



Review Article

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Whether Vitamin D Can Prevent Cancer or Not: Recent Research Progress in Vitamin D and Major Cancers

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Abstract

Vitamin D has been widely used as a supplementary component in food and drinks, for it helps human body utilize calcium and phosphorus to make stronger bones and teeth. Both nutrition and skin exposure to sunshine can make vitamin D. Scientists have been investigated the relationship between vitamin D and cancers. So far, certain evidences have been reported showing vitamin D helps curing or reduces the death rate of colon cancer, prostate cancer and breast cancer. In this paper we have reviewed recent progress of research in these fields and provide advice for future investigation.

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Introduction

Although cod liver oil has long been used as medicine treatment for rickets, it was until 1922 when McCollum and coworkers proved existence of a stable new vitamin in cod liver oil that promotes calcium deposit and they later named it vitamin D (McCollum et al., 1922). Unlike Vitamin A which is unstable in the presence of oxygen and/or elevated temperature (Hopkins, 1920), vitamin D is found to be stable towards oxygen and moderate heat. In fact, a notable advance led by American scientist Harry Steenbock (1920) who showed that UV irradiated rodent food can cure their rickets. This irradiation technology especially on milk and oats has fortified the food with vitamin D thereby eliminating the rickets.

Vitamin D₂, D₃: Structure and dietary sources

Ergosterol (Fig. 1A) is a fungal steroid from ergot and upon irradiation to exhibit antirachitic activity found by Windaus and Hess (1926). The structure of the irradiated product of ergosterol was proposed in the same year by three research groups, Askew et al. (1932), Reerink and Van Wijk (1931) and Windaus (1931). However, it was not until 1936 when Windaus and Thiele determined the accurate structure of irradiated ergosterol which later named as vitamin D₂, or calciferol (Fig. 1B) (Windaus and Thiele, 1936). Since vitamin D₂ or its precursor is found only in plants, people have long wondered the source of vitamin D in animals. 7-dehydrocholesterol (Fig. 1C) was isolated from hog skin by Windaus and Bock and found to exhibit antirachitic behavior upon

irradiation (Windaus and Bock, 1937), the product was later known as vitamin D3 or cholecalciferol (Fig. 1D).

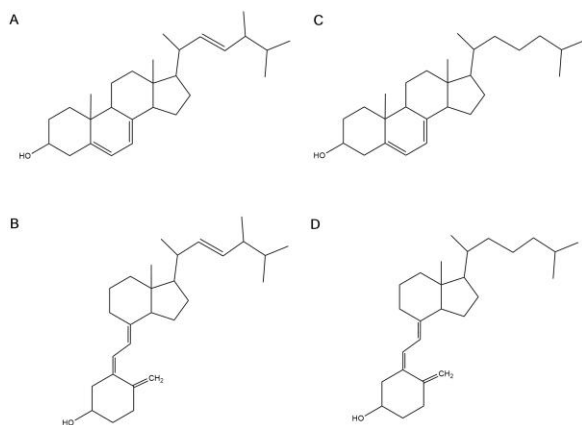


Fig. 1: Structure of ergosterol (A), calciferol or vitamin D-2 (B), 7-dehydrocholesterol (C), and cholecalciferol or vitamin D-3 (D) (Wolf, 2004).

Vitamin D3: Recommend intake and its sources (diet or skin synthesis under sunlight)

Although the US government recommend daily dietary vitamin D intake upper limit to be 1000 IU (Table 1),

recent research indicated that the intake limits could be much higher. Hollis (2007) reported that for women in their pregnancy and/or lactation, the actual dietary requirement could be as high as 6000 IU/day.

Heaney and coworkers (2003) studied 67 healthy males living in Omaha during winter and vitamin D3 was given daily upto 10,000 IU. The experiment lasted about 20 weeks, and no substantial side effects were reported.

Known physiological function and pathway of vitamin D

Vitamin D₃ activation

Vitamin D3 is the hormone precursor of the biologically active form 1,25-dihydroxyvitamin D, or calcitriol (Haussler et al., 2013). After vitamin D3 enters the circulation and transports to the liver, vitamin D 25-hydroxylase catalyzes hydroxylation reaction at C-25 position of vitamin D3 (Fig. 2) to first generate 25-hydroxyvitamin D, or calcidiol. Calcidiol acts as prohormone that again enters circulation and via 1-alpha hydroxylation reaction generates 1,25-dihydroxyvitamin D3 in the kidney (Fig. 2).

