Vitamin D3 and Cancer

This web site is dedicated to vitamin D and cancer. This is because exciting new research indicates that vitamin D, produced when skin is exposed to ultraviolet radiation (whether from the sun or sun lamps) as well as from supplementation with cholecalciferol, may help cancer patients. However, the research is far from complete.

Articles about vitamin D are beginning to appear everywhere. For years, most of us wrongly assumed we'd be fine if we drank a little milk and took a multivitamin pill. Now, studies are reporting most of us are vitamin D deficient and those deficiencies may well be causing numerous illnesses, especially cancer.

Recent medical research indicates human daily requirements for vitamin D may be up to ten times more than what is currently recommended. Proper vitamin D supplementation gives one a much better chance of preventing many major illnesses such as: Heart Disease, Hypertension, Arthritis, Chronic Pain, Depression, Inflammatory Bowel Disease, Obesity, Premenstrual Syndrome, Muscular Weakness, Fibromyalgia, Crohns Disease, Multiple Sclerosis, Autoimmune Illness, as well as cancer. And more are being added to this list almost daily.

Vitamin D As Prevention

How much vitamin D one should take daily to prevent cancer is still unknown. It is a question more complicated than it at first appears, for we get most of our vitamin D from the sun. Even a little sun will make some vitamin D, if it is the right time of day, the right latitude, and the right season of the year.

We get a little in our diet, almost all of it from milk or fish, but none of us get enough from our diet. We also get some in multivitamins, but multivitamins only contain 400 units, about 10% of the body's daily needs. It appears to us that the best thing to do is be conservative and maintain natural vitamin D blood levels year around, by receiving sunlight in the summer and supplementation in the winter. In this case, "natural" means calcidiol blood levels similar to humans living in a natural relationship with the sun, such as farmers in Puerto Rico or lifeguards in the United States. Both groups have calcidiol levels above 50 ng/mL.

So the amount an individual would need to prevent cancer really depends on how much sunlight exposure they receive in terms of duration, the time of year and time of day, and the amount of skin exposed. Vitamin D amount already being received through diet and supplements should be considered as well.

Vitamin D As Treatment

How much vitamin D should one take if they have cancer? We don't know as the research is far from complete. Although current research indicates vitamin D to be an effective tool in the fight against cancer, it should be used in addition to regular chemotherapy or surgery. Oncologists and surgeons work miracles every day.

Vitamin D and Breast Cancer

Most Common Malignancy for Women

Breast cancer is the most common malignancy of women in the western world. Many factors contribute to causing breast malignancy (it is multifactorial), though heredity is a major one. Certain diets help to prevent it, such as diets high in vegetables and fruit and low in fat. Adequate calcium is very important. The role of vitamin D in both the prevention and treatment of breast cancer is being intensively explored by scientists, and the results thus far have been promising.

No matter what cancer you have, or are trying to prevent, the question is: should cancer patients be left vitamin D deficient? The current research indicates the answer to this question is no, women with breast cancer should not allow themselves to be vitamin D deficient, and neither should their doctors.

If you have breast cancer, please remember that vitamin D is not a cure-all and should never be used as the main treatment for your cancer. Your oncologist will prescribe treatment that has proven efficacy and you should carefully follow their advice as the mainstay of treatment. At the same time, you should know that evidence suggests that the proper amount of vitamin D may help you in your fight against breast cancer.

Vitamin D In the Fight Against Breast Cancer

Let's have a look at selected studies from the scientific literature to see what clues exist about the role vitamin D may play in preventing, and treating, breast cancer.

Vitamin D Receptors and Calcitriol

In 1989, the prestigious medical journal, The Lancet, reported that the most active form of vitamin D (calcitriol) significantly reduced the growth of breast cancer in an animal model. Furthermore the researchers from St. Georges Hospital Medical School in London found women who had vitamin D receptor positive tumors had longer disease free intervals than women whose tumors had no measurable receptors for vitamin D. Lancet. 1989 Jan 28;1(8631):188–91.

Current research suggests most, if not all, women would have those vitamin D receptors unless they were deficient in vitamin D, that is, they would have those receptors if they were vitamin D replete. It seems as if the receptor is present in breast tissue if the most

active form of vitamin D has been present and that is only the case if vitamin D's less-active form, calcidiol, has been present. In other words, if you test vitamin D deficient breast cancer patients for vitamin D receptors, they will not have many; if you treat their deficiency, they will probably develop those receptors.

Not only does calcitriol (the form made in optimal quantities by your body when your vitamin D blood levels are ideal) inhibit breast cancer cells from growing, it makes those cells grow and die more like natural cells. Furthermore, vitamin D inhibits the formation of excessive blood vessel growth around the cancerous tumor, a process called anti-angiogenesis. Braz J Med Biol Res. 2002 Jan;35(1):1–9.

Sunlight Exposure Lowers Risk

In the 1990s, a group of scientists from the University of California at San Diego provided the first look at how many women may be dying needlessly from breast cancer due to low vitamin D blood levels. The researchers measured the amount of sunlight available to the women at the latitude where they lived and combined that with the frequency of cloudy weather, as sunny climates are associated with higher vitamin D levels. They found that women in the sunniest regions of the United States were about half as likely to die from breast cancer as were women who lived in less sunny regions. When the same researchers looked at the USSR before the country dissolved, they found that women who lived in the sunniest regions were three times less likely to develop breast cancer than were the women who lived in regions without as much sun. Prev Med. 1990 Nov;19(6):614–22. Int J Epidemiol. 1990 Dec;19(4):820–4.

In 1994, a researcher at the Memorial Sloan-Kettering Cancer Center reviewed the literature up to that date and concluded that higher intakes of vitamin D3 and calcium might reduce breast cancer by protecting against the carcinogenic effects of a high fat diet. He also pointed out the vitamin D intakes were far below the government recommendations in force at the time. Adv Exp Med Biol. 1994;364:109–14.

In 1997, researchers at the Manchester Royal Infirmary discovered that women with the highest levels of calcitriol in their blood had the best prognosis. Those women with the lowest levels had a more rapidly fatal course. They also found that women with breast cancer had low levels of calcidiol in their blood with average levels of about 16 ng/mL. Women who live in sunny climates, where breast cancer is more rare, frequently have blood levels three times higher. J Clin Endocrinol Metab. 1997 Jan;82(1):118–22.

