Endocrine (2019) 65:238–243
https://doi.org/10.1007/s12020-019-01985-y

MINI REVIEW

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Vitamin D, cancer, and dysregulated phosphate metabolism

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Received: 22 April 2019 / Accepted: 12 June 2019 / Published online: 23 June 2019

Abstract

Recently reported findings from major clinical trials show no cancer protection from vitamin D supplementation, and results from observational studies of vitamin D in cancer prevention are inconsistent. There is a need for new hypotheses to guide investigations of the controversies surrounding vitamin D supplementation and cancer. Bioactive vitamin D, 1,25(OH)2D, is an endocrine factor that regulates phosphate homeostasis by increasing dietary phosphate intestinal absorption. When phosphorus serum levels are high, as in hyperphosphatemia, an endocrine feedback mechanism lowers bioactive vitamin D which reduces intestinal phosphate absorption. Low vitamin D levels have been associated with cancer incidence, and tumorigenesis is associated with high levels of dysregulated phosphate in the body. In this mini-review, the author hypothesizes that hyperphosphatemia may be an intermediating factor in the association of lowered vitamin D levels and increased risk for tumorigenesis. Furthermore, this article challenges the UVB–vitamin D-cancer hypothesis which proposes that reduced cancer incidence at lower geographic latitudes is related to high levels of vitamin D from UVB exposure. The author proposes that reduced phosphorus content and availability in tropical and subtropical soil, and lower dietary phosphate intake from consumption of tropical and subtropical crops (as in the Mediterranean diet), may mediate the association of reduced cancer risk with lower latitudes.

Keywords Vitamin D · Phosphate · Cancer · Hyperphosphatemia · UVB · Mediterranean diet

Introduction

A promising role for vitamin D in cancer prevention has been suggested by decades of results from laboratory-animal and cellular studies, but the promise remains unfulfilled as findings of clinical studies in humans have been mixed [1]. Recently, the prospect of vitamin D reducing cancer in humans has been further diminished by findings from major clinical trials which show no reduction in cancer risk from vitamin D3 supplementation (cholecalciferol).

Results of the Vitamin D and Omega 3 Trial (VITAL), published in late 2018, found no reduced cancer incidence in a nationwide U.S. trial of 25,871 participants randomized to a 2000 IU daily dose of vitamin D3 or placebo, with a median follow-up period of 5.3 years [2]. Results were published in 2018 from the Vitamin D Assessment study (ViDA) of 5108 participants from Auckland, New Zealand, randomized to monthly high doses of vitamin D3 (100 K IU after an initial dose of 200 K IU) which found no significant change in cancer incidence after a median follow-up period of 3.3 years [3]. Results of a 2019 meta-analysis of randomized controlled trials did not find a reduction in total cancer incidence from vitamin D supplemented at high dosages, although it found a significant association with a reduction in total cancer mortality [4]. However, reduced cancer mortality could be attributed to survivor bias as cases who survive cancer might have different uncontrolled risk factors than lost cases [5]. Results were also published in 2017 of a trial of 2303 healthy postmenopausal women from rural counties in Nebraska who were supplemented with vitamin D3 and calcium, which did not lead to a significant reduction in cancer incidence after four years [6].

It has been suggested that doses of vitamin D have pharmacological effects which suppress tumors when adapted for use as an anticancer agent [7], but commonly-used doses of 2000 IU vitamin D have been found to promote cancer biomarkers [8]. No hypothesis has successfully explained the puzzling discrepancy between laboratory and clinical research findings involving vitamin D

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supplementation and cancer. This puzzle remains unsolved as recent observational findings show inverse associations between cancer and circulating levels of vitamin D3 (25 (OH)D) [9–11], while other recent observational studies found no association between vitamin D and cancer [12–14].

