taking Vitamin D had stronger bones than those who did not take the vitamin. Years later, researchers went back to that study and found that the women who took Vitamin D also had fewer cancers.

But before Vitamin D becomes the “new aspirin,” more research needs to be carried out.

Vitamin D works in very complicated ways, she says. It changes the way cells work. In fact, there is medical speculation that it may block cancer cell proliferation or improve immune system functions. But its role is not fully understood.

Lifestyle also has to be part of the equation. Dr. Parker is looking at how obesity, which we know can cause cancer, and exercise, which we know prevents cancer, could interact with Vitamin D. “At the population level, I am trying to understand how all these things fit together,” says Dr. Parker. “It’s very complex.” Dr. Parker describes it as looking for a piece of a jigsaw puzzle. “We know some of the jigsaw pieces, but not all,” she says.

Meanwhile, there is very little evidence that taking Vitamin D can harm you. Perhaps in huge doses it could cause kidney stones, but that has not been proven.

“On the average, 1,000 units a day is safe and is probably effective in reducing the risk of colon cancer and maybe other cancers as well,” says Dr. Parker.

So does she take Vitamin D and recommend it? Absolutely. “I take 1,000 units of Vitamin D – one day on and one day off,” she says.

- Wed May 20, 2009 7:38pm EDT REUTERS

Vitamin D may reduce decline in mental agility

LONDON (Reuters) - Getting more of the "Sunshine vitamin" may make you brighter later in life, according to a study published on Thursday that bolsters evidence vitamin D may help older people stay mentally fit.

The findings also raise the prospect that people who do not get enough of the vitamin could use supplements to keep the brain fully functioning as they age, David Lee and colleagues at the University of Manchester reported.

"At the population level, we are talking about large numbers of people. If there is a link it could potentially have a significant effect," Lee, who led the study, said in a telephone interview. "It is so easy to rectify with supplementation."

Vitamin D, produced by the body when skin is exposed to sunlight, is also found in certain foods such as oily fish. It helps cells absorb calcium and is important for bone health.

Recent studies have also indicated vitamin D may protect against cancer, artery disease and tuberculosis.

While others have suggested a link with mental ability, the findings so far have been inconsistent, Lee and colleagues reported in the Journal of Neurology Neurosurgery and Psychiatry.

The researchers compared the cognitive performance of more than 3,000 European men aged 40 to 79 and found those with low vitamin D levels did more poorly on a task designed to test mental agility.

The findings are some of the strongest evidence yet of such a link because of the size of the study and because the researchers adjusted for a number of lifestyle factors believed to affect mental ability when older, Lee said.

"We were able to take into account their educational level, their depression, their levels of physical activity and measures of physical performance," he said.

"When we adjusted for all these other health and lifestyle factors we still found that there was a link between vitamin D and the cognitive outcome."

The researchers do not know exactly how vitamin D and mental agility may be connected but said possible suggestions include the vitamin's role in increasing certain hormonal activity or the protection of neurons in the brain.

They also stressed their findings should not spur people to bask in the sun, which can increase the risk of skin cancer.

- **Alternative Medicine Review , March, 2008 by John J. Cannell, Bruce W. Hollis**

The recent discovery--from a meta-analysis of 18 randomized controlled trials--that supplemental cholecalciferol (vitamin D) **significantly reduces all-cause mortality** emphasizes the medical, ethical, and legal implications of promptly diagnosing and adequately treating vitamin D deficiency. Not only are such deficiencies common, and probably the rule, vitamin D deficiency is implicated in most of the diseases of civilization. Vitamin D's final metabolic product is a potent, pleiotropic, repair and maintenance, seco-steroid hormone that targets more than 200 human genes in a wide variety of tissues, meaning it has as many

mechanisms of action as genes it targets. One of the most important genes vitamin D up-regulates is for cathelicidin, a naturally occurring broad-spectrum antibiotic. Natural vitamin D levels, those found in humans living in a sun-rich environment, are between 40-70 ng/mL, levels obtained by few modern humans. Assessing serum 25-hydroxy-vitamin D (25(OH)D) is the only way to make the diagnosis and to assure treatment is adequate and safe. Three treatment modalities exist for vitamin D deficiency: sunlight, artificial ultraviolet B (UVB) radiation, and vitamin D supplementation. Treatment of vitamin D deficiency in otherwise healthy patients with 2,000-7,000 IU vitamin [D.sub.3] per day should be sufficient to maintain year-round 25(OH)D levels between 40-70 ng/mL In those with serious illnesses associated with vitamin D deficiency, such as cancer, heart disease, multiple sclerosis, diabetes, autism, and a host of other illnesses, doses should be sufficient to maintain year-round 25(OH)D levels between 55-70 ng/ mL. Vitamin D-deficient patients with serious illness should not only be supplemented more aggressively than the well, they should have more frequent monitoring of serum 25(OH) D and serum calcium. Vitamin D should always be adjuvant treatment in patients with serious illnesses and never replace standard treatment. Theoretically, pharmacological doses of vitamin D (2,000 IU/kg/day for three days) may produce enough of the naturally occurring antibiotic cathelicidin to cure common viral respiratory infections, such as influenza and the common cold, but such a theory awaits further science. (Altern Med Rev 2008; 13(1):6-20)