Test for Calcidiol Levels, Not Calcitriol

However, studies that measure blood levels of calcitriol miss the important fact that blood levels do not reflect tissue levels. In fact, blood levels of calcitriol are quite different than tissue levels which can not be measured. However, tissue levels can be estimated from calcidiol levels as calcidiol is converted into calcitriol in the tissues and that conversion is directly proportional to the blood level of calcidiol. Simply put, this means that higher

blood levels of calcidiol, resulting in higher tissue levels of calcitriol to fight breast cancer.

In 1999, researchers at the University of North Carolina School of Medicine reported that white women with the lowest blood levels of calcitriol were five times as likely to develop breast cancer as were women with the highest levels but the relationships did not hold for black women. More importantly, the researchers found that women with breast cancer had very low levels of calcidiol in their blood, with an average level of 15 ng/mL for white women and only 8.9 ng/mL for black women, which is severely deficient. This extraordinarily low level of calcidiol in blacks probably explained the researchers finding about calcitriol. Blacks were so deficient in vitamin D that their kidneys could not make enough calcitriol to compensate for their low calcidiol levels. Remember, as vitamin D deficiency worsens, the kidney activates more and more calcidiol into calcitriol to maintain serum calcium leaving very little left over for the tissues to fight cancer. Public Health Nutr. 1999 Sep;2(3):283–91.

Also in 1999, researchers at the Northern California Cancer Center and the University of Miami followed 5009 women for 20 years, as part of a large NHANES I study. Of the women followed, 190 subsequently developed breast cancer. The researchers did not have data on the womens' blood calcidiol levels available, so they looked at other markers of vitamin D levels: living in sunny climates, sun damaged skin (an indication of amount of past sun exposure), a history of occupational and/or recreational sun exposure, and dietary intake of vitamin D.

Sun Exposure Best Source For Vitamin D

All of these factors reduced the risk of breast cancer. Dietary vitamin D reduced the risk a little (due to the tiny doses of vitamin D consumed) but women with high occupational and recreational sun exposure who also lived in a sunny climate reduced their risk three fold. Remember, 90% of our vitamin D comes from sun exposure. Vitamin D from diet and supplements is close to insignificant due to the small amounts consumed. Cancer Epidemiol Biomarkers Prev. 1999 May;8(5):399–406.

Cholecalciferol To Elevate Calcidiol Levels

In 2002, researchers at St. George's Hospital Medical School in London reviewed the multiple mechanisms by which calcitriol prevents breast cancer. Calcitriol arrests the aberrant progression of breast cancer by regulating cell cycles, forcing apoptosis (cell death), resists signals from substances that cause cancer cells to grow, inhibiting invasion into normal tissue, and prevents metastasis. All in all, calcitriol, the most potent form of vitamin D, appears to be the perfect chemotherapeutic agent to both prevent and treat breast cancer. Unfortunately, the researchers appeared to be unaware that the best way to elevate tissue levels of calcitriol is to elevate blood calcidiol levels. The best way to elevate calcidiol levels is to take physiological doses of cholecalciferol plain vitamin D3. Endocr Relat Cancer. 2002 Mar;9(1):45–59.

Analogs and High Blood Calcium

Instead of giving simple cholecalciferol to patients with breast cancer, the medical-industrial complex continued to test the potentially profitable vitamin D analogs which are patenable variations of calcitriol. The vitamin D analogs are chemical modifications of calcitriol which try to retain calcitriol's ability to fight breast cancer while not causing the high blood calcium that calcitriol usually causes. Several different vitamin D analogs were tested and many worked great in the test tube. However, just like calcitriol, they usually caused high blood calcium (hypercalcemia) when given to humans.

Vitamin D3 Not Patentable

No one seemed to care that optimal doses of cholecalciferol would raise tissue levels of cancer fighting calcitriol quite high, would not cause hypercalcemia, and should work well against breast cancer. Remember, cholecalciferol occurs naturally, can not be patented, and is dirt cheap. Therefore, the idea that it could help breast cancer offered no financial incentives to drug companies or researchers hoping to discover a drug they could patent. Also, few of the scientists working to cure cancer had any but the most rudimentary understanding of basic vitamin D physiology, pharmacology, or toxicology. Recent Results Cancer Res. 2003;164:333–48.

Vitamin D, Calcium, and Mammograms

Then, things started coming to a head in the last few years. In 2004, a group at the University Hospital in Quebec confirmed that vitamin D, especially when taken with calcium, significantly reduced abnormal mammograms. In fact they found women with the highest vitamin D intake had only one fourth as may abnormal densities on their mammogram as did women with the lowest intake. Cancer Epidemiol Biomarkers Prev. 2004 Sep;13(9):1466–72.

Breast Cancer Cells Activate Vitamin D

Researchers in Germany then tested fresh breast cancer cells to see if they could activate vitamin D. Up until then, only breast cancer cells grown in test tubes had been tested. The researchers found fresh breast cancer cells could indeed activate vitamin D. Indeed those cells seemed to be hungry for the vitamin D as the cells showed increased production of the enzymes necessary to activate vitamin D. It seemed all that was missing was the vitamin D. Recent Results Cancer Res. 2003;164:239–46.

Then researchers in Norway discovered that women who were diagnosed with breast cancer during the summer and fall, the season where vitamin D levels are the highest, had the best prognosis. The researchers concluded that high vitamin D levels during the course of cancer treatment may improve the prognosis of women with breast cancer. Colon and prostate cancer showed similar improvements. Cancer Causes Control. 2004 Mar;15(2):149–58.

Vitamin D's Promise

Since then, numerous studies on the effects of vitamin D in regards to breast cancer have indicated that vitamin D3 holds great promise. Yet there is still so much more to learn about vitamin D and its relation to cancer and overall health in general. As more and more studies are performed on vitamin D, we anticipate that the future holds even more good news to come.

Vitamin D and Colon Cancer

Colorectal cancer is the second most common form of cancer in the western world. About 150,000 Americans will be told they have colon cancer this year and 50,000 will die. Your chance of developing colon cancer, sometime in your life, is about 1 in 15. Blacks are particularly affected by colorectal cancer, as well as other cancers, with both a higher incidence and mortality from colon cancer than non-blacks. We believe this is due to a widespread vitamin D deficiency within the black community.

Many factors contribute to causing colon cancer (it is multifactorial) but diet is probably the most important factor. Certain diets promote colon cancer, such as diets high in fat and red meat and other diets help prevent colon cancer, especially diets high in fiber, calcium, fruits and vegetables. Scientists first discovered the possible importance of vitamin D in preventing colon cancer more than 20 years ago.

