This monograph was prepared by The Ottawa Integrative Cancer Centre (OICC), in collaboration with the Complementary Medicine Education and Outcomes (CAMEO) Research Program. It is part of a series of monographs being developed to share results of a review of the research evidence related to common therapies and products used within cancer patient care.

The following monograph is designed to summarize evidence-based research and does not advocate for or against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published.

Please note that this monograph does not include an exhaustive list of all potential adverse events; individuals may experience unique side effects. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a licensed health care provider. Prior to using a new therapy or product, always consult a licensed health care provider.

For the safe use of natural health products, please consider the following:

- Consult a licensed health care provider prior to using a natural health product and make a plan to monitor its effectiveness and any side effects. This is particularly important for pregnant or breast-feeding women and people with serious medical conditions.
    - To help prevent interactions with your prescribed medication, ensure your health care provider is aware of any drugs or natural health products you may be using. Make sure to note all natural health ingredients listed in compound products.
    - Read and follow all instructions on the product label.
- If purchasing natural health products in Canada, look for Health Canada approved products. Look for Natural Product Number (NPN) or Homeopathic Medicine Number (DIN-HM) on the label to identify licensed products. Avoid internet pharmacies, as the quality of products cannot be guaranteed and products might not be licensed for sale through Health Canada. For more information, visit http://www.hc-sc.gc.ca/dhp-mps/prodnatur/about-apropos/cons-eng.php

Please note: While the aim was to draw from the most extensive research, in some circumstances the information used was limited by the selection and caliber of available research studies. Full references are available in the corresponding full-length monographs found on the CAMEO website.

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VITAMIN D

Proper Name
Vitamin D; vitamin D3 (cholecalciferol); vitamin D2 (ergocalciferol)

Common Name
Vitamin D; "the sunshine vitamin"

Common Uses in Cancer Care
Prevention of cancer development and recurrence;
Optimization of vitamin D status may improve cancer treatment outcomes and survival;
Treatment of musculoskeletal pain, especially secondary to aromatase inhibitors;
Prevention of bone density loss secondary to hormonal therapies.

Route of Administration
Oral

Mechanism of Action
The actions of vitamin D are quite complex, as the vitamin D receptor is present on most types of cells in the body. Vitamin D has anti-proliferative effects, immune modulating effects, and assists with calcium absorption and deposition in relation to bone health.

Clinical Evidence related to Prevention of Breast Cancer
One of two large RCTs found that supplementation with 1100 IU vitamin D + 1400mg calcium daily over 4 years reduced risk of all cancer by 60%. Effects on individual cancer types were not evaluable (1). The second RCT, the Women's Health Initiative found not significant effect from supplementation of a very small dose of vitamin D, 400 IU per day, which may be related to the low dosage used (2).

Six out of six case control studies assessing circulating 25(OH)D reported inverse associations between 25(OH)D and risk of breast cancer. There was a threshold for protective effects at 60 nmol/L or greater compared to <30 nmol/L (24 vs 12.5 ng/mL), as well as for 75 to 150 nmol/L compared to 50 nmol/L (30 to 60 vs 20 ng/mL)(3-8). Only 2 cohort studies assessed 25(OH)D and risk of breast cancer; both showed no impact on risk on development of breast cancer (9, 10).

Clinical Evidence related to Prevention of Breast Cancer Recurrence or Survival
All three cohort studies assessing 25(OH)D and risk of recurrence or distant disease found aninverse association, meaning that vitamin D appeared to be protective against recurrence and distant disease(11-13). This effect was evident at vitamin D levels of 75 nmol/L or higher (30 ng/mL). Low vitamin D levels have also been associated with increasing oncotype score (14), and cytological atypia on screening biopsies and increased Ki-67 expression (15).

Clinical Evidence related to Effectiveness for Aromatase Inhibitor Induced Arthralgia

One cohort study found that supplementation achieving levels of 25(OH)D >100 nmol/L (40 ng/mL) reduced musculoskeletal symptoms associated with aromatase inhibitor therapy (16). A second study found similar associations with reduced musculoskeletal pain (17). Two uncontrolled trials and one RCT also demonstrated that vitamin D supplementation of 10,000 per day over a period of 4 months (18), or 50,000 IU per week for up to 16 weeks (19, 20) resulted in significant improvements in pain secondary to aromatase inhibitors. In addition, these dosing schedules were reported to be safe, with the only adverse events reported being hypercalcuria or hypercalcemia seen only in two patients who were diagnosed with primary hyperparathyroidism (18).

Clinical Evidence related to Estrogenic Effects

Since vitamin D acts through the vitamin D receptor (VDR) present on cells throughout the body, it does not exert estrogenic effects through interactions with the estrogen receptor (ER).

Adverse Events andSide Effects

High dose vitamin D appears to have a relatively good safety profile. Human trials have reported very few incidents of hypercalcemia or hypercalcuria(n=3) in several studies utilizing dosages of up to 10,000 IU per day or 50,000 IU per week over a period of 3-4 months (18-22). High dose vitamin D dosing should be accompanied by regular monitoring of 25(OH)D, calcium, and parathyroid hormone levels.

Interactions with other Therapies, including Drugs and Natural Health Products

There is little data on potential interactions between vitamin D and chemotherapy drugs. Vitamin D may decrease arthralgia induced by aromatase inhibitors.

Cautions and Contraindications

High dose vitamin D supplementation should not be initiated without proper assessment and monitoring. Vitamin D has been shown to be safe at dosages up to 4000 IU per day during pregnancy (23) and up to 6400 IU during lactation (24).

Dosing, frequency and length of treatment

Dosing should be discussed with your healthcare provider. Although high dose vitamin D dosing schedules have been shown to be quite safe, doses greater than 4000-5000 IU per day should not be undertaken without an assessment of current vitamin D status, blood 25(OH)D. Vitamin D should be dosed to achieve levels greater than 75nmol/L, and up to 150 nmol/L.

According to a dosing schedule developed by Aloia (among non-cancer patients), vitamin D supplementation based on baseline 25(OH)D levels was able to achieve levels >75 nmol/L (30 ng/mL) after 18 weeks in all patients. The strategy was such that patients with levels 50-80 nmol/L (32 ng/mL) were given a dose of 2000 IU per day; while those with levels <50 nmol/L (20 ng/mL) were given 4000 IU per day; and dosages were adjusted at 8 weeks based on 25(OH)D levels at that time. (Aloia) It is possible that higher dosage may be superior for cancer patients, particularly those undergoing treatment

with aromatase inhibitors, however this should be determined with the assistance of a healthcare provider.

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Funding for this project was provided by the Canadian College of Naturopathic Medicine