Introduction

A recent meta-analysis of 18 randomized controlled trials (RCT) found that cholecalciferol (vitamin D) significantly reduced total mortality. This discovery is all the more remarkable because of the relatively low doses of vitamin D used (mean close 528 IU (13 mcg)) and because the finding persisted across a number of subgroup analyses. In spite of the low doses used and the short duration of the trials, vitamin D's mortality reduction was seven percent. Indeed, the recent discovery that statins significantly increase 25-hydroxy-vitamin D (25(OH)D) levels raise the possibility that some--or all--of the mortality reduction of statins may be mediated through increases in vitamin D levels.

Lappe et al recently reported the first RCT of vitamin D in preventing internal cancers and found a 60-percent reduction in such cancers by increasing baseline 25(OH)D levels from 29 ng/mL to 38 ng/mL with 1,100 IU (28 mcg) per day. Baseline and treatment-induced serum 25(OH)D levels were strong and independent predictors of cancer risk. Lappe et al's study left open the possibility that higher doses and higher treatment-induced 25(OH)D levels might prevent even more cancers. (Note that 25(OH)D levels are reported in the literature as either ng/mL or nmol/L; 1.0 ng/mL equals 2.5 nmol/L.)

Besides cancer, vitamin D deficiency is associated with cardiovascular disease, hypertension, stroke, diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, osteoporosis, periodontal disease, macular degeneration, mental illness, propensity to fall, and chronic pain. A recent review presented considerable evidence that influenza epidemics, and perhaps even the common cold, are brought on by seasonal deficiencies in antimicrobial peptides (AMP), such as cathelicidin, secondary to seasonal deficiencies in vitamin D. Results of an RCT support the theory, finding 2,000 IU of vitamin D/day for one year virtually eliminated

self-reported incidence of colds and influenza Even the current triple childhood epidemics of autism asthma, and type 1 diabetes, all of which blossomed after sun-avoidance advice became widespread, might be the tragic and iatrogenic sequela of gestational or early childhood vitamin D deficiencies brought on by medical advice to avoid the sun.

Claims that vitamin D may help prevent such a wide variety of diseases seem incredible until one realizes vitamin D is not a vitamin; rather, it is the only known substrate for a potent, pleiotropic, repair and maintenance, seco-steroid hormone with a single endocrine function, but multiple autocrine functions. Previously, many practitioners thought vitamin D's activity was principally its endocrine function--the regulation of serum calcium--and was thus mainly involved in bone metabolism. Indeed, the classic endocrine function of vitamin D begins when the kidney hydroxylates 25(OH)D into 1,25[(OH).sub.2]D, which then acts, both directly and indirectly, to maintain serum calcium.

- **Vitamin D and prevention of breast cancer: pooled analysis.**

Garland CF, **Gorham ED**, **Mohr SB**, **Grant WB**, **Giovannucci EL**, **Lipkin M**, **Newmark H**, **Holick MF**, **Garland FC**.
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BACKGROUND: Inadequate photosynthesis or oral intake of Vitamin D are associated with high incidence and mortality rates of breast cancer in ecological and observational studies, but the dose-response relationship in individuals has not been adequately studied. METHODS: A literature search for all studies that reported risk by of breast cancer by quantiles of 25(OH)D identified two studies with 1760 individuals. Data were pooled to assess the dose-response association between serum 25(OH)D and risk of breast cancer. RESULTS: The medians of the pooled quintiles of serum 25(OH)D were 6, 18, 29, 37 and 48 ng/ml. Pooled odds ratios for breast cancer from lowest to highest quintile, were 1.00, 0.90, 0.70, 0.70 and 0.50 (p trend<0.001). According to the pooled analysis, individuals with serum 25(OH)D of approximately 52 ng/ml had 50% lower risk of breast cancer than those with serum <13 ng/ml. This serum level corresponds to intake of 4000 IU/day. This exceeds the National Academy of Sciences upper limit of 2000 IU/day. A 25(OH)D level of 52 ng/ml could be maintained by intake of 2000 IU/day and, when appropriate, about 12 min/day in the sun, equivalent to oral intake of 3000 IU of Vitamin D(3). CONCLUSIONS: Intake of 2000 IU/day of Vitamin D(3), and, when possible, very moderate exposure to sunlight, could raise serum 25(OH)D to 52 ng/ml, a level associated with reduction by 50% in incidence of breast cancer, according to observational studies.

