Vitamin D, Sunlight and Cancer Connection

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Abstract: It has been more than 100 years when it was first appreciated that increased sun exposure reduced risk of dying of cancer. The most beneficial effect of sun exposure is the production of vitamin D in the skin. Recent evidence suggests that most cells in the body not only have a vitamin D receptor but also have the capacity to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. Once formed, 1,25-dihydroxyvitamin D can inhibit cellular proliferation, induce cellular maturation, inhibit angiogenesis and ultimately cause apoptosis to prevent malignancy. A multitude of studies have associated improved vitamin D status with decreased risk for developing several deadly cancers including colon, breast, pancreatic and ovarian cancers. Patients with cancer are at high risk for vitamin D deficiency. Sensible sun exposure, vitamin D fortification and vitamin D supplementation should be encouraged to improve the vitamin D status of children and adults not only for bone health but for reducing risk of developing and dying of cancer. The goal is to achieve a blood level of 25-hydroxyvitamin D of 40-60 ng/mL. This can be accomplished by children taking 600-1000 and adults 1500-2000 international units (IU) vitamin D daily from diet and supplements along with sensible sun exposure when the sun is capable of producing vitamin D in the skin.

Keywords: Vitamin D, Sunlight, Cancer, 25-hydroxyvitamin D.

INTRODUCTION

At the turn of the last century exposure to sunlight was heralded as a method of curing skin diseases including lupus vulgaris, a disease caused by a tuberculosis infection of the skin. This resulted in Finsen receiving the Nobel Prize in 1903 [1]. In 1921 Hess and Unger reported that exposure to sunlight was an effective treatment for rickets [2]. At approximately the same time Hoffman in 1915 compared cancer mortality in cities according to latitude between 1908 and 1912 and reported that cancer mortality increased in adults living farther from the equator [3]. Peller and Stephenson [4] observed a relationship between the morbidity and mortality of cancer and exposure to sunlight. They concluded that exposure to enough solar radiation caused a decrease in the incidence of malignant tumors in organs that were not at all accessible to treatment. They did however realize that this was accompanied by an increase in non-melanoma skin cancer which they considered as treatable. They analyzed the incidence of cancer in a population with increased exposure to solar UV radiation, i.e. U.S. Navy personnel aboard ships and observed that the rate of nonmelanoma skin cancer was 8 times higher in the Navy personnel while the total number of deaths from other cancers was 60% less than in the civilian population [4-5]. This was followed with the observation by Apperley [6] who analyzed the incidence and mortality of cancer in Northeastern and Southern states in the United States and in Canada and concluded that there was a highly significant correlation between reduced cancer mortality in adults who’ve engaged in agricultural activities outdoors. He also demonstrated that adults living in the Northeast were at higher risk for developing malignant deadly cancers compared to adults living in the South (Fig. 1).

In the 1980s-1990s the Garland conducted several epidemiologic studies to evaluate the correlation between sun exposure, cancer and the vitamin D connection [7-9]. They demonstrated a strong negative correlation between latitude, increased sun exposure and vitamin D status and the risk of many different cancers including colon, breast, ovarian and melanoma [7-11]. These correlations were supported by the observation that breast and colon cancer mortality rates increased in cities with high levels of UV absorbing pollution thus preventing the vitamin D producing solar ultraviolet B (UVB) radiation from reaching the earth’s surface [5]. These observations were followed by several other reports including those of Grant who observed a total of more than 13 cancers were reduced by adequate exposure to solar UVB radiation. He calculated in a span of 24 years, 1970-1994, a total of 566,400 Americans lost their lives due to cancer because of inadequate exposure to solar UVB radiation. He also estimated between 50,000-63,000 Americans and 19,000-25,000 British citizens in the United Kingdom die prematurely from cancer each year due to vitamin D deficiency [12-14].