There are many potential confounding factors that could account for conflicting findings in investigations of supplemented vitamin D and cancer. Classifying serum levels of vitamin D as deficient, insufficient, normal, excessive, and toxic is an area of ongoing debate [15, 16], and the threshold of supplemented vitamin D that produces an effect in participants with normal baseline vitamin D levels may not reach the same threshold in participants with insufficient baseline levels. Factors that disrupt the metabolic conversion of the storage form of vitamin D, calcidiol, into the bioactive form, calcitriol, may also account for variable findings in the outcome of vitamin D supplementation on cancer. Individuals with genotypes that affect the expression of the vitamin D receptor have been found to respond differently to vitamin D supplementation in various types of cancers, and variable responses to vitamin D supplementation can be influenced by bodyweight, gender, and age-related hormonal interactions in cancer [17]. Additionally, emerging evidence suggests that vitamin D metabolism is dysregulated in cancer [18], which implies that the link between vitamin D and cancer may involve metabolic mechanisms that are much more complex than straightforward vitamin D deficiency. There is a need to generate new hypotheses for further investigation of the controversies surrounding vitamin D supplementation and cancer [19].

The author has previously discussed controversies and adverse effects associated with supplemented vitamin D [20, 21], which include hypercalcemia and vascular calcification. In this mini-review, evidence is presented suggesting that dysregulated phosphate may be a mediating factor in the negative association of vitamin D levels with cancer risk, supporting a novel hypothesis that might help explain decades of inconsistent findings between clinical and laboratory research on vitamin D and cancer. Furthermore, this evidence supports the introduction of another novel hypothesis which challenges the UVB–vitamin D-cancer hypothesis, a long-standing hypothesis linking sunlight exposure with vitamin D and cancer prevention.

Endocrine regulation of phosphate homeostasis

To explain how dysregulated phosphate may mediate the association of vitamin D with cancer, one must begin with an understanding of vitamin D's regulatory role as an endocrine factor in phosphate homeostasis [22], briefly summarized here. Phosphorus, an essential dietary micronutrient, is incorporated into nucleic acids DNA and RNA and is a component of phospholipids found in cell membranes. Inorganic phosphorus (Pi) functions within cells as a negatively charged phosphate anion (PO_4^{3-}) in enzymatic activation and inactivation, and is involved in cell signaling via phosphorylation of proteins. Phosphorus also plays a role in energy metabolism and mineralizes bone in combination with calcium. Phosphate regulation is controlled systemically by a sensitive network of endocrine factors which include bioactive vitamin D (1,25(OH)2D, calcitriol), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23) along with its cofactor Klotho. Dysregulation of this systemic network disturbs phosphate homeostasis and is associated with cellular pathologies that can increase morbidity and mortality involving almost every organ system of the body.

Vitamin D regulation of phosphate homeostasis

Bioactive 1,25(OH)2D regulates phosphate homeostasis by increasing intestinal absorption of dietary Pi to help maintain normal serum phosphate levels, mainly by increasing the expression of type II sodium-dependent phosphate co-transporters (NaPi2b) in the intestinal mucosa [22]. 1,25 (OH)2D is produced from circulating 25-hydroxyvitamin D (25(OH)D, cholecalciferol) through the enzymatic action of 1α-hydroxylase (CYP27B1) which is expressed by the kidneys. 1,25(OH)2D action also suppresses PTH synthesis, preventing reduced renal Pi reabsorption and increased urinary phosphate excretion caused by PTH. Of relevance, serum phosphate levels that rise above normal (hyperphosphatemia) suppress renal production of 1,25(OH)2D, forming a feedback loop between intestinal absorption and serum Pi. Increased FGF23 secretion also works to lower rising serum phosphate by increasing urinary phosphate excretion and by lowering 1,25(OH)2D serum levels. Additionally, vitamin D has been found to influence the gastrointestinal microbiome, which has been causally linked to colorectal cancer [23], and changes in the microbiome associated with vitamin D may modify the intestinal Pi absorption mechanism, although further investigations are needed.

