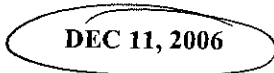


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Beneficial Effects of Sun Exposure on Cancer Mortality

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For more than 50 years, there has been documentation in the medical literature suggesting that regular sun exposure is associated with substantial decreases in death rates from certain cancers and a decrease in overall cancer death rates. Recent research suggests that this is a causal relationship that acts through the body's vitamin D metabolic pathways. The studies reviewed here show that (a) sunlight activation is our most effective source of vitamin D; (b) regular sunlight/vitamin D "intake" inhibits growth of breast and colon cancer cells and is associated with substantial decreases in death rates from these cancers; (c) metabolites of vitamin D have induced leukemia and lymphoma cells to differentiate, prolonged survival of leukemic mice, and produced complete and partial clinical responses in lymphoma patients having high vitamin D metabolite receptor levels in tumor tissue; (d) sunlight has a paradoxical relationship with melanoma, in that severe sunburning initiates melanoma whereas long-term regular sun exposure inhibits melanoma; (e) frequent regular sun exposure acts to cause cancers that have a 0.3% death rate with 2,000 U.S. fatalities per year and acts to prevent cancers that have death rates from 20-65% with 138,000 U.S. fatalities per year; (f) there is support in the medical literature to suggest that the 17% increase in breast cancer incidence during the 1991-1992 year may be the result of the past decade of pervasive anti-sun advisories from respected authorities, coinciding with effective sunscreen availability; and (g) trends in the epidemiological literature suggest that approximately 30,000 U.S. cancer deaths yearly would be averted by the widespread public adoption of regular, moderate sunning. Advising the public to seek regular moderate sun exposure finds good support in the scientific literature as a means of lowering cancer mortality. © 1993 Academic Press, Inc.

EARLY RESEARCH

Prior to 1950, numerous scientific studies were done on the health benefits of sunlight. Kime (1) has comprehensively reviewed the work of these early investigators.

The research relating sun exposure to cancer causation and prevention dates back to 1936, when Peller (2) noted that in those environments and occupations in which skin cancer was increased, other cancers were diminished. In 1937, Peller and Stephenson (3) showed that sailors in the U.S. Navy, who had extremely high sun exposure, had eight times the expected rate of skin cancer, but only two-fifths the expected rate of internal cancer. Based on these findings, they suggested that we deliberately expose people to skin-cancer-causing levels of sunlight or suitable artificial light. Their reasoning was that skin cancer is slow growing and easily treated and that such exposure would greatly reduce the numbers of less accessible frequently fatal internal cancers.

In 1941, Apperly (4) reported that overall cancer death rates increased with distance from the equator, and were further decreased in areas where a large percentage of the population was engaged in the sun-intensive occupation of farming. Compared with cities located between 10° and 30° latitude, cities between

30° and 40° latitude averaged 85% higher overall cancer death rates, cities between 40° and 50° latitude averaged 118% higher cancer death rates, and cities between 50° and 60° latitude averaged 150% higher cancer death rates. After reviewing his data, the author concluded: "A closer study of the action of solar radiation on the body might well reveal the nature of cancer immunity."

RECENT RESEARCH

Studies published during the past 20 years demonstrate that the link between sun exposure and cancer prevention acts through the vitamin D metabolic pathways.

Vitamin D and Sunlight

In addition to its low cost and "high patient acceptance," sunlight activation of 7-dehydrocholesterol in the skin has significant advantages as a vitamin D source compared with diet and supplementation. Webb and Hollick (5) have discussed how sunlight activation bypasses any gastrointestinal vitamin D malabsorption problem and also avoids the overdose toxicity potential present with oral vitamin D intake by the self-limiting production of D₃-inactive previtamin D₃ photoisomers. The importance of sunlight in supplying human vitamin D needs was demonstrated by Haddad and Hahn (6), who reported that even in high-latitude, often-overcast Britain, sunlight provides 70% or more of the vitamin D present in the blood of Caucasians.

Breast Cancer

Support for a biochemical relationship between sun exposure and cancer inhibition came in 1979, when Eisman *et al.* (7) of the University of Melbourne reported that a human breast cancer cell line had receptor sites for 1,25-dihydroxyvitamin D₃ (1,25-(OH)₂-D₃), the most active metabolite of vitamin D. Thereafter, this same group showed that 1,25-(OH)₂-D₃ receptors were present in the tissues of 73% of the malignant breast tumors they sampled; they also reported that pregnant and lactating rabbits have these receptors in their breast tissue, while virgin rabbits do not (8). To date, to this author's knowledge, there has been no follow-up research into the possible link between pregnancy-lactation history and vitamin D-induced breast cancer resistance. A three-part study in 1989 by Colston *et al.* (9) found that vitamin D metabolites inhibit human breast cancer tissue growth *in vitro*, and *in vivo* in rats, and that patients whose tumor tissue bore 1,25-(OH)₂-D₃ receptors had significantly longer disease-free survival than those whose tumors lacked these receptors.