If you have colon cancer, please remember that vitamin D is not a cure-all and should never be used as the main treatment for your cancer. Your oncologist will prescribe treatment that has proven efficacy and you should carefully follow their advice as the mainstay of treatment. At the same time, you should know that evidence suggests that the proper amount of vitamin D will help you in your fight against colon cancer.

Vitamin D In the Fight Against Colon Cancer

Let's review some selected studies from the scientific literature to see what clues exist about the role vitamin D may play in preventing, and treating, colon cancer.

Sunlight Exposure Lowers Cancer Risk

In 1980, Cedric and Frank Garland, while at Johns Hopkins University, reported that death from colon cancer was significantly less likely in those who lived in sunny areas. The Garland brothers believed vitamin D best explained this observation. Int J Epidemiol. 1980 Sep;9(3):227–31.

In 1985, scientists studied 2100 men for 19 years. They discovered that colon cancer was more than twice as likely in the men that consumed the least amount of vitamin D and calcium. As about 90% of the average persons vitamin D comes from the sun, it was

comforting to know that even small amounts of vitamin D in the diet helped prevent colon cancer. Lancet. 1985 Feb 9;1(8424):307–9.

In 1989, the Garland brothers presented further evidence that vitamin D deficiency played a key role in colon cancer. They analyzed air pollution data from 20 Canadian cities finding that the cities where polluted air obscured vitamin D producing sunlight had higher death rates from both colon and breast cancer. Furthermore, they pointed out that colon cancer rates were 4–6 times higher in North America and Northern Europe when compared to the incidence of colon cancer in countries close to the equator. Can J Public Health. 1989 Mar–Apr;80(2):96–100.

Blood Calcidiol Level and Cancer Risk

Later that same year the Garlands presented even stronger evidence, this time in the prestigious British journal, *the Lancet*. For the first time, researchers linked blood vitamin D levels to risk of developing colon cancer. They found an amazingly strong correlation which revealed that a person was five times less likely to develop colon cancer if that person's blood calcidiol level was between 33–41 ng/mL. For the first time, a direct correlation was shown between vitamin D blood levels and the risk of getting colon cancer. As cancer is a dynamic process, with normal cells turning cancerous as time progresses, this study strongly suggested that vitamin D may have an important role in treating colon cancer. Lancet. 1989 Nov 18;2(8673):1176–8.

In 1992, researchers at the University of Washington independently confirmed the Garland brothers work. They analyzed cancer registries in the United States and found people who live in cloudy northern areas (Michigan, Connecticut, western Washington, etc.) were up to 80% more likely to develop colon cancer than those who lived in sunny areas (Utah, New Mexico, etc.). Cancer Causes Control. 1992 Jan;3(1):95–9.

Vitamin D Obtained Throught Diet Helpful

In 1993, researchers from the University of Minnesota, analyzing the data of more than 35,000 women from the Iowa Womens Health Study, found that vitamin D and calcium in the diet significantly reduced the risk of colon cancer. Women with the lowest vitamin D intake were twice as likely to develop colon cancer. Remember, diet supplies only 10% of the vitamin D as most people get almost all their vitamin D from sun exposure. Even so, this study confirmed earlier findings and showed that even small amounts of vitamin D in the diet were helpful. Am J Epidemiol. 1993 Jun 15;137(12):1302–17.

Supplemental Vitamin D Even More Important

In 1996, researchers at Harvard confirmed that vitamin D taken in the diet or in supplements reduced the risk of colon cancer. Furthermore, they found supplemental vitamin D was more important than vitamin D from diet. It is important to remember that little vitamin D is obtained from either diet or supplements, compared to the enormous

quantities available from sunlight. Even so, the men with the highest total vitamin D intake were about one-half as likely to develop colon cancer compared to men with the lowest total intake. Am J Epidemiol. 1996 May 1;143(9):907–17.

Later in 1996, researchers at Harvard reported results for women. They followed 89,000 nurses over 12 years and found the nurse's risk of developing colon cancer was reduced by vitamin D, similar to men. In fact, they found the relative risk for women with the highest total vitamin D intake was 0.42, meaning those women with the lowest vitamin D intake were more than twice as likely to develop colon cancer. J Natl Cancer Inst. 1996 Oct 2;88(19):1375–82.

In 1997, researchers in Finland confirmed the Garland brothers' original findings on vitamin D blood levels and colon cancer. Again, they found that the risk of colorectal cancer was highest in those with the lowest blood levels. Perhaps more ominous for the people of Finland (which is very far north and gets little sunlight) was the very low levels of vitamin D in the blood of Finns. The average person in Finland had blood levels of only 13 ng/mL, a level now known to be associated with numerous serious illnesses, not just cancer. Cancer Causes Control. 1997 Jul;8(4):615–25.

Calcitriol—Nature's "Defense Strategy" Against Cancer

Finally, in 1997, researchers at the University of Vienna first suggested that vitamin D may help treat colon cancer. They discovered that colon cancer cells, when grown in a test tube, retain the ability to make calcitriol, the active form of vitamin D that has multiple anticancer properties. They further proposed that calcitriol in the tissues may be nature's "defense strategy" to fight cancer. J Steroid Biochem Mol Biol. 1997 May;62(1):21–8.

In 1999, researchers in Israel, found that calcitriol levels were twice as high in patients with less aggressive colon cancer but were quite low in those with advanced metastatic disease. They concluded that higher calcitriol levels may prevent "further transformation of the cells or may induce cell differentiation, growth inhibition or apoptosis (normal cell death)." That is, they suggested that higher serum calcitriol levels prevented the cancer from progressing, implying it might be useful in treatment, especially in early stages. However, it is important to remember that, although tissue calcitriol levels are most important in fighting cancer, they can not be measured. Colon tissue can make large amounts of tissue calcitriol, if and only if, enough calcidiol is available in the blood. Blood calcidiol levels can easily be increased by taking the correct amount of vitamin D3 supplements. Cancer. 1999 Aug 1;86(3):391–7.

Colon Cancer Cells Activate Vitamin D

In 2001, researchers at Boston University found that colon cancer cells can activate vitamin D, turning calcidiol into calcitriol. Their findings clearly implied that patients with colon cancer might be helped by optimizing the amount of calcidiol in their blood. The authors even warned that "vitamin D deficiency could accelerate colon cancer

growth." That is, the cancer cells themselves can make calcitriol, if enough calcidiol is available for them to do so. Remember, every molecule of calcitriol in your tissues comes from a molecule of calcidiol in your blood. Lancet. 2001 May 26;357(9269):1673–4.