In contrast to the complex multifactor endocrine system which tightly regulates renal hydroxylation of cholecalciferol in the production of calcitriol [24], excessive amounts of cholecalciferol synthesized from 7-dehydrocholesterol in the skin during sun exposure are directly downregulated by photodegradation [25]. This mechanism implies that the body obtains all the cholecalciferol it requires naturally from sufficient sun exposure, disposing of any excessive amounts synthesized in the skin.

Dysregulated phosphate and tumorigenesis

The author has previously reviewed the association of dysregulated phosphate metabolism with tumorigenesis, summarized very briefly here [26, 27]. Cancer is a disease of dysregulated cell growth, and phosphorus, the least abundant element forming nucleic acids DNA and RNA, is a rate-limiting factor in biological growth [28]. Cancer patients were found to have above-normal levels of serum phosphate relative to patients without cancer [29], and cancer cells have been found to store up to twice as much phosphorus as normal cells [30]. Type II sodium-dependent phosphate co-transporters (NaPi2b) are expressed in greater numbers within the membranes of cancer cells than in normal cells [31]. Ribosomal RNA biosynthesis is increased as excess phosphorus is incorporated into nucleic acids [32], thus helping provide additional protein for cancer cell growth and tumorigenesis.

Lung tumors [33] and skin cancer [34] were caused by feeding high levels of dietary phosphate to experimental animals, and high levels of dietary phosphate were found to be associated with high-grade cancer of the prostate in the Health Professionals Follow-Up Study [35]. Research shows that high amounts of phosphate stimulate cell signaling in cancer growth [36] and tumor neovascularization [37], and are associated with metastasis [38] and chromosome instability [39]. The effects of dysregulated phosphate also contribute to malnutrition and systemic inflammation [40], which are conditions associated with cachexia in terminally ill cancer patients.

Another research finding which has important dietary implications is that ketogenic diets (defined as 90% or more calories from fat) have shown efficacy in cancer treatment [41]. The usual explanation for this finding cites the high reliance of cancer cells on anaerobic glucose metabolism. However, a very large 500-gram tumor utilizes only 9.8 grams of carbohydrates a day, which is easily supplied during restricted carbohydrate feeding [42], in addition to glucose supplied by gluconeogenesis from the lysis of protein and fat. It is noteworthy that a greater proportion of calories supplied from fat in the ketogenic diet lowers the diet's overall phosphate content [26], which could help explain the efficacy of ketogenic diets in treating cancer.

Vitamin D-hyperphosphatemia-cancer hypothesis

The research evidence in this mini-review provides a basis to propose a novel hypothesis which explains the association of low vitamin D levels with increased cancer risk. Figure 1 shows that hyperphosphatemia causes endocrine lowering of 1,25(OH)2D while simultaneously increasing the risk of tumorigenesis. Further studies need to investigate evidence that supports, refutes, or modifies this Vitamin D-hyperphosphatemia-cancer hypothesis.

UVB–vitamin D-cancer hypothesis

The UVB–vitamin D-cancer hypothesis is a prominent hypothesis linking lower latitudes and greater sun exposure to reduced cancer incidence and/or mortality [43]. Although UV radiation exposure increases skin cancer risk [44], evidence of cancer mortality reviewed in 2006 found that health benefits outweighed risks of UV radiation exposure [45]. A 2012 ecological study supported the UVB–vitamin D-cancer hypothesis based on an analysis of geographical cancer incidence [46]. However, another 2012 study found no protective effect on internal cancers in patients with basal cell carcinoma which is strongly associated with prolonged sun exposure [47].

In a related line of evidence, fruit and vegetable consumption is associated with cancer prevention [48], but reduced cancer risk is often not confirmed in clinical trials examining intake of isolated nutrients and other dietary factors [49, 50]. Furthermore, fruit and vegetables are poor sources of vitamin D, which adds to the conundrum linking vitamin D and cancer prevention. Of relevance, fresh whole fruit and green leafy vegetables generally are lower in phosphorus than other natural whole foods. Table 1, based on edible portions of foods from the USDA standard reference database [51], shows a small sample of fruits and nuts grown in tropic and semi-tropic regions that have a very low phosphorus caloric density (mg of phosphorus per calorie).