- **Lack of Sunshine Causes One Million Deaths a Year**

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If vitamin D3 levels among populations worldwide were increased, 600,000 cases of breast and colorectal cancers could be prevented each year, according to researchers from the Moores

Cancer Center at the University of California, San Diego (UCSD).

This includes nearly 150,000 cases of cancer that could be prevented in the United States alone.

The researchers estimate that 250,000 cases of colorectal cancer and 350,000 cases of breast cancer could be prevented worldwide by increasing intake of vitamin D3, particularly in countries north of the equator.

The study examines the dose-response relationship between vitamin D and cancer, and is the first to use satellite measurements of sun and cloud cover in countries where blood serum levels of vitamin D3 were also taken.

Serum vitamin D levels during the winter from 15 countries were combined, then applied to 177 countries to estimate the average serum level of a vitamin D metabolite among the population.

An inverse association between serum vitamin D and the risk of colorectal and breast cancers was found.

Protective effects began when 25-hydroxyvitamin D levels (the main indicator of vitamin D status) ranged from 24 to 32 nanograms per milliliter (ng/ml). In the United States, late winter 25-hydroxyvitamin D levels ranged from 15 to 18 ng/ml.

Previous research has suggested that raising levels to 55 ng/ml was actually optimal to prevent cancer, the researchers said.

To increase your vitamin D3 levels, the researchers recommended a combination of dietary methods, supplements and sunlight exposure of about 10 to 15 minutes a day, with at least 40 percent of your skin exposed

- **Reduce Your Risk of Cancer With Sunlight Exposure**

By William B. Grant, Ph.D.
SUNARC

With all of the publicity that UV radiation (UVR) is an important cause of skin cancer, premature skin aging and cataract formation, one might think that avoidance of UVR would be the best policy. Not so fast. If protection against UVR were the most important thing, all humans would have very dark skin, since the melanin in dark skin protects against skin cancer and premature skin aging.

Skin pigmentation becomes paler the closer one's ancestors lived to the polar-regions, evidently to balance cutaneous production of vitamin D with protection against free radicals and DNA damage from UVR [Jablonski and Chaplin, 2000]. In addition, even a cursory look at the geographic variation in cancer mortality rates in the United States [Devesa et al., 1999] indicates that some environmental factor has to explain why mortality rates for a number of internal cancers are approximately twice as high in northeastern, highly-urbanized states than in southwestern, more rural states.

Diet and smoking are, of course, important risk factors for many types of cancer [Doll and Peto, 1981]. But in order for diet to explain the geographic variation in cancer rates, Americans would need to be eating drastically different diets by region. However, anyone who has travelled throughout the United States knows that the food choices do not vary much anywhere in the contiguous 48 states.

The Risk of Cancer Lessens With More Sun Exposure

The key to understanding this geographic pattern was provided by Cedric and Frank Garland in 1980 [Garland and Garland, 1980]. They reasoned that sunlight, through the production of vitamin D, reduced the risk of colon cancer in the sunny areas compared to that in the darker areas. They performed an ecologic study of annual solar irradiance versus colon cancer mortality rates and found a strong inverse correlation, i.e. the more sunlight, the less cancer. (An ecologic study treats entire populations defined geographically as entities, with values for disease outcome and environmental or dietary factors averaged for each entity.)

Their paper received little notice at first, perhaps because UVR was commonly associated with skin cancer, perhaps because the ecologic approach was falling out of favor [Doll and Peto, 1981]. Undaunted, they extended their work through the use of stored serum 25-hydroxyvitamin D (25(OH)D)--the common form of circulating vitamin D--values for another purpose along with a determination of colorectal cancer incidence among the serum donors, finding a significant inverse correlation between 25(OH)D and colorectal cancer rates [Garland et al., 1985]. The list of cancers for which ultraviolet B (UVB) (290-315 nm) and vitamin D is protective was extended through a variety of observational epidemiologic studies by the end of the 1990s to include breast, ovarian and prostate cancer and non-Hodgkin's lymphoma [Grant, 2002b].