Later in 2001, researchers at the University of Vienna confirmed that colon cancer cells can make calcitriol but noted that ability may be lost as the cancer progresses or in highly aggressive, poorly-differentiated tumors. Furthermore, they warned that one of the metabolites of calcitriol is increased in poorly-differentiated tumors and that the metabolite may be stimulating tumor growth. Biochem Biophys Res Commun. 2001 Jul 27;285(4):1012–7.

First Study Performed Using Humans

In 2002, researchers at St. Luke's-Roosevelt Hospital in New York were the first to administer vitamin D to humans to see if it reduced precancerous cellular changes in the colon. Rectal biopsies were performed before and after the administration of vitamin D and calcium. One group got only calcium, the second group got calcium and vitamin D (only 800 units) and the third group took calcitriol twice a day. The researchers found no improvement between groups, but, much to their surprise, they found strong correlations between calcidiol blood levels and precancerous lesions. As blood calcidiol levels increased, precancerous cellular changes decreased, especially when combined with calcium. The fewest precancerous changes were in a patient with a calcidiol level of 60 ng/mL. Cancer Epidemiol Biomarkers Prev. 2002 Jan;11(1):113–9.

In 2002, researchers from the University of Helsinki showed that soy extracts significantly increase the production of calcitriol in mouse colon both by increasing its production and by decreasing its degradation. This discovery explained the well-known fact that populations that consume high amounts of soy products have lower cancer rates. J Nutr. 2002 Nov;132(11 Suppl):3490S–3493S.

Later in 2002, researchers from the National Cancer Institute confirmed the Garland brothers' finding from 20 years earlier. Sun exposure significantly reduced one's risk of dying from colon cancer. Occup Environ Med. 2002 Apr;59(4):257–62.

Vitamin D and Calcium Work Together

In 2003, researchers at Dartmouth confirmed that deficiencies of both vitamin D and calcium were involved in the reoccurrence of colon polyps, a condition known to lead to colon cancer. It turns out both calcium and vitamin D work together to prevent colon cancer. J Natl Cancer Inst. 2003 Dec 3;95(23):1765–71.

More Vitamin D Benefits To Learn

Since then numerous studies on the protective effects of vitamin D in regards to several different cancers, including colon cancer, have been successful in demonstrating that

vitamin D3 is indeed a viable weapon in the fight against cancer. There is still so much we have yet to discover about vitamin D, we anticipate even more good news to come.

Vitamin D and Prostate Cancer

Prostate cancer kills 31,000 American men every year, the second leading cause of cancer deaths among men. This year, more than 220,000 American men will be diagnosed with the disease, making prostate cancer the leading cancer among men. Early diagnosis is important as surgery can be curative. After the cancer has spread, especially to bone, treatment options are more limited. Castration, usually chemical, will delay the cancer from spreading for several years, but then the treatment options are quite limited.

Many experts will tell you that vitamin D should not be taken for prostate cancer until well-controlled scientific studies prove it helps. The problem with that approach is two-fold. First, you may die waiting for the studies to be conducted and two, it misses the point. The point is this: men with prostate cancer should not allow themselves to be vitamin D deficient and neither should their doctors.

If you have prostate cancer, please remember that we still have a lot to learn about vitamin D and it should not be considered as the main treatment for your cancer. Your oncologist will prescribe treatment that has proven efficacy and you should carefully follow their advice as the mainstay of treatment. At the same time, you should know that evidence suggests that the proper amount of vitamin D3 may help you in your fight against prostate cancer.

Vitamin D In the Fight Against Prostate Cancer

Let us look at selected studies from the scientific literature to see what clues exist about the role vitamin D may play in preventing and treating prostate cancer.

In 1990, Schwartz proposed that vitamin D deficiency may underlie the major risk factors for prostate cancer including age, black race, and northern latitudes. He pointed out that all these factors are associated with decreased synthesis of vitamin D. Mortality rates from prostate cancer in the U.S. are inversely correlated with ultraviolet radiation, the principal source of vitamin D. Schwartz GG, Hulka BSIs vitamin D deficiency a risk factor for prostate cancer? (Hypothesis).Anticancer Res. 1990 Sep–Oct;10(5A):1307–11.

Sunlight and Vitamin D

In 1992, Hanchette and Schwartz again proposed that sunlight and vitamin D may play a role in prostate cancer. They pointed out that men in the United States were ten times more likely to develop prostate cancer than men in Japan, where men consume higher amounts of vitamin D due to their consumption of fatty fish.

Although the authors did not mention it, Japanese men also consume soy, which inhibits the breakdown of calcitriol (activated vitamin D) in the tissues. Furthermore, traditional Japanese men consume higher quantities of omega-3 fatty acids than their American counterparts. These fats are now known to dissociate vitamin D metabolites from their binding protein, thus raising active levels of those metabolites in the blood.

To support their hypothesis, Hanchette and Schwartz analyzed American prostate cancer deaths in relation to sunlight and discovered a 0.0001 negative correlation—what is a very significant association. That is, they found that men who received more sunlight were less likely to die from prostate cancer. Hanchette CL, Schwartz GGGeographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation.Cancer. 1992 Dec 15;70(12):2861–9.

In the same year, Schwartz discovered that death rates from prostate cancer were correlated with death rates from multiple sclerosis, another disease know to be associated with lack of sunlight. Again, he proposed that lack of vitamin D may a causative factor in both diseases. Schwartz GGMultiple sclerosis and prostate cancer: what do their similar geographies suggest?Neuroepidemiology. 1992;11(4–6):244–54.

In 1993, Skowronski and colleagues discovered that all three of the prostate cancer cell lines they studied possessed a vitamin D receptor and that the active form of vitamin D, calcitriol, "dramatically inhibited" the growth of two of the three cell lines. Skowronski RJ, Peehl DM, Feldman DVitamin D and prostate cancer: 1,25 dihydroxyvitamin D3 receptors and actions in human prostate cancer cell lines.Endocrinology. 1993 May;132(5):1952–60.