VITAMIN D: SUNLIGHT AND DIETARY SOURCES

Humans have depended on sun exposure throughout evolution for their vitamin D requirement [15]. Vitamin D was essential for the development and maintenance of the vertebrate skeleton. During exposure to sunlight 7-dehydrocholesterol that is present in the plasma membrane of the living cells in the epidermis is converted to previtamin D3 [16]. Once formed previtamin D3 undergoes a thermally induced rearrangement of its double bonds to form vitamin D3. Vitamin D3 is ejected out of the plasma membrane into the extracellular space and diffuses into the dermal capillary bed for transport to the liver (Fig. 2).

The major natural dietary sources of vitamin D3 are from oily fish and cod liver oil (Table 1). Vitamin D2 that was discovered in the 1930s is obtained naturally from mushrooms exposed to sunlight and artificial ultraviolet radiation. Vitamin D2 is commercially produced from the ultraviolet irradiation of yeast while vitamin D3 is either obtained from fish oils or made from lanolin [17]. Various countries fortify some foods including dairy, cereals, orange juice and margarine with vitamin D. These countries include the United States, Canada, Mexico, Sweden and Finland. Typically there is no more than 100 international units (IU) in a serving. Most countries in Europe still forbid the fortification of foods with vitamin D. This is due to the misconception that an outbreak of hypercalcemia in young children in Great Britain was due to the over fortification of milk with vitamin D. However it is likely that these children suffered from a rare disease known as Williams syndrome. It is now recognized that the hypercalcemia observed in this disease is due to a hypersensitivity to vitamin D [18].

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and the cancer [18-34].

VITAMIN D METABOLISM FOR CALCIUM HOMEOSTASIS AND BONE HEALTH

Once vitamin D (D represents either D$_3$ or D$_3$) is ingested from the diet or made in the skin it travels to the liver where it is metabolized to 25-hydroxyvitamin D [25(OH)D]. 25(OH)D is the major circulating form of vitamin D and is used by physicians to determine a patient's vitamin D status [17] (Fig. 2).

25(OH)D however is at physiologic concentrations biologically inactive on calcium and bone metabolism. It requires an additional hydroxylation on carbon-1 in the kidneys to form 1,25-dihydroxyvitamin D [1,25(OH)$_2$D]. Once formed 1,25(OH)$_2$D enters the circulation and travels into the small intestine where it interacts with the vitamin D receptor (VDR) unlocking genetic information that results in an increase in the efficiency of dietary calcium and phosphorus absorption [17]. It also travels to the skeleton and interacts with the VDR in the osteoblasts which provides a signal to monocyctic osteoclasts to mature into multinucleated giant cells which are responsible for mobilizing calcium out of the skeleton to maintain calcium homeostasis [18-20].

VITAMIN D METABOLISM AND THE CANCER CONNECTION

By the mid-1990s it was generally accepted that living at higher latitude and being at higher risk for vitamin D deficiency was associated with increased risk of developing malignant tumors [5-14]. It was initially hypothesized that increased sun exposure or increased vitamin D intake resulted in an increase in the renal production of 1,25(OH)$_2$D which in turn had anticancer properties. However this hypothesis was challenged because an increase in the production of 1,25(OH)$_2$D would potentially cause hypercalemia. Furthermore it was well-established that the renal production of 1,25(OH)$_2$D was tightly regulated by calcium, phosphorus, parathyroid hormone and fibroblast growth factor 23 [17].