The first epidemiological work on the relationship between sun exposure and breast cancer came in 1989, when Cedric and Frank Garland and Edward Gorham (10) of the University of California, San Diego, reported that breast cancer mortality in Canadian cities was predictably elevated by increased ultraviolet-screening acid haze. In 1990, this same team published a study of breast cancer rates in the western Soviet Union, where latitude differentials are dramatic (11). Although the results were complicated by a similarly dramatic disparity in socioeconomic status, there was still a very strong negative correlation between avail-

able sunlight and breast cancer incidence ($R = 0.75$, $P = 0.001$). It is noteworthy that Latvia, suffering from high latitude, industrial air, and affluence, had a three-fold higher breast cancer incidence than did poor, sunny, and agrarian Tadjikistan.

Also in 1990, the Garland-Gorham team found that women from areas of the United States with less available sunlight died 40–60% more frequently of breast cancer than women who lived in places like Honolulu and Tampa (12). The dramatic variation in breast cancer rates according to geographic area in the United States had been known for some time, but had previously gone unexplained (13). The Garland research (12) accounted for the geographic variation in breast cancer in a way that had been previously overlooked, showing a very strong negative correlation ($R = -0.80$, $P < 0.0001$) between available sunlight and breast cancer death rates.

Colon Cancer

In 1980 Frank and Cedric Garland presented the first modern epidemiological research suggesting a direct protective effect of sunlight vitamin D on cancer (14), showing that colon cancer was decreased in areas of the United States with greater sun exposure. In 1985, further research by the Garlands showed decreased colon cancer rates with higher oral vitamin D and calcium intake in a prospective study (15). Wargovich and Lointier followed in 1987 with a report that $1,25-(OH)_2-D_3$ suppressed growth of human colon cancer cells *in vitro* (16). In 1989, the Garland brothers, joined by Edward Gorham and others, demonstrated that increased blood levels of 25-hydroxyvitamin D were associated with lower colon cancer incidence rates (17).

Breast and Colon Cancer and Acid Haze

It has been noted for many years that populous areas tend toward higher death rates from certain cancers (13), but support for any-explanations has been weak. This changed in 1989, when, as previously mentioned, the Garland-Gorham team showed that breast and colon cancer mortality rates were predictably increased in Canadian cities having higher levels of acid haze, which screens ultraviolet rays and lessens vitamin D synthesis (10). They also reported a breast and colon cancer mortality gradient in Italy that showed strong positive correlation with both acid haze and latitude levels (18).

Cancers of the Blood and Lymph Tissues

Abe *et al.* have shown that $1,25-(OH)_2-D_3$ induces differentiation in mouse (19) and human (20) myeloid leukemia cells, returning these cells to normal morphology, and prolongs the survival of mice inoculated with these tumor cells (21). Mangelsdorf *et al.* (22) have demonstrated that human myeloid leukemia cells treated with $1,25-(OH)_2-D_3$ differentiate into apparently fully functional monocytes and macrophages. Reitsma *et al.* have shown this effect to act by suppressing the *c-myc* oncogene (23) and that this suppression ceases when $1,25-(OH)_2-D_3$ enrichment is terminated (24). In testing freshly isolated specimens from 10 con-

secutive patients with acute myeloid leukemia, Ossenkoppele *et al.* (25) found that leukemic tissue from four of them would differentiate in the presence of 1,25-(OH)₂-D₃.

Provvedini *et al.* (26) reported that receptors for 1,25-(OH)₂-D₃ were present in malignant human B and T lymphocytes but not in normal resting cells of this type. Olsson *et al.* (27) showed that human histiocytic lymphoma cells differentiate in the presence of 1,25-(OH)₂-D₃. A study by Cunningham *et al.* (28) of 10 patients with non-Hodgkin's lymphoma given oral calcitriol (1,25-(OH)₂-D₃) at 1 mcg daily reported 1 partial and 2 complete clinical responses in the 3 patients of 10 treated who had measurable D₃ receptors greater than 150 fmol/g of biopsied tissue; the 7 nonresponders all had D₃ receptor measurements of less than 50 fmol/g of tissue.