Calcitriol

Over the next several years, four studies appeared to disprove the vitamin D hypothesis. In each case, various metabolites of vitamin D were drawn on large numbers of men who were then followed over many years to see which men developed prostate cancer. Although some of the studies found that activated vitamin D (calcitriol) levels in the blood protected against colon cancer, none of the studies showed that low calcidiol levels (25-hydroxyvitamin D) were associated with risk of developing prostate cancer. Schwartz's hypothesis appeared to be disproved. Corder EH, Guess HA, Hulka BS, Friedman GD, Sadler M, Vollmer RT, Lobaugh B, Drezner MK, Vogelman JH, Orentreich NVitamin D and prostate cancer: a prediagnostic study with stored sera.Cancer Epidemiol Biomarkers Prev. 1993 Sep–Oct;2(5):467–72. Braun MM, Helzlsouer KJ, Hollis BW, Comstock GWProstate cancer and prediagnostic levels of serum vitamin D metabolites (Maryland, United States)Cancer Causes Control. 1995 May;6(3):235–9. Gann PH, Ma J, Hennekens CH, Hollis BW, Haddad JG, Stampfer MJCirculating vitamin D metabolites in relation to subsequent development of prostate cancer.Cancer Epidemiol Biomarkers Prev. 1996 Feb;5(2):121–6. Nomura AM, Stemmermann GN, Lee J,

Kolonel LN, Chen TC, Turner A, Holick MFSerum vitamin D metabolite levels and the subsequent development of prostate cancer (Hawaii, United States)Cancer Causes Control. 1998 Aug;9(4):425–32.

However, in 1995 Miller and colleagues expanded their earlier work and examined seven prostate cancer cell lines. They found all seven lines had receptors for vitamin D. They also showed that activated vitamin D (calcitriol) inhibited the growth of four of seven prostatic carcinoma cell lines and found that the more vitamin D receptors, the greater the inhibition. Furthermore, they found that the enzyme that breaks down calcitriol in the tissues (24-hydoxylase) reduced that inhibition. That is, the more 24-hydroxylase, the less the cancer cells were inhibited by activated vitamin D. Not only did this mean that activated vitamin D may retard prostate cancer growth, it suggested that substances which interfere with 24-hydroxylase may also prove useful in treating prostate cancer. Miller GJ, Stapleton GE, Hedlund TE, Moffat KAVitamin D receptor expression, 24-hydroxylase activity, and inhibition of growth by 1alpha,25-dihydroxyvitamin D3 in seven human prostatic carcinoma cell lines.Clin Cancer Res. 1995 Sep;1(9):997–1003.

Vitamin D Acknowledged

Later in 1995, Feldman and colleagues at Stanford University confirmed Miller's findings and stated, "Based on these findings, we postulate that vitamin D may have protective actions on the development and/or progression of prostate cancer...We further hypothesize that vitamin D supplementation may have beneficial effects on retarding the development and/or progression of prostate cancer." For the first time, cancer researchers at a major university seemed to be saying that evidence existed that cholecalciferol (plain vitamin D3) may be useful in preventing and treating prostate cancer. Feldman D, Skowronski RJ, Peehl DMVitamin D and prostate cancer.Adv Exp Med Biol. 1995;375:53–63.

Cholecalciferol

In 1998, Gross and colleagues at Stanford conducted the first clinical trial of a vitamin D metabolite in treating advanced prostate cancer. However, instead of raising the tissue levels of activated vitamin D (calcitriol) by supplementing with oral vitamin D (cholecalciferol), they chose to give calcitriol itself. In spite of circumventing the natural system to raise prostate calcitriol levels, they found calcitriol decreased the rate of progression of PSA blood levels (a test of prostate cancer's progression) in 6 of the 7 patients. Elevations in blood calcium levels (hypercalcemia) seriously limited the use of calcitriol and the cancer eventually progressed. (No one knows what would have happened to those seven men if they had been given equipotent doses of vitamin D3 cholecalciferol. Cholecalciferol has to be given in massive doses (40,000 units) over an extended period of time (months) to cause significant hypercalcemia. In addition, the tissue production of calcitriol is not rate limited, suggesting that oral cholecalciferol is effective in raising tissue levels of

calcitriol. Gross C, Stamey T, Hancock S, Feldman DTreatment of early recurrent prostate cancer with 1,25-dihydroxyvitamin D3 (calcitriol)J Urol. 1998 Jun;159(6):2035–9.

Calcidiol

In 1998, Schwartz, the same scientist who had first postulated that vitamin D deficiency played a role in prostate cancer, confirmed that prostate cells, including most prostate cancer cell lines, were able to activate vitamin D. Schwartz and his colleagues concluded that "these data suggest a potential role for 25(OH)D (*calcidiol*) in the chemoprevention of invasive prostate cancer." As the easiest way to raise calcidiol is through oral supplementation with vitamin D3, this meant scientists at another major American medical school were suggesting that plain, inexpensive, non-prescription vitamin D may help prostate cancer. Schwartz GG, Whitlatch LW, Chen TC, Lokeshwar BL, Holick MFHuman prostate cells synthesize 1,25-dihydroxyvitamin D3 from 25-hydroxyvitamin D3.Cancer Epidemiol Biomarkers Prev. 1998 May;7(5):391–5.

In the year 2000, Ahonen and colleagues conducted a careful study of calcidiol levels in young men and followed them for the development of prostate cancer. Unlike earlier studies, he found a relationship between low vitamin D blood levels and prostate cancer. Ahonen found young men with calcidiol levels below 40 nmol/L (16 ng/mL) were three times more likely to develop prostate cancer than were men with higher levels.

Just as important, he found these men were six times more likely to develop invasive cancers. This finding implied a treatment effect for vitamin D as the prevention of invasiveness is a key goal of treatment. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa PProstate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland).Cancer Causes Control. 2000 Oct;11(9):847–52.

Later in 2000, Barreto and colleagues at Wake Forest University School of Medicine were the first see if calcidiol inhibited prostate cell growth. They found that calcidiol was just as effective as calcitriol in inhibiting growth. The concluded that their findings "support the use of 25(OH)D as a chemotherapeutic agent in the treatment of prostate cancer." As oral cholecalciferol is the best way to raise calcidiol levels, it became clear that another group of cancer researchers at a major university medical center was calling for the use of vitamin D in prostate cancer. Barreto AM, Schwartz GG, Woodruff R, Cramer SD25-Hydroxyvitamin D3, the prohormone of 1,25-dihydroxyvitamin D3, inhibits the proliferation of primary prostatic epithelial cells.Cancer Epidemiol Biomarkers Prev. 2000 Mar;9(3):265–70.