Table 1. Vitamin D reference intakes from government-supported independent consensus panels (Yetley et al., 2009).

Intake	Government-supported independent [μ g (IU)/d]		Scientist and professional groups
	Adequate intake	Dietary reference	
Adequate intakes			
7 m – 3 y	5 (200)	7 (280)	10 (400)
4 – 18 y	5 (200)	--	10 (400)
19 – 50 y	5 (200)	--	\geq 25 (1000)
51 – 65 or 70 y	10 (400)	--	\geq 25 (1000)
> 65 or 70 y	15 (600)	10 (400)	\geq 25 (1000)
Pregnant and lactating women	5 (200)	10 (400)	150 (6000)
Upper intakes			
All persons \geq 1 y	50 (2000)	25 (1000)	250 (10,000)

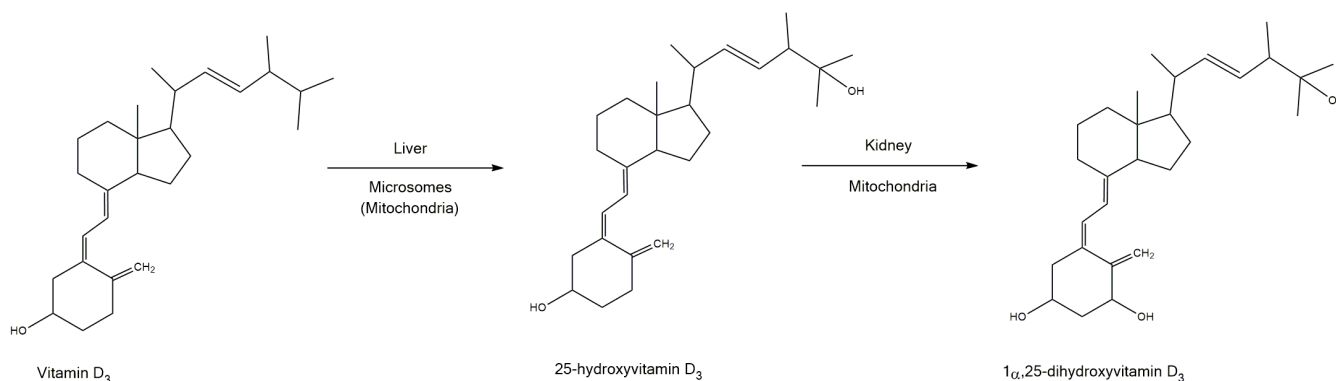


Fig. 2: Vitamin D3 conversion to 25-hydroxyvitamin D in the liver mitochondria by vitamin D 25-hydroxylase. In the kidney, 25-hydroxyvitamin D is further hydroxylated to form the 1,25-dihydroxyvitamin D by 1-alpha-hydroxylase (DeLuca, 2014).

Vitamin D 25-hydroxylase is a member of cytochrome P450 (CYP) enzyme family that found in the liver to carry out 25-hydroxyvitamin D or calcidiol synthesis. The actual genes that express this enzyme is still under discussion. Cheng and coworkers (2004) studied a patient with diagnosed vitamin D deficiency and found the CYP2R1 gene is mutated resulting low level of the Vitamin D 25-hydroxylase expression that is responsible for the selective 25-hydroxyvitamin D deficiency. Recently, Zhu et al. (2013) performed mouse studies and found knockout this CYP2R1 gene greatly reduce but did not eliminate the expression of Vitamin D 25-hydroxylase. However, there is still another unidentified enzyme that potentially catalyzes this hydroxylation. Fig. 3 reveals the circulating level of 25-hydroxyvitamin D and how it is related to biological functions of vitamin D.

Circulating level of 25-hydroxyvitamin D is recommended as indicator of vitamin D sufficiency by Hollis (2005). Circulation level of 32 ng/ml is considered insufficient while level over 100 ng/ml is regarded as toxic. Level between 32 ng/ml and 100 ng/ml is considered as the normal range (Fig. 3).