It had been known that activated macrophages [21] and cultured human keratinocytes [22] had the capacity to convert 25(OH)D$_3$ to 1,25(OH)$_2$D$_3$. Schwartz and colleagues [23,24] in the mid-1990s reported that prostate cells grown from biopsies had the capacity to convert 25(OH)D$_3$ to 1,25(OH)$_2$D$_3$ (Fig. 3). They further demonstrated that a prostate cancer cell line LNCaP which had a VDR lacked the 25-hydroxyvitamin D-1-hydroxylase (cyp 27B1;1-OHase) (Fig. 3). When these cells were incubated with 25(OH)D$_3$ their proliferative activity was not affected and they were unable to produce 1,25(OH)$_2$D$_3$. However when the cells were transfected with the 1-OHase gene, 25(OH)D$_3$ inhibited their (Fig. 4). It was also demonstrated that the cells converted $^3$H-25(OH)D$_3$ to $^3$H-1,25(OH)$_2$D$_3$ [24]. At the same time several investigators reported that cells from the lung, breast, colon, brain among many other cell types also had the capacity to convert 25(OH)D$_3$ to1,25(OH)$_2$D$_3$ [25-29]. Based on these observations it was concluded that the likely reason for why increased sun exposure and improved vitamin D status was associated with a reduced risk for deadly cancers was that higher circulating levels of 25(OH)D provided the substrate for the various tissues and organs that had a 1-OHase to locally produce 1,25(OH)$_2$D. Once formed 1,25(OH)$_2$D unlocks nuclear signals that could control cell growth and prevent malignancy, induce apoptosis and/or prevent angiogenesis [30-32]. 1,25(OH)$_2$D also enhances the expression of the 25-hydroxyvitamin D-24-hydroxylase (cyp 24A1; 24-OHase). This enzyme causes the oxidation of the side chain to form a water-soluble biologically inactive calcitriolic acid (Fig. 2).

ANTIPROLIFERATIVE ACTIVITY OF 1,25(OH)$_2$D$_3$ AND ANALOGS

It is estimated that more than 2000 genes may be directly or indirectly regulated by 1,25(OH)$_2$D$_3$ [20,21,33]. In the early 1980s it was first appreciated that leukemic cells that had a VDR. When they were exposed to 1,25(OH)$_2$D$_3$ their proliferation was inhibited and the cells matured into normal appearing macrophages [34,35]. This was followed by the observation that 1,25(OH)$_2$D$_3$ inhibited human keratinocyte proliferation and induced terminal differentiation [36]. These exciting observations were immediately tested for their clinical utility in treating leukemia [37] and the
hyperproliferative skin disorder psoriasis [38]. Unfortunately patients with leukemia developed hypercalcemia and went into blastic phase and died [37]. Psoriasis patients treated with topical [38] or oral 1,25(OH)\textsubscript{2}D\textsubscript{3} [39] responded well to therapy without developing hypercalcemia. Since these initial clinical studies several other studies had been conducted with 1,25(OH)\textsubscript{2}D\textsubscript{3} and its analogs to treat liver carcinoma and prostate cancer [40-42]. These studies were halted due either to hypercalcemia or lack of efficacy. 1,25(OH)\textsubscript{2}D\textsubscript{3} and its analogs have been effective in treating psoriasis and remain a first line treatment for this enigmatic hyperproliferative skin disorder [38,39,42-44].
MECHANISMS FOR 1,25(OH)\textsubscript{2}D\textsubscript{3} TO INHIBIT TUMOR GROWTH

Although the exact mechanisms by which 1,25(OH)\textsubscript{2}D\textsubscript{3} regulates cellular proliferation and differentiation is not fully understood it is known that 1,25(OH)\textsubscript{2}D\textsubscript{3} can control cell replication by regulating cell cycle genes including p27, p21 and p53 [30,40,45-47]. The proteins bind and inactivate cyclin dependent kinase complexes in the G1 phase causing the cell to remain in the G1 phase of the cell cycle. 1,25(OH)\textsubscript{2}D\textsubscript{3} also decreases p27 degradation and its downstream effect is to inhibit cellular proliferation, cell migration and apoptosis. Similarly 1,25(OH)\textsubscript{2}D\textsubscript{3} increases the expression of p21 which can induce apoptosis and G2/M cell cycle arrest [45-47] (Fig. 5). 1,25(OH)\textsubscript{2}D\textsubscript{3} has been demonstrated to inhibit proliferation of endothelial cells and decrease VEGF expression. The VDR knockout mice have increased blood vessel size and volume compared to wild type mice [48].

Therefore it has been suggested that vitamin D through its local conversion of 25(OH)D to 1,25(OH)\textsubscript{2}D is responsible for controlling genes that keep cells in a normal proliferative state.
However if the cell becomes hyperproliferative, 1,25(OH)\(_2\)D can induce cell death or alternatively inhibit angiogenesis to prevent a nutrient supply to the malignant cell preventing its proliferation.