Chen and colleagues at Boston University School of Medicine then demonstrated that calcidiol was just as effective as calcitriol in inhibiting growth of prostate cancer cell lines in the test tube. They also found that a vitamin D analogue already

on the market, one known to cause less hypercalcemia than other analogues (patentable modifications of calcitriol), was also effective in inhibiting cancer growth. However, their findings about calcidiol again emphasized that readily available vitamin D should help fight prostate cancer. In fact, the authors concluded calcidiol might be a good candidate for "human trials in prostate cancer." Now four different groups of scientists, from four major university medical centers, were calling for the use of vitamin D in prostate cancer. Chen TC, Schwartz GG, Burnstein KL, Lokeshwar BL, Holick MFThe in vitro evaluation of 25-hydroxyvitamin D3 and 19-nor-1alpha,25-dihydroxyvitamin D2 as therapeutic agents for prostate cancer.Clin Cancer Res. 2000 Mar;6(3):901–8.

Sun Exposure, Skin Type, and Reduced Risk

In 2001, Luscombe and colleagues at the School of Medicine in North Straffordshire Hospital in England published three studies linking ultraviolet exposure and skin type to the development of prostate cancer. They found that cumulative outdoor exposure, outdoor occupations and skin type was associated with reduced risk of advanced stage tumors. They also found that childhood sunburns dramatically reduced the risk of developing prostate cancer, probably because those with fair skin are more likely to burn but also find it easier to make vitamin D in their skin. Furthermore, they found that people who have difficulty making the skin pigment melanin (a natural sun screen) are much less likely to develop prostate cancer. Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, Fryer AA, Strange RCProstate cancer risk: associations with ultraviolet radiation, tyrosinase and melanocortin-1 receptor genotypes.Br J Cancer. 2001 Nov 16;85(10):1504–9. Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, Fryer AA, Strange RCOutcome in prostate cancer associations with skin type and polymorphism in pigmentation-related genes.Carcinogenesis. 2001 Sep;22(9):1343–7. Luscombe CJ, Fryer AA, French ME, Liu S, Saxby MF, Jones PW, Strange RCExposure to ultraviolet radiation: association with susceptibility and age at presentation with prostate cancer.Lancet. 2001 Aug 25;358(9282):641–2.

In addition, in 2001 Zhao and Feldman at Stanford University studied the one prostate cancer cell line, *DU 145*, that does not respond to calcitriol. They found this cell line, which is poorly differentiated and derived from brain metastasis, can be made to respond to calcitriol by adding drugs which inhibit the breakdown of calcitriol. This raised the possibility that prostate cancers which did not respond to vitamin D could be made responsive by the addition of a metabolic inhibitor. Farhan and colleagues at the University of Vienna Medical School soon showed that the isoflavonoid found in soybeans, called genistein, is a powerful metabolic inhibitor of the enzyme that breaks down calcitriol. Zhao XY, Feldman DThe role of vitamin D in prostate cancer.Steroids. 2001 Mar–May;66(3–5):293–300. Farhan H, Wahala K, Adlercreutz H, Cross HSIsoflavonoids inhibit catabolism of vitamin D in prostate cancer cells.J Chromatogr B Analyt Technol Biomed Life Sci. 2002 Sep 25;777(1–2):261–8.

In 2003, Chen and Holick at Boston University School of Medicine reiterated their call for the use of vitamin D in prostate cancer. After reviewing most of the research on the subject, the authors concluded, "adequate exposure to sunlight or oral supplementation might provide a simple way to increase synthesis of calcitriol in the prostate and, therefore, decrease the risk of prostate cancer." They added, "adequate vitamin D nutrition should be maintained, not only for bone health in men and women, but because it might decrease the risk of prostate cancer and mitigate metastatic disease should it develop." Chen TC, Holick MFVitamin D and prostate cancer prevention and treatment.Trends Endocrinol Metab. 2003 Nov;14(9):423–30.

In 2003, Bodiwala and colleagues in England studied sun exposure and skin type and again found that men who sunbathed or otherwise exposed themselves to sunlight were less likely to develop prostate cancer. They also identified men with various combinations of skin type and reduced sun exposure, which were up to 13 times more likely to develop prostate cancer. Bodiwala D, Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, Fryer AA, Strange RCAssociations between prostate cancer susceptibility and parameters of exposure to ultraviolet radiation.Cancer Lett. 2003 Oct 28;200(2):141–8. Bodiwala D, Luscombe CJ, French ME, Liu S, Saxby MF, Jones PW, Ramachandran S, Fryer AA, Strange RCSusceptibility to prostate cancer: studies on interactions between UVR exposure and skin type.Carcinogenesis. 2003 Apr;24(4):711–7. Bodiwala D, Luscombe CJ, Liu S, Saxby M, French M, Jones PW, Fryer AA, Strange RCProstate cancer risk and exposure to ultraviolet radiation: further support for the protective effect of sunlight.Cancer Lett. 2003 Mar 31;192(2):145–9.

Also in 2003, Beer and colleagues at the Oregon Health and Science University again tested calcitriol as a treatment for prostate cancer. They found a significant reduction in the rate of increase in PSA, a marker of the cancer's growth, although no patient achieved the hoped for 50% reduction. Unfortunately, none of the patients received oral vitamin D supplementation, which would have been more effective in raising prostate calcitriol levels. In fact, none of the patients were even tested or treated for vitamin D deficiency. Beer TM, Lemmon D, Lowe BA, Henner WDHigh-dose weekly oral calcitriol in patients with a rising PSA after prostatectomy or radiation for prostate carcinoma.Cancer. 2003 Mar 1;97(5):1217–24.

Calcitriol Breakdown Reduced by Soy Isoflavonoids

In 2003, two studies from at the University of Vienna Medical School confirmed that the isoflavonoids in soy dramatically reduce the breakdown of calcitriol in prostate cancer cells. In fact, they found that such products profoundly inhibit the enzyme that metabolizes calcitriol, reducing its activity to almost zero. This again raised the possibility that such compounds could be combined with vitamin D to treat prostate cancer. Cross HS, Kallay E, Farhan H, Weiland T, Manhardt TRegulation of extrarenal vitamin D metabolism as a tool for colon and prostate cancer

prevention.Recent Results Cancer Res. 2003;164:413–25. Farhan H, Wahala K, Cross HSGenistein inhibits vitamin D hydroxylases CYP24 and CYP27B1 expression in prostate cells.J Steroid Biochem Mol Biol. 2003 Mar;84(4):423–9. Cross HS, Kallay E, Lechner D, Gerdenitsch W, Adlercreutz H, Armbrecht HJPhytoestrogens and vitamin D metabolism: a new concept for the prevention and therapy of colorectal, prostate, and mammary carcinomas.J Nutr. 2004 May;134(5):1207S–1212S.