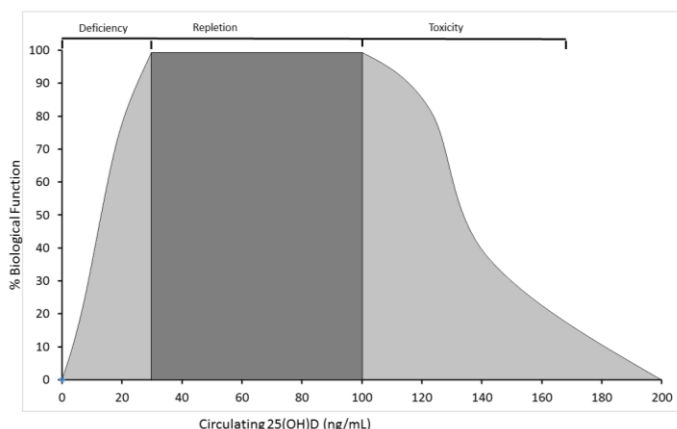


Fig. 3: Relationship of circulating 25(OH) D with biological function.

The 1-alpha-hydroxylase is also a member of the P450 family in renal that catalyze 25-hydroxyvitamin D to generate the fully active form of vitamin D, or 1,25-dihydroxyvitamin D, calcitriol (Takeyama et al., 1997). In turn, the enzyme 1-alpha-hydroxylase activity is also inhibited by its end product 1,25-dihydroxyvitamin D. Genetic study by Dardenne et al. (2001) found inactivation of the gene CYP27B1 in mice results in pseudovitamin D deficiency rickets. Once synthesized, 1,25-dihydroxyvitamin D plays a key role with regulation of calcium homeostasis and cellular differentiation (Bikle and Pillai, 1993).

Li and coworkers (2002) reported inverse relationship between circulating 1,25-dihydroxyvitamin D levels and the blood pressure, therefore, 1,25-dihydroxyvitamin D also participate in blood pressure regulations.

As a member of nuclear hormone receptor superfamily, vitamin D receptor (VDR) or calcitriol receptor mediates biological functions of 1,25-dihydroxyvitamin D (Baker et al., 1998). VDR recognize 1,25-dihydroxyvitamin D through the formation of ligand-receptor complex that via genomic responses regulated calcium and phosphate metabolisms and thereby affects bone density (Amling et al., 1999). A review by Norman (2006) described the broad regulatory effects of VDR on, for example, immune system, hair follicle, muscle, adipose tissue, bone marrow and cancer cells. This review will focus on the effects and regulatory mechanisms of VDR on cancer cells.

Colon cancer

Garland and Garland (1980) studied annual mean daily solar radiation and correspondence with colon cancer mortality rates (Fig. 4).

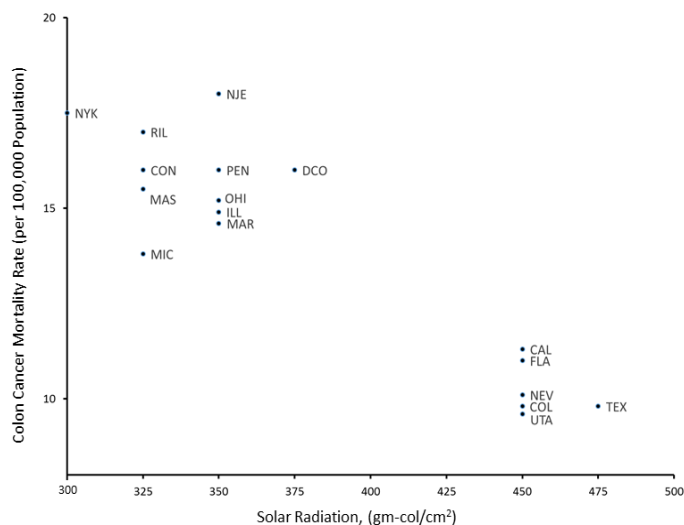


Fig. 4: Annual mean daily solar radiation (g-cal/cm²) and annual age-adjusted colon cancer death rates per 100,000 populations.

According to this study, New Hampshire, New York and Vermont with lowest daily solar radiation have colon cancer rates about two times as high as places with highest daily solar radiation such as New Mexico and Arizona. Garland and coworkers (1989) further studied blood samples from more than 25,000 volunteers in Maryland and show the people with serum 25-

hydroxyvitamin D concentration of 20 ng/ml or more exhibit three-fold decrease in colon cancer incidents. Bischoff-Ferrari and coworkers (Bischoff-Ferrari et al., 2006) reported that to minimize the risks of colon cancer, serum 25-hydroxyvitamin D level needs to be over 90 nmol/l or 36 ng/ml (Fig. 5).

