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**Ultraviolet B exposure, Vitamin D, and Risk of Cancer**

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The evidence that ultraviolet-B (UVB) exposure through production of vitamin D reduces risk of many types of cancer and prolongs survival after diagnosis is now overwhelming. (Solar UVB radiation is from 290 to 315 nm.) The UVB-vitamin D-cancer hypothesis was first proposed by the brothers Cedric and Frank Garland after they saw the map of colon cancer mortality rate in the U.S. by county for the period 1950-69 as prepared by the National Cancer Institute [Mason et al., 1975]. Colon cancer had the strongest indication of a pronounced geographical variation in mortality rate of all the cancers studied: the lowest rates were in Arizona, southern California, and New Mexico while the highest rates were in the New England states. They were beginning graduate students in Johns Hopkins School of Public Health and had just driven from San Diego to Baltimore to begin their studies. They knew it was very sunny in the southwest, but more cloudy and hazy in the northeast. They also reasoned that since vitamin D production was the most important physiological effect of solar radiation, vitamin D must be what actually reduced the risk of cancer. They wrote up their hypothesis and spent six years trying to get it published and finally succeeded in getting it accepted by a journal published in the United Kingdom [Garland and Garland, 1980]. They subsequently showed that breast [Garland et al., 1990] and ovarian cancer [Lefkowitz and Garland, 1994] had similar relations with solar UVB doses. This type of study is called an ecological study.

They also did studies to show that dietary vitamin D and calcium reduced the risk of colon cancer [Garland et al., 1985] and that higher serum 25-hydroxyvitamin D [25(OH)D] concentrations were associated with reduced risk of developing colon cancer [Garland et al., 1989].

When the updated cancer mortality rate maps were published in 1999 [Devesa et al., 1999], I began my study of the UVB-vitamin D-cancer hypothesis. The maps now had ten rather than five shade of color, used larger numbers of cancer deaths, and showed death rates by both counties and state economic areas (SEAs) (aggregations of counties). In the new Atlas, 15 types of cancer had the distinctive pattern of low rates in the southwest and high rates in the northeast. I worked at NASA at the time, and happened to find the map of solar UVB doses at the surface of the U.S. for July 1992 in a Scientific American paper [Leffel and Brash, 1996]. The determinations were made using data from the Tropospheric Ozone Mapping Spectrometer (TOMS). (see, also, the map at this website). I determined the values of UVB for each SEAs and did statistical correlations between those values and the cancer mortality rates by SEA. I submitted the manuscript to the journal Cancer and it was quickly accepted [Grant, 2002]. However, after publication, people began to want to see all states included (I omitted three states along the U.S.-Mexico border due to high rates of stomach and some other cancers due to the high Mexican-Hispanic population there) as well as other cancer risk-modifying factors included. I changed to the data averaged by state and included alcohol consumption, Hispanic heritage, lung cancer as an index of smoking (and diet), poverty status, and urban/rural residence. I submitted various versions of the manuscript to nine major medical journals, each of which reviewed the manuscript but rejected it. Finally, with Cedric Garland as a coauthor, the manuscript was accepted as a German conference proceedings paper in a journal published in Greece and [Grant and Garland, 2006]. Prof. Meis Moukayed and I published a review of ecological studies of UVB and cancer in 2013 [Moukayed and Grant, 2013].

As scientifically useful as ecological studies are, they are not used to set health policy, especially when they show that UVB is involved, given the current fear of UV exposure promoted by dermatologists and sunscreen companies.

The next type of study that was widely used to determine whether vitamin D reduces risk of cancer and increases survival is called observational. Generally people are enrolled in a cohort study and have blood drawn at the time of enrollment. Those that develop cancer or some other disease as well as an equal number of those without (controls) have their serum 25(OH)D concentration determined from that blood, and statistical analyses are conducted to see how incidence or survival varies with respect to concentration. However, there is a problem: 25(OH)D concentration varies with time due to seasonal variations in solar UVB doses, changes in supplement use or diet, or advancing age (vitamin D production rates decrease for the elderly). Thus, the longer the follow-up time, the lower the chance of finding that higher 25(OH)D concentration is associated with lower risk of cancer. Thus, I proposed using case-control studies where blood is drawn at the time of cancer diagnosis [Grant, 2011],[Grant, 2015]. Many researchers think that having cancer can affect 25(OH)D concentrations so that case-control studies might not give valid results. I pointed out that breast cancer develops very rapidly so that it is important to use case-control studies, and that 11 studies from seven countries give the same 25(OH)D concentration-breast cancer incidence relationship.

Observational studies have also found better cancer survival for those with many types of cancer [Grant and Peiris, 2012], [Tretli et al., 2012].