Three studies in 2004 examined the association between vitamin D levels and prostate cancer. Two of the studies found no association between vitamin D levels and the subsequent risk of developing prostate cancer. A third study, from Finland, actually raised the possibility that both low and high vitamin D levels are associated with prostate cancer.

Tissue Calcidiol Levels

Careful analysis of the Finnish paper revealed 57 of the 67 men with high vitamin D blood levels who subsequently developed prostate cancer were from Norway. In Norway, increased consumption of vitamin A (associated with increased risk of prostate cancer) through cod liver oil is common.

In addition, in a letter to the editor, Reinhold Vieth proposed that that the Finnish finding was best explained by annual variations in calcidiol levels causing low tissue calcitriol levels. In their response to Vieth, the authors accepted his explanation as the probable cause for their findings and also proposed that tissue calcidiol levels, not just tissue calcitriol levels, may be protective. Jacobs ET, Giuliano AR, Martinez ME, Hollis BW, Reid ME, Marshall JRPlasma levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and the risk of prostate cancer.J Steroid Biochem Mol Biol. 2004 May;89–90(1–5):533–7. Platz EA, Leitzmann MF, Hollis BW, Willett WC, Giovannucci EPlasma 1,25-dihydroxy- and 25-hydroxyvitamin D and subsequent risk of prostate cancer.Cancer Causes Control. 2004 Apr;15(3):255–65. Tuohimaa P, Tenkanen L, Ahonen M, Lumme S, Jellum E, Hallmans G, Stattin P, Harvei S, Hakulinen T, Luostarinen T, Dillner J, Lehtinen M, Hakama MBoth high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries.Int J Cancer. 2004 Jan 1;108(1):104–8.

Vitamin D "Important" in Prevention of Deaths

Then, researchers in Norway showed that patients diagnosed with prostate cancer in the summer and fall, when vitamin D levels are the highest, have a significantly better prognosis than patients diagnosed in the winter or spring. The authors concluded that their "study supports the hypothesis that vitamin D may influence cancer specific mortality in a beneficial way. A possible mechanism to explain our results might be a combined action of vitamin D and cancer treatment that amplifies the treatment effect. It confirmed, in addition to traditional cancer treatment,

vitamin D would be of particular importance in the primary prevention of deaths from cancer." Robsahm TE, Tretli S, Dahlback A, Moan JVitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway).Cancer Causes Control. 2004 Mar;15(2):149–58.

Calcidiol An Active Steroid Hormone

Lu and his group from Finland then demonstrated for the first time that calcidiol is an active steroid hormone in prostate cells. Up until this time, most scientists believed calcidiol was only a prehormone and had to be metabolized into calcitriol before it could regulate genes. Although much less potent than calcitriol, calcidiol is present in much higher concentrations. It now appeared calcidiol is a steroid hormone as well as calcitriol and is active in suppressing cell proliferation in prostate tissue. Lou YR, Laaksi I, Syvala H, Blauer M, Tammela TL, Ylikomi T, Tuohimaa P25-hydroxyvitamin D3 is an active hormone in human primary prostatic stromal cells.FASEB J. 2004 Feb;18(2):332–4. Epub 2003 Dec 04.

Cancer Chemoprevention With Vitamin D

Young and his group at Boston University School of Medicine then confirmed that tissue calcitriol concentrations are virtually uncontrolled. That is, the usual mechanisms that regulate blood calcitriol concentrations, calcium and parathormone, do not regulate tissue calcitriol levels in prostate cells. In fact, calcitriol did not exhibit negative feedback, and reduce its own production, until pharmacological amounts of calcitriol were introduced. The authors also pointed out that soy would further increase tissue levels and concluded their finding should "encourage the further development of nutritionally-based models for prostate cancer chemoprevention using vitamin D." Young MV, Schwartz GG, Wang L, Jamieson DP, Whitlatch LW, Flanagan JN, Lokeshwar BL, Holick MF, Chen TCThe prostate 25-hydroxyvitamin D-1 alpha-hydroxylase is not influenced by parathyroid hormone and calcium: implications for prostate cancer chemoprevention by vitamin D.Carcinogenesis. 2004 Jun;25(6):967–71. Epub 2004 Jan 16.

First Human Interventional Trial

In late 2004, Woo, Vieth and colleagues from the University of Toronto presented a groundbreaking paper at the November NIH conference on vitamin D and cancer. They showed that 2,000 units of simple vitamin D3 (cholecalciferol) either reduced or prevented further increases in PSA in the majority of men with advancing prostate cancer. For the first time, a human interventional trial indicted that simple vitamin D was effective in fighting cancer.

Still More To Discover

Since then numerous studies have revealed the powerful anti-cancer properties that vitamin D has. Many questions remain unanswered—many questions are always unanswered, that is the nature of science. But each day brings with it new answers, and vitamin D still has many secrets to reveal.

Vitamin D In Cancer Prevention and Treatment

Before reading about vitamin D and cancer, it would be helpful is one was familiar with the different forms of vitamin D, namely cholecalciferol, calcidiol, and calcitriol.

Cholecalciferol

vitamin D3

> Cholecalciferol is the naturally occurring form of vitamin D. It is the substance made in large quantities in your skin when sunlight strikes your bare skin. It can also be taken as a supplement. Cholecalciferol is vitamin D. All other compounds are either metabolic products or chemical modifications.

Calcidiol

25(OH)D or 25D

> Calcidiol (25-hydroxyvitamin D) is a prehormone in your blood that is directly made from cholecalciferol. When being tested for vitamin D deficiency, calcidiol is the only blood test that should be drawn. When someone refers to vitamin D blood levels, they are usually referring to calcidiol levels. Your doctor can order calcidiol levels but both your doctor and the lab will know the calcidiol blood test as 25-hydroxyvitamin D.