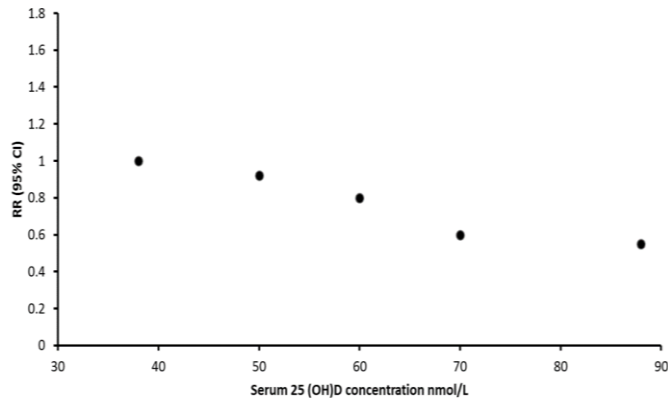


Fig. 5: The relative risk (RR) in 95% confidence intervals (CI) of colon cancer as related to serum 25-hydroxyvitamin D level.

Lamprecht and Lipkin (2003) discussed the molecular mechanisms of anti-cancer effects of vitamin D and potential chemotherapeutics based on of preclinical experimental studies and some human clinical trials. Cross and coworkers (2001) found that human colon cells possess the ability to synthesize both 1,25-dihydroxyvitamin D and also VDR protein. In a substantial number of colon cancer patients, VDR expression increase with the progression of their tumor. This suggest that in moderate colon cancer (grade G2 or earlier stage) cells, the cells can still upregulate the tumor progression through elevated synthesis of 1,25-dihydroxyvitamin D and production of VDR. However, in highly malignant cancer (grade G3 and higher) cells, the enzyme activity for synthesis of 1,25-dihydroxyvitamin D or VDR genes are highly compromised therefore fail to promote cells differentiation and inhibit proliferation. Alvarez-Díaz et al. (2012) identified microRNAs (or miRNAs) can also participate in the regulatory functions of 1,25-dihydroxyvitamin D on colon cancer. MiRNAs are

short non-coding RNAs that regulate mRNA translations; recently miRNAs are found to act as oncogenes or tumor gene suppressors (Esteller, 2011).

Prostate cancer

Hanchette and Schwartz (1992) studied prostate cancer among males in the United States and found black males (age adjusted) on average have as high as two folds’ of prostate cancer incidents than white males. This is due to the fact that pigmentation reduces vitamin D synthesis (Harris, 2006). Notably, American black males also have higher risks of prostate cancer than their African counterparts. This can be related to higher UV irradiation in Africa.

Hanchette and Schwartz (1992) also observed the trend of increased prostate cancer cased in the Northeast compared to the Southwest within the United States among white male subjects (Fig. 6). Corder and coworkers (1993) studied 250,000 serum samples among which 90 black and 91 white males are diagnosed with

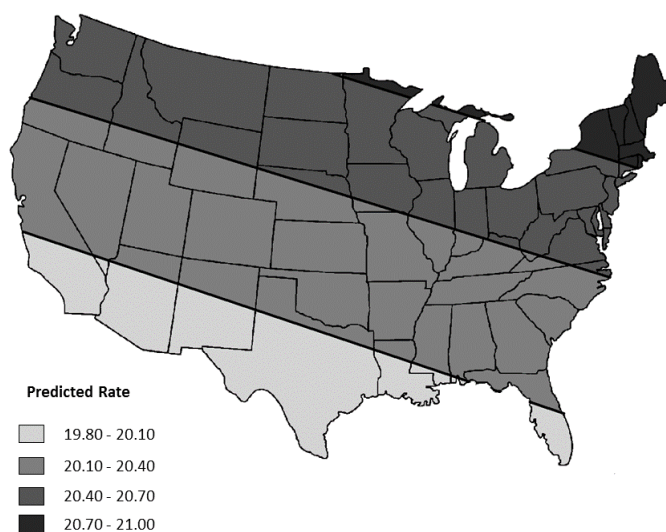


Fig. 6: Fitted first-order trend surface analysis of prostate cancer cases as related to geographical distributions from the Northeast to the Southwest.