**VITAMIN D NUTRITION AND CANCER IN WOMEN, MEN AND MICE**

There is overwhelming scientific evidence suggesting that vitamin D sufficiency is important for the prevention of a wide variety of deadly cancers. Woo et al. [49] reported that men with metastatic prostate cancer had as much as a 50% decrease in their PSA in response to 2000 IU/d vitamin D\(_3\) for up to 21 months. Lappe et al. [50] reported a more than 60% reduction in the development of all cancers in a small study of postmenopausal women who received calcium supplementation along with 1100 IU/d (Fig. 6) [50]. The Women's Health Initiative (WHI) reported that calcium and vitamin D supplementation in postmenopausal women did not influence the incidence of colorectal cancer. However women who had a blood level of 25(OH)D <12 ng/mL (to convert
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ng/mL into nmol/L multiply by 2.496) had a 253% increased risk for developing colorectal cancer during the 8 years of study compared to women who were vitamin D sufficient at the beginning of the study and had a blood level of 25(OH)D of 24 ng/mL [51]. Further a subgroup analysis restricted to women not on personal calcium and/or vitamin D suggested that the women who took the calcium 1000 mg and 400 IU vitamin D₃ daily for 8 years had a 14-20% reduced risk for developing breast cancer and a 17% reduced risk for developing colorectal cancer [52]. The importance of vitamin D in reducing risk of colorectal cancer is also supported by the observation that the vitamin D receptor polymorphisms was associated with colorectal cancer and in the same study a 34% reduced risk of developing colorectal cancer was seen in adults who had blood levels of 25(OH)D of 31-34 ng/mL [53]. A recent meta-analysis for the US Preventative Services Task Force regarding vitamin D supplementation concluded that for each 4 ng/mL increase in blood 25(OH)D concentrations was associated with a 6% (95% CI 3-9%) reduced risk for colorectal cancer [54].

Animal studies have also supported the concept that an adequate amount of nutritional vitamin D reduces tumor growth. Tangpricha et al. [55] observed that mice who received an adequate amount of vitamin D in their diet to maintain their blood levels of 25(OH)D of 26 ±6 ng/mL had a 40% reduction in the tumor size of a mouse colon cancer compared to mice who were on a vitamin D deficient diet and had undetectable levels of 25(OH)D. (Fig. 7) To determine if vitamin D nutrition could also influence a human tumor’s growth, a study was conducted in athymic mice that were injected subcutaneously with an androgen insensitive prostate cancer cell line DU-145. The tumor volume was dramatically reduced by more than 50% in the mice that had adequate vitamin D in their diet and had maintained a blood level of 25(OH)D of 28.1±2.2 ng/mL compared to the mice on a normal calcium vitamin D deficient diet that had a blood level of 25(OH)D that was undetectable [56].

CANCER RESISTANCE TO VITAMIN D

Several studies have reported that cancer patients are at high risk for being vitamin D deficient [30,41,57,58]. This is due in part to them being advised to avoid sun exposure because of their chemotherapy. In addition they often have gastrointestinal side effects including nausea from the chemotherapy reducing dietary vitamin D intake and causing vitamin D malabsorption. Therefore it
is important to correct the vitamin D nutritional deficiency in patients who have cancer. The vitamin D may help improve mood, nonspecific muscle aches and pains and could potentially enhance the therapeutic efficacy of the chemotherapy along with improving overall feeling of wellbeing.

However vitamin D by itself is not a treatment for cancer. The role of vitamin D in reducing risk and growth of cancers is due to its pleiotropic effects on regulating cellular proliferation, differentiation, apoptosis and angiogenesis once 25(OH)D is converted to 1,25(OH)2D [59, 60]. Unfortunately cancer cells have found a variety of mechanisms to reduce vitamin D’s effectiveness in fighting the malignancy. First and foremost the cancer can increase the destruction of 1,25(OH)2D by inducing the cyp24a1 which results in the oxidation of the side chain into the watersoluble calcitroic acid. Human prostate cancer cells that have robust expression of the cyp24a1 are unresponsive to the anti-proliferative activity of 1,25(OH)2D [40, 47]. Malignant colon cancer cells also express the transcription factor SNAIL which is important for cell movement and exists in both invertebrates and vertebrates. SNAIL also binds VDR and prevents it from acting as a transcription factor to regulate cellular proliferation and differentiation. By doing so it prevents 1,25(OH)2D- VDR complex from binding to beta-catenin which is a known factor that enhances cellular proliferation. SNAIL1 was also shown to also inhibit expression of VDR and E-cadherin which is important for cellular adhesion and differentiation [61] (Fig. 8).