Melanoma and Squamous-Basal Cancers of the Skin

The recent increases in melanoma and squamous-basal skin cancers have been used to justify advising everybody to either stay out of the sun or wear sunblock (29). However, as shown below, there is reason to believe that these recommendations are flawed.

Koh *et al.* (29) described squamous and basal cell skin cancers as most prevalent on the head-neck and forearms-hands where cumulative sun exposure is greatest, while melanoma is most prevalent on generally covered parts of the body. Boring *et al.* (30) estimated 600,000 cases and 2,000 deaths (0.3% death rate) in 1991 from squamous-basal skin cancer. Melanoma, however, has a 20% fatality rate because of its typically early metastasis, producing 6,500 U.S. deaths in 1991 from 32,000 cases (30).

The literature review and four studies that follow suggest a paradoxical relationship in which melanoma is initiated by severe sunburning, but inhibited by nonburning sun exposure. Koh *et al.* (29), in their 1990 article on sunlight and melanoma, reviewed a substantial body of research indicating a causative relationship between "blister and peel" sunburning before the age of 20 and melanoma onset later. However, a 1981 study by Colston *et al.* (31) reported that melanoma cells have receptors for 1,25-(OH)₂-D₃ and that this vitamin D metabolite slows the doubling time of melanoma cells *in vitro*. Also, in 1987, Eisman *et al.* (32) demonstrated growth suppression of melanoma cells in a laboratory environment using 1,25-(OH)₂-D₃. Consistent with the findings of Colston (31) and Eisman (32), Vagero *et al.* (33) have shown that people who work outdoors get more total sun exposure but have a lower incidence of melanoma than office workers. Additionally, Crombie (34) observed that melanoma seldom occurs on areas of the skin that get regular sun exposure, also suggesting the preventive effect of consistent sunning.

Sun-Promoted vs Sun-Inhibited Cancers

For more than 10 years, U.S. health authorities have pervasively (35) and effectively (36, 37) advised against all sun exposure, including regular moderate exposure. Since melanoma has been shown to be inhibited by vitamin D and regular sun exposure (31-34), these advisories against regular moderate exposure can only be correctly based on solar promotion of squamous-basal skin cancers,

which have a death rate of 0.3% and cause only 2,000 U.S. deaths yearly. In contrast, about 138,000 people in the United States die each year of cancers with death rates of 20–65% which have been shown to be inhibited by vitamin D, its metabolites, and regular sun exposure.

The epidemiological studies (3, 4, 10–12, 14, 18) show trends suggesting that widespread public adoption of routine sunbathing would result in approximately a one-third lowering of breast and colon cancer death rates, or about 32,000 fewer U.S. cancer deaths yearly. An increase in squamous–basal skin cancer would also be expected, but even a 100% increase, with 2,000 additional deaths per year, would still leave a net 30,000 fewer U.S. cancer deaths. A decrease in deaths from leukemia, lymphoma, and melanoma would also be expected (19–28), but the lack of epidemiological studies makes this prediction more difficult to quantify (Table 1).

Sunscreen Use and Cancer Rates

American Cancer Society statistics show that estimated breast cancer incidence recently increased 17% in 1 year, from 150,000 new cases in 1990 to 175,000 in 1991 (30, 38). In a search for the cause of this dramatic increase, the following must be considered: (a) previously cited research showing that decreased sun exposure causes increased breast cancer (10–12, 18); (b) research showing that the past decade of anti-sun advisories has resulted in decreased sun exposure with increased sunscreen use (35–37); (c) research linking chronic sunscreen use to decreased blood levels of 25-OH-D₃, the necessary precursor to 1,25-(OH)₂-D₃ (39); (d) research showing that decreased tissue levels of 1,25-(OH)₂-D₃ is associated with increased growth rates of breast cancer (9). From these research findings, it appears reasonable to speculate that the cause of this increase in breast cancer is that for more than a decade our population has been encouraged as never

TABLE 1
SUN-PROMOTED VS SUN-INHIBITED CANCERS

Cancer site	U.S. new cases	U.S. deaths	Deaths as % of cases
(a) Colon–rectum	157,500	60,500	38.4*
(b) Female breast	175,000	44,500	25.4*
(c) Non-Hodgkin's lymphoma	37,200	18,700	50.3*
(d) Granulocytic leukemia	11,600	7,600	65.5*
(e) Melanoma	32,000	6,500	20.3*
(f) Nonmelanoma skin cancer	>600,000	2,000	0.3*
Derived totals			
Sun-inhibited cancers (total, lines a–e)	413,300*	137,800*	33.3*
Sun-promoted cancers (total, line f)	>600,000*	2,000*	0.3*

Source: Cancer Statistics 1991, by the American Cancer Society (30).