Table 2: The odds of prostate cancer for each quartile of 25-D and 1,25-D compared to their lowest quartiles .

Quartile of 25-D (ng/mL)	Quartile of 1,25-D (pg/mL)			
	1 (5-26)	2 (27-32)	3 (33-39)	4 (40-81)
1 (3-18)	1.00	0.53	0.28	0.15
2 (19-23)	0.96	0.58	0.35	0.21
3 (24-28)	0.93	0.63	0.43	0.29
4 (29-52)	0.90	0.69	0.53	0.41

They observed protective effects of higher 1,25-dihydroxyvitamin D level associated with lower risks of prostate cancer, especially for the subjects with lowest levels of 25-hydroxyvitamin D, quartile 1 (Table 2). They also reported the relationship of lower serum 1,25-dihydroxyvitamin concentration with less risks of prostate cancer only applicable to male above the median age of 57 years, however, no significant correlation can be derived for younger subjects. Krishnan and Feldman (2010) provided detailed review on the molecular mechanisms of how 1,25-dihydroxyvitamin D could potentially inhibit progression of prostate cancer. Cancer related inflammation is often accompanied by the production of cytokines (small proteins that are related to cell signaling) and Prostaglandins (PGs, lipid compounds that hormone-like physiological effects). 1,25-dihydroxyvitamin is found to participate in the

regulation of the production of prostaglandins and some cytokines therefore possessing therapeutic opportunity for preventing or treatment of early stage prostate cancer.

Breast cancer

Garland and coworkers (1990) studied the relationship between solar irradiation and age adjusted breast cancer mortality rate per 100,000 population and found higher solar irradiation in the southern urban region such as Phoenix or Tampa have much lower risks than the northeast urban region, for example, New York or Chicago (Fig. 7). Lowe et al. (2005) studied 179 patients diagnosed with breast cancer in UK and correlated their serum 25-hydroxyvitamin D level with 179 control subjects (Table 3).