CONCLUSION
There are several thousand publications that have associated sunlight and vitamin D deficiency with increased risk for developing and dying of a wide variety of cancers [62-65]. The fact that the VDR exists in most cells in the body and that the cells have the capability of producing 1,25(OH)2D provides a strong rationale to support the hypothesis that maintaining a healthy vitamin D status with a 25(OH)D in the desired range of 40-60 ng/mL as recommended by the Endocrine Society’s Practice Guidelines [66], may reduce risk for malignancy and improve survival rates for several cancers [58, 67-70].

The major source of vitamin D for most children and adults is exposure to sunlight. Unfortunately for more than 40 years has been the message to avoid all direct sun exposure because of concern for developing “skin cancer” [71, 72]. There is no debate that excessive sun exposure especially on the face and dorsum of the hands increases risk for nonmelanoma skin cancers including basal cell and squamous cell carcinomas [73]. These cancers are easy to detect and easy to treat and if detected early and appropriately treated are curable. However what is of great concern is the deadly skin cancer melanoma. Unlike the non-melanoma skin cancers most melanomas occur on the least sun exposed areas [73]. More importantly occupational sun exposure has been associated with a reduced risk for melanoma [73, 74]. In the 'skin cancer capital' Australia, it has been estimated that more than 40% of the population is now at risk for vitamin D deficiency [75]. A survey of Australian dermatologists in the summer revealed that 87% had a blood level of 25(OH)D <20 ng/mL [76]. The sun-safe message in Australia and New Zealand had been modified in part due to recognizing the widespread consequence which is vitamin D deficiency and insufficiency. The New Zealand Bone and Mineral Society in cooperation with the Australian College of Dermatologists and the Cancer Council for Australia in 2008 had recommended a balance between avoiding the increased risk for skin cancer and achieving enough ultraviolet radiation to maintain adequate vitamin D levels [30]. This message was reinforced by the 2012 Consensus Statement on Vitamin D and Sun exposure in New Zealand that advises on sun exposure requires balancing the risk of skin damage and skin cancer against the risk of vitamin D deficiency. They recommended
• For the general population, some sun exposure is recommended for vitamin D synthesis.
• For older adults who are mobile and living independently, the same sun safety messages apply as for the general population. Physical activity outdoors should be encouraged.
• Physical activity is associated with increased vitamin D levels. Being active while outside may enable more skin to be exposed, increase vitamin D production and reduce the length of time required for vitamin D synthesis.” [77] The Canadian Cancer Society which now recommends that all Canadian adults ingest 2000 IU/d of vitamin D. In addition the Canadian Dermatologic Association, National Council on Skin Cancer Prevention (US) and the World Health Organization Collaborative Center for the Promotion of Sun Protection are recognizing the need to minimize the health risks associated with excessive ultraviolet B radiation exposure while maximizing the potential benefits of optimum vitamin D status, supplementation, and small amounts of sun exposure for obtaining adequate vitamin D. It has been estimated that an adult in a bathing suit receiving an amount of sun exposure that causes a slight pinkness to the skin 24 hours later (one minimal erythemal dose; MED) is equivalent to
Fig. (8). Top, micrographs of SNAIL-HA and mock-infected cells. Arrows indicate the phenotypic change induced by SNAIL. Bar, 50 µm. Below, immunostaining of ectopic SNAIL expression using an antibody to HA. Bar, 10 µm. Left normalized SNAIL, VDR and E-cadherin mRNA levels were measured by real-time RT-PCR. Right, protein expression was estimated by western blot. Numbers refer to fold increase over untreated mock-infected cells. SNAIL inhibits the induction of L1-NCAM and filamin by 1,25(OH)2D3. Wild-type (left) but not mutant (right) SNAIL proteins inhibit VDR transcriptional activity (4XVDRE-tk-luciferase). Reproduced with permission (59).
ingesting a single dose of 20,000 IU of vitamin D (Fig. 9). Exposure of healthy adults with skin types 2, 3 and 4 to 0.5 MED once a week for 3 months was more effective in maintaining serum 25(OH)D levels than taking an oral dose of 1000 IU vitamin D$_3$ daily (Fig. 10). Furthermore it has been demonstrated that vitamin D produced in the skin from sun exposure last 2-3 times longer in the circulation compared to when it is taken as an oral supplement [78].