* Values derived by calculating ACS statistics.

before to avoid sun exposure; meanwhile, because of the concurrent emergence of very effective topical sun blockers, effectively avoiding sun exposure has become very easy.

Furthermore, a substantial body of knowledge provided in a recent literature review suggests that regular sunscreen use is associated with higher risk of melanoma (40). Increased risk of basal cell cancer has been noted among women who use sunscreens (41).

Other Cancers

Manolagas, in his comprehensive 1987 article on the relevance of vitamin D to cancer, reviewed research showing 1,25-(OH)₂-D₃ receptors to be present in cell lines derived from tumors of the breast, colon, monocytic and lymphocytic leukemias, melanotic and amelanotic melanomas, lung, cervix, papillomas, and osteogenic sarcomas (42). Only with breast and colon cancer has the relationship with vitamin D and sunlight been well documented. The other cancers need substantial further research to better establish their responses to sun exposure and vitamin D.

CONCLUSIONS AND RECOMMENDATIONS

The benefits of regular sun exposure appear to outweigh substantially the risks of squamous-basal skin cancer, accelerated aging, and melanoma from burning, all of which can be mitigated. In contrast to Peller's (2, 3) and Apperly's (4) time, we may, as a result of our improved understanding, be able to use sun exposure now to dramatically lower our death rates from internal cancers and melanoma without suffering any consequent increased incidence in squamous-basal skin cancer. We are also in a position to be able to mitigate the accelerated aging and melanoma risks.

Preventing melanoma is largely a matter of preventing sunburning, especially in children and adolescents. As the melanoma research has demonstrated, the best prevention is regular exposure, thereby maintaining a protective tan and high vitamin D blood and tissue levels. This is especially important in early spring preparation for the very intense sun of early summer. Sun exposure and burning potential are dramatically affected by the altitude of the location, the sun-reflective nature of the environment, the angulation of the sun in the sky, the purity or pollution of the air, the sensitivity of the skin, and the degree to which the skin is tanned. These variables must be considered carefully. Until further guidelines are available, it is probably best to start with a few minutes a day and increase this gradually according to individual response. It must be noted that a very few individuals have abnormal skin conditions that make any sun exposure harmful.

The squamous-basal skin cancer and accelerated aging risks can be mitigated by spreading the exposure over the whole body, while selectively shading the thin, sensitive, and cancer-prone skin of the head and neck. It appears that hats should be used.

The dramatic increase in skin cancers over the past decade has been extensively discussed with regard to ozone layer depletion. However, the change in styles of

Deaths as
% of cases

- 38.4*
- 25.4*
- 50.3*
- 65.5*
- 20.3*
- 0.3*

33.3*

0.3*

dress that has resulted in the almost complete abandonment of the hat as an article of clothing for the past 30 years offers a hypothetical timeframe of carcinogenesis more in line with our knowledge of skin cancer. In view of the recent suggested link between sunscreen use and increased melanoma incidence (40), physical shading appears to be the safest way to limit sun exposure.

The research cited here demonstrates the need for regular exposure to the sun (3, 4, 10-12, 14, 18). Additionally, Webb and Holick (5) have shown that vitamin D synthesis continues for 3 days after sun exposure. Therefore it seems prudent to recommend sunbathing at least every 3-4 days, if practical. Short daily exposure, perhaps during lunch time, would appear to be the best.

Studies of the geographic distribution of cancer deaths in general (2-4) and certain cancers in particular (10-14, 18) show that sun exposure can be an ineffective source of vitamin D in the higher latitudes, colder climates, and regions of polluted air, especially during fall and winter. Personal supplementation or dietary alteration appears to be seasonally appropriate in these locales. Cross-cultural studies suggest that diet can be an effective source of vitamin D for cancer prevention and that 400-800 IU daily is an effective and relatively safe dose (42). Sun exposure, if available, eliminates the dietary risks of vitamin D toxicity and intestinal malabsorption.

The research studies presented here suggest that dermal activation of vitamin D from regular, moderate sun exposure has a strong protective effect in the prevention of breast and colon cancer; has a weaker protective effect in melanoma, leukemia, and lymphoma; and acts to lower overall cancer death rates. These studies emphasize cancers with high death rates, rather than the high-incidence, generally nonfatal dermal cancers. The combined findings of these studies suggest that advising the public to seek regular moderate solar exposure is supported by a broad view of the available scientific research as an effective means of lowering cancer mortality.

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