Calcitriol

1,25(OH)2D3 or 1,25D3

> Calcitriol (1,25-dihydroxyvitamin D) is made from calcidiol in the kidneys and in tissues and is the most potent steroid hormone derived from cholecalciferol. In fact, it is the most potent steroid hormone in the human body. It is sometimes referred to as the active form of vitamin D. Calcitriol levels should never be used to determine if you are deficient in vitamin D.

The Vitamin D and Cancer Connection

The earliest modern connection to cancer and vitamin D was due to an interesting observation that was made sometime in the 1930s. The observation was that people who spent years in the sun (and subsequently developed a relatively benign form of skin cancer called squamous cell skin cancer) were less likely to develop deadly internal

cancers, such as colon, breast and prostate cancer. This led to one of the first modern theories of cancer, namely that squamous cell skin cancer conferred immunity against more deadly forms of cancer.

The immunization theory turned out to be false but the observation that associated more skin cancers with less internal cancers held. How could the sun cause nonmelanoma skin cancers (which kill about 1,500 Americans a year) but prevent more serious cancers (which kill hundreds of thousands of Americans every year)?

It wasn't until the late 1980s that the Garland brothers, now epidemiologists at the University of California at San Diego, discovered the answer. First they discovered that sunlight reduced your risk of colon cancer. Next they discovered that women exposed to sunlight were one-half as likely to die from breast cancer as were women who spent less time in the sun. Then a researcher named Gary Schwartz discovered the same thing about prostate cancer. Both groups of researchers thought vitamin D was the likely explanation.

Then, the Garlands discovered that low calcidiol levels were strongly correlated with developing colon cancer. That would explain the earlier observation that squamous cell skin cancer lowered one's risk of serious internal cancers. Those who developed skin cancer had spent a lot of time in the sun and thus developed both squamous cell skin cancer and high calcidiol blood levels.

The Perfect Anti-cancer Drug

Research scientists in the 1980s had already discovered that calcitriol had profound anti-cancer effects, both in the test tube and in animals. It not only reduced the unregulated growth of cancer cells by promoting normal cell death (apoptosis); vitamin D prevented new cells from becoming cancerous (promoted differentiation). It even helped prevent cancer cells from spreading (metastasis) and inhibited cancer cells from developing new blood supply (angiogenesis). In short, calcitriol seemed like the perfect anti-cancer drug.

However, for many years scientists believed only one form of vitamin D, calcitriol was important in cancer. As calcitriol is the most active form of vitamin D, the scientists just assumed it was the only form to study. They seemed to be unaware that the Garland's discoveries implied that calcidiol, the storage from of vitamin D in the body, was also important in cancer.

Medical Industry Ignores Vitamin D's Promise

Somewhere along the line, the vitamin D and cancer story took a tragic twist. As vitamin D could not be patented, it held little interest for the medical industry. Plain vitamin D3 held no promise for financial gain for drug companies or for the researchers who are often financially involved in such companies. Therefore, the medical industry

seemed to ignore the evidence that simple vitamin D helped prevent cancer and that adequate vitamin D nutrition may help retard the growth of cancer.

Nor did the cancer scientists seem realize that vitamin D takes at least two pathways in the body. One path, called the *endocrine* function, produces calcitriol in the kidney to help maintain blood calcium levels. The second pathway, called the *autocrine* and the *paracrine* functions of vitamin D, produces calcitriol in the tissues. The tissue pathway is more important than the endocrine function as far as cancer is concerned. Scientists failed to realize that the easiest way to raise tissue calcitriol levels is to raise blood calcidiol levels. Furthermore, the easiest way to raise blood calcidiol levels is to go into the sun, use a sunlamp, or take the correct amount of vitamin D by supplementation.

Vitamin D Analogs Developed Instead

Instead, the medical industry turned their attention to developing chemical modifications of the most active form of vitamin D, calcitriol. Called vitamin D analogs, these drugs held the promise for a tremendous profit if studies showed they were active against cancer. Although good reasons existed to support clinical trials with plain, natural vitamin D in cancer patients, the medical industry concentrated on developing vitamin D analogs instead. To date, more than 2000 such analogs have been developed and some have been tested on cancer patients. The results have been disappointing because the drugs cause high blood calcium via the endocrine function of vitamin D.

The possibility that such analogs may help cancer patients should not be discounted. However, development of the analogs bypassed a crucial and ethical medical question: Does plain vitamin D3 help cancer patients? The medical industry was not interested in the answer to this question and instead concentrated on forming numerous companies to exploit the potential anti-cancer properties of vitamin D analogs.

Analog Researchers and Ethics in Medicine

Now, let's take a closer look at how the vitamin D analogs are studied because those studies raise important scientific, ethical, and legal questions. Analog researchers, who often own stock in the company developing the analog, select two groups of patients, a control group and a treatment group. However, neither group is tested or treated for vitamin D deficiency. In fact, the patients are neither informed about the possible anti-cancer effects of simple vitamin D nor informed they will not be tested for vitamin D deficiency. Current research indicates that the vast majority of these cancer patients (both treatment and control groups) are likely to be vitamin D deficient.

The researcher then gives the treatment group the vitamin D analog and the control group gets a sugar pill. Most vitamin D analog studies have not shown any benefit, or they showed only slight improvement, in the treatment groups. However, as both the treatment and control groups are usually advanced cancer patients, both groups usually end up dying without ever being tested or treated for routine vitamin D deficiency.

Some analog researchers point out that some cancer cells lose the ability to activate vitamin D (transform vitamin D into calcitriol) and thus it makes no sense to study plain vitamin D. However, these researchers forget that the majority of cancer cells retain the ability to activate vitamin D and that calcitriol's anti-cancer activity is paracrine as well as autocrine. They also don't realize that the only reasonable, scientific, vitamin D analog question is: Do the vitamin D analogs add anything to the treatment of cancer patients who are vitamin D replete?

The only scientific and ethical way to study the effect of vitamin D analogs in cancer patients is to first treat both the control and the treatment groups with enough vitamin D until their blood tests show they are no longer vitamin D deficient. Then give the analog to the treatment group and the sugar pill to the control group. That way, any additive effect of the analog over simple vitamin D will be clear.

The failure to conduct these studies lied at the feet of the medical industry as well as those of the *National Institutes of Health*. The NIH receives billions of dollars of taxpayer money to study such questions and is not supposed to be influenced by profit.

Fortunately, numerous studies are now being performed on the anti-cancer properties of both natural vitamin D3 and vitamin D analogs. Vitamin D3 is showing more and more promise with each new study—and not only for cancer, but for numerous other health disorders as well.