How Vitamin D Reduces the Risk of Cancer

The mechanisms by which vitamin D reduces the risk of cancer are fairly well understood. They include enhancing calcium absorption (in the case of colorectal cancer) [Lamprecht and Lipkin, 2003], inducing cell differentiation, increasing cancer cell apoptosis or death, reducing metastasis and proliferation, and reducing angiogenesis [van den Bemd and Chang, 2002]. In addition, 25(OH)D downregulates parathyroid hormone (PTH) [Chapuy et al., 1987]. Since IGF-I stimulates tumor growth and high quantities are a consequence of the standard American diet [Grant, 2002a; 2004], vitamin D can be considered one partial antidote to the American diet.

When I decided to investigate the role of UVB and vitamin D in reducing the risk of cancer, after I convinced myself that dietary factors could not explain the geographic variation of cancer mortality rates in the United States, I posed two questions to address:

- For how many cancers is UVB/vitamin D protective?
- How many Americans die prematurely each year due to inadequate levels of vitamin D?

I started with the maps of cancer mortality rates in the Atlas of Cancer Mortality [Devesa et al., 1999] and found the UVB irradiance/dose map for the United States for July 1992 made using data obtained by NASA's Total Ozone Mapping Spectrometer (TOMS) to use as a proxy for

vitamin D production. In this study, I determined that UVB was inversely correlated with mortality rates for 12 types of cancer, including five types of cancer already identified plus an additional seven, and estimated that 17, 000 to 23,000 Americans died prematurely each year due to insufficient vitamin D [Grant, 2002b].

While the study was generally accepted, critics pointed out that I had ignored a number of factors that affect the risk of cancer and which could, perhaps, explain much of the variation in mortality rates. To respond to these critics, I extended the analysis by including a number of cancer risk factors for which I could find state-averaged values.

These factors included lung cancer mortality rates (an index for the adverse health effects of smoking), fraction of the population considered of Hispanic heritage (Hispanics are counted as white Americans in the Atlas), alcohol consumption rates, degree of urbanization, and fraction of the population living below the poverty level.

Sun Exposure (UVB) Protects Against 16 Types of Cancer

The new study links UVB as protective to a total of 16 types of cancer, primarily epithelial (pertaining to the surface) cancers of the digestive and reproductive systems [Grant, submitted]. Six types of cancer (breast, colon, endometrial, esophageal, ovarian, and non-Hodgkin's lymphoma) were inversely correlated to solar UVB radiation and rural residence in combination. This result strongly suggests that living in an urban environment is associated with reduced UVB exposure compared to living in a rural environment.

Another 10 types of cancer including bladder, gallbladder, gastric, pancreatic, prostate, rectal and renal were inversely correlated with UVB but not urban residence. Ten types of cancer were significantly correlated with smoking, six types with alcohol, and seven types with Hispanic heritage. Poverty status was inversely correlated with seven types of cancer. Since the results for alcohol, Hispanic heritage, and smoking for white Americans agree well with the literature [Trapido et al., 1995; Thun et al., 2002], they provide a high level of confidence in the approach and its results for UVB radiation.

Over 40,000 Americans Die Annually From Cancer Caused by Vitamin D Deficiency

From this analysis, it was estimated that 45,000 Americans die from cancer annually related to inadequate levels of vitamin D: half from UVB doses based on location, and half based on living in an urban environment with reduced solar radiation exposure.

Papers continue to appear supporting the UVB/vitamin D-cancer connection. The latest is from Norway, showing that the detection of breast, colon, and prostate cancer has a seasonal cycle correlated with vitamin D production by sunlight [Robsahm et al., 2004]. This paper is important since it shows that vitamin D effectively fights cancer even in the later stages.

How Much Vitamin D is Required to Prevent Cancer?

The amount of ingested vitamin D and/or UVB exposure required for optimal protection against cancer is still being determined. Each person responds differently to UVB exposure and oral

intake of vitamin D depending on such factors as skin pigmentation, body mass index (vitamin D is fat soluble), age, condition of digestive tract, other dietary factors, etc.

Dietary vitamin D is insufficient alone to significantly reduce the risk of most cancers since the ingested amounts, up to 200 to 400 I.U. per day, are too low [Grant and Garland, in press]. Evidently, 600 to 1000 I.U per day are required to reduce the risk of vitamin-D-sensitive cancers, except possibly prostate cancer, for which population-average values of serum 25(OH)D are associated with the minimum risk [Tuohimaa et al., 2004; Grant, in press].