Of course observational studies do not satisfy health officials either. They want clinical trials of vitamin D in the form of randomized controlled trials, just like for pharmaceutical drugs. Such trials are required in order to show that the agent has a beneficial effect and does not cause harm. Such trials generally go through three states, pilot, efficacy, and lack of harm. Such trials have two basic assumptions: 1, that the trial is the only source of the agent; and 2, there is a linear dose-response relationship. Of course, neither assumption is satisfied for vitamin D trials. There are large personal variations in change of 25(OH)D with respect to vitamin D dose [Garland et al., 2011] and non-linear relationships between 25(OH)D concentration and health outcome [Grant and Boucher, 2017]. In addition, many vitamin D trials to date have involved people with average or above average 25(OH)D concentrations who were given modest amounts of vitamin D. Thus, it should not be surprising that only three vitamin D clinical trials to date have found reductions in cancer incidence. The first was a trial involving postmenopausal women in Nebraska participating in a study of vitamin D3 and calcium for the prevention of osteoporosis. They were given 1000 IU/d vitamin D3 plus 1450 mg/d calcium, 1450 mg/d calcium, or a placebo. Those taking just calcium had reduced risk of all-cancer incidence, but it was not statistically significant. However, those taking vitamin D3 plus calcium did have a significantly reduced risk of cancer [Lappe et al., 2007].

The second trial was the Women's Health Initiative (WHI). Women took 400 IU/d vitamin D3 plus 1500 mg/d calcium or placebo. "In the WHI CaD, interactions between the use of either personal calcium or vitamin D supplements and CaD were found for total, breast, and colorectal cancers but not for fracture or mortality. In 15,646 women (43%) who were not taking personal calcium or vitamin D supplements at randomization, CaD significantly decreased the risk of total, breast, and invasive breast cancers by 14-20% and nonsignificantly reduced the risk of colorectal cancer by 17%. In women taking personal calcium or vitamin D supplements, CaD did not alter cancer risk (HR: 1.06-1.26)." [Bolland et al., 2011].

The most recent clinical trial was again conducted in Nebraska [Lappe et al., 2017].. There were 1156 women in the treatment group and 1147 in the control group. Nearly all of the women were white and the mean age was 65 yrs. The mean body mass index was 30, and baseline 25(OH)D concentration was near 33 ng/ml. Those in the treatment arm were given 2000 IU/d vitamin D3 plus 1500 mg/d calcium while those in the control arm were given a placebo. The mean 25(OH)D concentration for those in the treatment arm rose to 44 ng/ml. During the four years of the trial, 45 women in the treatment arm and 64 in the placebo arm developed cancer. Unfortunately, that was one more cancer case than permitted for the results to be considered significant, i.e., the P value was just over 0.05 at 0.06. However, those with 25(OH)D concentrations over 45 ng/ml had significantly reduced risk of developing cancer as shown in the online supplement to the published paper. JAMA did not let them state that in the published paper since it had not been specified as an outcome in the trial protocol. In a subsequent analysis, it was shown that the results of this trial were very nearly as expected based on the likely 25(OH)D concentration distribution among the participants, the vitamin D dose, and the number of participant-years involved [Grant and Boucher, 2017]. This analysis was followed by a second paper suggesting that vitamin D clinical trials be based on measurements of 25(OH)D concentrations, not vitamin D dose [Grant et al., 2017].

Further support for the role of vitamin D in reducing risk of cancer incidence and death comes from studies of the mechanisms. The mechanisms include those related to cellular differentiation, proliferation and apoptosis as well as angiogenesis around tumors and metastasis [Ma et al., 2016], [Moukayed and Grant, 2013], [Moukayed and Grant, 2017].

Some of my recent reviews on the UVB-vitamin D-cancer hypothesis: [Grant, 2016], [Grant et al., 2016], [Grant, in press].

In summary, UVB exposure and vitamin D can greatly reduce the risk of cancer incidence and death. For optimal protection, serum 25(OH)D concentrations should be above 40-50 ng/ml (100-125 nmol/l). To reach these levels could take 2000 to 5000 IU/d vitamin D3. The only caveat is for prostate cancer, for which both low and high 25(OH)D concentrations have been found associated with increased risk [Grant et al., 2016]. The mechanism for that finding is not known, but may be related to calcium effects since calcium is a risk factor for prostate cancer [Skrajnowska et al., 2017] and vitamin D increases calcium absorption from food and supplements.

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Note: Abstracts of most of these publications can be found through searching pubmed.gov with the title. If the publication is freely available, the URL where it can be found is given. If not freely available, the paper may be available from the author. Email addresses of the authors are generally given at pubmed.gov

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