Although a few studies have suggested that raising blood levels of 25(OH)D above 30 ng/mL increases risk for all-cause mortality [79] and prostate cancer [80] a preponderance of studies have not supported these observations. There has been a lot of discussion about the so-called J curve regarding mortality and vitamin D status. It was suggested that elderly adults with blood levels of 25(OH)D >30 ng/mL were at higher risk for mortality [79]. However one of the studies used in the analysis suggested that mortality continued to be reduced in both men and women until a blood level of 25(OH)D reached 50 ng/mL and that there may have been a slight increase in mortality above this level and only in women not men [81]. Thomas et al. [82] recently reported improvement in vitamin D status reduced risk for all-cause and cardiovascular mortality. In this prospective study 1801 adults with documented metabolic syndrome and after adjusting for confounders they observed a 75% reduction in all-cause mortality and 66% reduction in cardiovascular disease mortality with 85% and 76% reductions in mortality associated with congestive heart
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Fig. (11). A Schematic Representation of the Major Causes for Vitamin D Deficiency and Potential Health Consequences. Holick copyright 2010. Reproduced with permission.

Table 2. Vitamin D Intakes Recommended by the IOM and the Endocrine Practice Guidelines Committee

<table>
<thead>
<tr>
<th>Life Stage Group</th>
<th>AI</th>
<th>EAR</th>
<th>RDA</th>
<th>UL</th>
<th>Daily Allowance (IU/d)</th>
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<td>0 to 6 mo</td>
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<td>1,000 IU (25 µg)</td>
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<td>6 to 12 mo</td>
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<td>1,500 IU (38 µg)</td>
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<td>1–3 y</td>
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<td>4-8 y</td>
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<td>&gt; 70 y</td>
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failure and sudden death. These data support recent meta-analyses showing that low 25(OH)D levels are a risk factor for mortality in CKD patients and in general populations. The lowest mortality risk in general populations was observed at 25(OH)D levels between 30 to 35 ng/mL [83,84]. A meta-analysis of RCTs confirmed that vitamin D supplementation significantly reduces all-cause mortality [85].

Not only will enhancing a child’s and adult’s vitamin D status reduce risk for developing cancer including lymphoma, prostate and breast cancer among many others [86-90] but will also reduce risk of other chronic illnesses including autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and type 1 diabetes, infectious diseases, type 2 diabetes and cardiovascular disease (Fig. 11). Unless the person has a hypersensitivity to vitamin D due to a granulomatous disorder such as sarcoidosis or has a lymphoma that is capable of producing 1,25(OH)₂D in an unregulated fashion there is no downside to increasing a person’s vitamin D intake [66].

<table>
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<tr>
<th>Life Stage Group</th>
<th>AI</th>
<th>EAR</th>
<th>RDA</th>
<th>UL</th>
<th>Daily Allowance (IU/d)</th>
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<td>1,500 – 2,000</td>
<td>10,000</td>
</tr>
</tbody>
</table>

* Mother’s requirement 4,000 – 6,000 (mother’s intake for infant’s requirement if infant is not receiving 400 IU/d)

NOTE: AI = Adequate Intake; EAR = Estimated Average Requirement; IU = International Units; RDA = Recommended Dietary Allowance; UL = Tolerable Upper Intake Level.

**REFERENCES**