The current understanding is that serum 25(OH)D levels should be in the 30 to 40 ng/ml (75-100 nmol/L) range for cancer prevention and optimal health. The only way to determine one's 25(OH)D levels is through blood tests, which can be ordered through a physician or nutritionist. It should be noted that the UVB dose required to generate these levels is much less than would ordinarily be considered a risk factor for skin cancer, etc.

The time required in the sun is probably 15 to 30 minutes per day with at least hands and face exposed in the mid-latitudes during summer [Reid et al., 1986], but depends on a number of personal factors. The optimal time for solar UVB production of vitamin D may be around the middle of the day when the ratio of UVB to UVA (315-400 nm) is highest and the required exposure times are shortest.

However, this works only when the sun is elevated high enough--for the four to five darkest months of the year it is impossible to produce any vitamin D from sunlight in Boston [Webb et al., 1988]. When solar UVB is not available, one has to rely on stored vitamin D (weeks to months), artificial UVB, dietary supplements, many types of fish, or fortified foods, which now include milk and orange juice.

How Can You Protect Yourself From Inadequate Vitamin D Levels?

While the scientific results to date increasingly support the hypothesis that UVB and vitamin D reduce the risk of many types of cancer as well as many other types of disease including musculoskeletal diseases, autoimmune diseases and hypertension, it will likely be some time before the health system embraces this hypothesis and acts to recommend higher values of 25(OH)D, which would require increased UVB exposure (natural and artificial) and dietary supplements.

However, the informed individual who carefully studies the literature can very likely reduce his or her risk of cancer and a number of other diseases by careful exposure to UVB, being particularly careful to avoid any sunburning, and adequate intake of vitamin D.

More information on the protective role of UVB against breast and colorectal cancer, other cancers, and other diseases can be found at my Web site, www.sunarc.org.

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Langley Research Center. He is the author or coauthor of over 60 articles in peer-reviewed journals, has edited two books of reprints, and contributed half a dozen chapters to other books.

He published the first paper linking diet to Alzheimer's disease and identifying the major dietary components that are risk and risk reduction factors. He has also studied the links between dietary sugars and heart disease and obesity, diet and breast, colon and prostate cancer, and UVB/vitamin D and cancer and autoimmune diseases. He recently retired from NASA and founded Sunlight, Nutrition and Health Research Center (SUNARC), where he will continue and extend his health research and educational efforts.

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- **Association between 25-hydroxyvitamin D levels and cognitive performance in middle-aged and older European men.**

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BACKGROUND Although there is evidence that vitamin D inadequacy may be linked to adverse cognitive outcomes, results have been inconsistent. The aim of our study was to examine the association between 25-hydroxyvitamin D (25(OH)D) levels and cognitive performance in middle-aged and older European men. METHODS This population-based cross-sectional study included 3,369 men aged 40 to 79 years from eight centres enrolled in the European Male Ageing Study (EMAS). Cognitive function was assessed using the Rey-Osterrieth Complex Figure test (ROCF), the Camden Topographical Recognition Memory test (CTRM) and the Digit Symbol Substitution test (DSST). Serum 25(OH)D levels were measured by radioimmunoassay. Additional assessments included physical activity, functional performance and mood/depression. Associations between cognitive function and 25(OH)D were explored using locally weighted and linear regression models. RESULTS 3,133 men, mean (+/-SD) age 60+/-

11 years were included in the analysis. The mean 25(OH)D concentration was 63+/-31 nmol/L. In age-adjusted linear regressions higher levels of 25(OH)D were associated with higher scores on the ROCF-copy (beta per 10 nmol/L=0.096; 95%CI 0.049-0.144), CTRM (beta per 10 nmol/L=0.075; 95%CI 0.026-0.124) and DSST (beta per 10 nmol/L=0.318; 95%CI 0.235-0.401) tests. After adjusting for additional confounders, 25(OH)D levels were associated with the DSST test only (beta per 10 nmol/L=0.152; 95%CI 0.051-0.253). Locally weighted and spline regressions suggested the relationship between 25(OH)D and cognitive function was most pronounced at 25(OH)D concentrations below 35 nmol/L. CONCLUSION In this study lower 25(OH)D levels were associated with poorer performance on the DSST test. Further research is warranted to determine whether vitamin D sufficiency may play a role in preserving cognitive function in older adults.