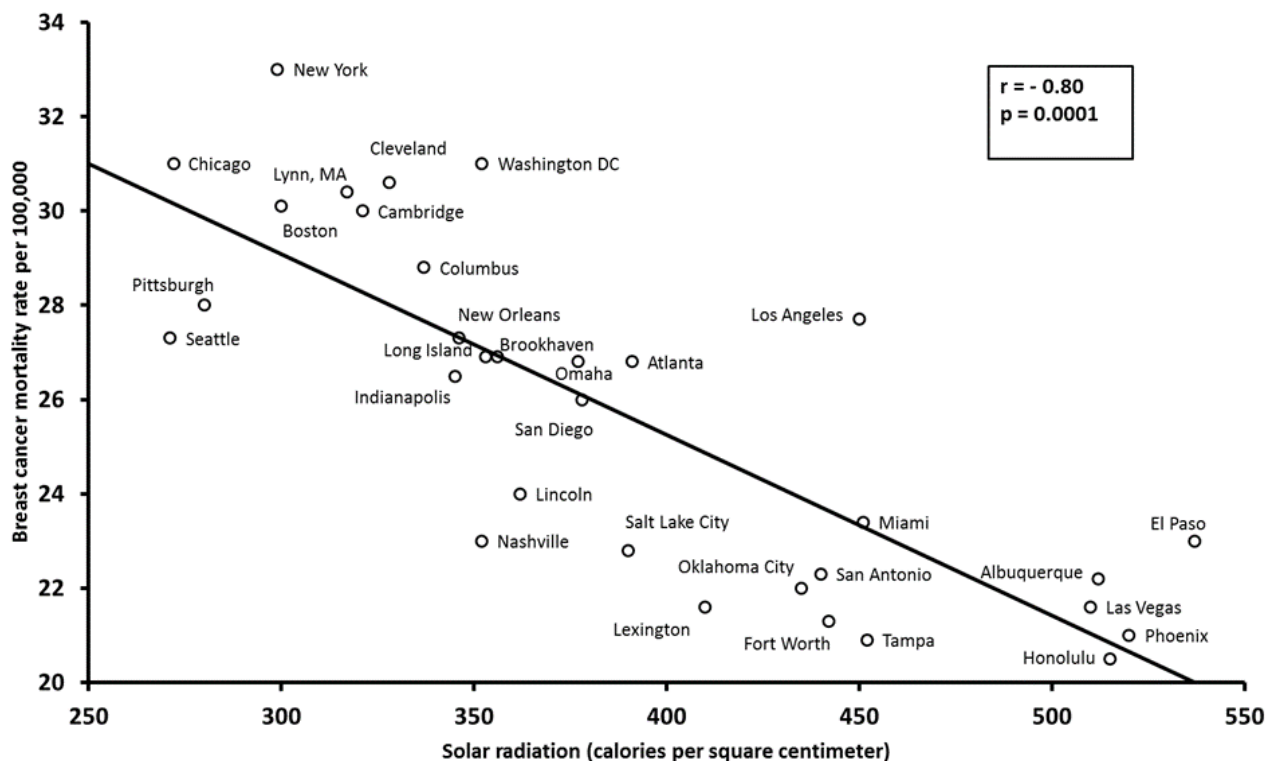


Fig. 7: Age-adjusted breast cancer mortality rates by solar radiation levels, counties with 90+% urban populations, United States, 1950-1969 (Lowe et al., 2005).

Table 3. Number of controls and cases in each 25(OH)D quartile and odds ratio (OR) for breast cancer risk for each quartile.

Quartile (nM)	Controls n (%)	Cases n (%)	OR (95%CI)	p-value
1 (<50)	21 (12)	54 (30)	5.83 (2.31-14.7)	<0.001
2 (50-100)	79 (44)	69 (39)	1.83 (0.83-4.03)	0.13
3 (100-150)	54 (30)	43 (24)	1.61 (0.71-3.64)	0.25
4 (>150)	25 (14)	13 (7)	1	

CI: confidence interval

According to this study, women in quartile 1 (<50nM or 20 ng/ml) 25-hydroxyvitamin D have more than 5 times higher risks of breast cancer than women in quartile 4 (> 150 nM or 60 ng/ml). Krishnan and coworkers [39] found 1,25-dihydroxyvitamin D can regulate progression of breast cancer through reduction effects of synthesis of estrogen (primary female hormone) and prostaglandins (PGs) therefore inhibiting the proliferation of cancer cells. Therefore, dietary vitamin D supplement could play protective roles in breast cancer prevention and early stage treatment.

Summary and advice for future work

In this review, we summarized discovery of vitamin D, a historical and effective medicine for treatment of rickets through its important effects on bone metabolism. Vitamin D can be synthesized from UV radiation on the skin or through dietary supplement. US government recommend daily dietary vitamin D intake upper limit to be 1000 IU, however, recent research suggest this number could be much higher. Vitamin D is converted to 25-hydroxyvitamin D in the liver; serum 25-hydroxyvitamin D level is a main indicator of whether body has enough vitamin D. Bischoff-Ferrari and coworkers suggested the optimum level of 25-hydroxyvitamin D in human serum is about 40 ng/ml. 25-hydroxyvitamin D can be further metabolized to form 1,25-dihydroxyvitamin D in the kidney, which is active form of vitamin D. 1,25-dihydroxyvitamin D can bind to vitamin D receptor (VDR) proteins and act as nuclear hormone that could play a number of crucial physiological functions. Historically, epidemic researchers have found that for colon, prostate and breast cancer mortality rates are higher in the Northeast urban areas than the rates in southwest urban region. These trends have been related to higher sunlight radiation in the South latitude therefore more vitamin D synthesized from the skins. Researchers also found subjects with serum 25-hydroxyvitamin D level greater than 60 ng/ml have much less risks of developing cancer than the control group whose serum 25-hydroxyvitamin D is less than 20 ng/ml. Molecular mechanisms of anti-cancer effects of 1,25-dihydroxyvitamin D have been related to its regulatory effects on the synthesis of estrogen, cytokins and Prostaglandins. Protective roles of 1,25-dihydroxyvitamin D of preventing of treating early stages colon, prostate and breast cancer have been established. However, clinical trials of 1,25-dihydroxyvitamin D in particular hormone refractive prostate cancer (HRPC) test on these recurring cancer is still under development.

Conflict of interest statement

Authors declare that they have no conflict of interest.

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