Table 1 shows that the phosphorus caloric density of cereals and legumes grown in temperate regions is much higher than that of tropical and subtropical fruits and nuts. Additionally, the phosphorus caloric density of green leafy vegetables is high, but these foods are generally not consumed in large amounts, and the overall amount of dietary

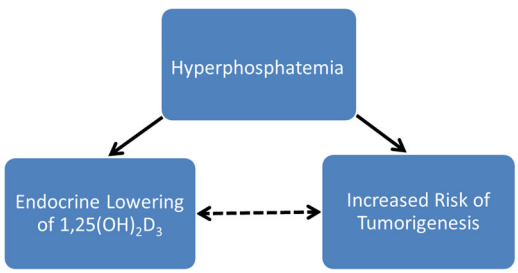

Fig. 1 Vitamin D-hyperphosphatemia-cancer hypothesis. Hyperphosphatemia causes endocrine lowering of 1,25(OH)2D, and is a factor that increases risk of tumorigenesis. It is hypothesized that hyperphosphatemia mediates the association of low bioactive vitamin D with increased cancer risk (dotted arrow)

Table 1 Phosphorus in agricultural crops; USDA standard reference

Tropical & Subtropical Fruit & Nuts	Phosphorus mg/kcal
Olive	0.02
Pineapple	0.16
Fig	0.19
Pear	0.19
Blueberry	0.21
Apple	0.21
Grapefruit, Florida Red	0.21
Mango	0.22
Date	0.22
Kaki	0.24
Banana	0.25
Papaya	0.26
Macadamia Nut	0.26
Durian	0.27
Grapes	0.29
Orange	0.30
Honeydew	0.31
Coconut	0.32
Avocado	0.33
Raisin	0.34
Cherimoya	0.35
Watermelon	0.37
Tangerine	0.38
Jackfruit	0.38
Pecan	0.40
Soursop	0.41
Temperate Grains & Legumes	
Rice, Brown, Medium Grain, Raw	0.72
Corn, Sweet, Yellow, Raw	1.03
Wheat, Flour, Whole Grain	1.02
Soy Flour, Full Fat, Raw, Crude Protein	1.13

phosphorus they provide is low. On the other hand, cereals provide the largest source of dietary phosphorus in the United States [52], along with other leading sources of phosphorus such as dairy and meat.

The Mediterranean basin is a subtropical region—recent studies show that a Mediterranean dietary pattern, which is high in fruit and vegetables, is associated with reduced cancer mortality [53], and with risk reductions for cancer of the esophagus and stomach [54], bladder [55], colon and rectum [56], prostate [57], breast [58], lung [59], and non-melanoma skin cancer [60]. Reduced cancer risk linked to the Mediterranean dietary pattern is associated with the low saturated fatty acid and high fiber content of the plant-based foods in the diet [61], but lower phosphate in the fruits and vegetables of the Mediterranean diet should not be overlooked as a potential protective factor against cancer. Note that the high-fat olive, a staple fruit consumed in the Mediterranean diet, is exceptionally low in phosphorus caloric density, being approximately ten times lower than other fruits listed in Table 1. The low phosphorus caloric density of many tropical and subtropical fruits and nuts is explained by low total soil phosphorus and reduced phosphorus solubility/availability in tropical and subtropical soils relative to temperate region soils [62, 63]. Some tropical nuts not listed in Table 1 include the Brazil nut which is high in phosphorus. Of relevance, the Brazil nut tree grows to between 100 and 150 feet in height and has a very extensive root system compared to other tropical crops [64].

This reviewed evidence supports a novel latitude-phosphorus-cancer hypothesis that is posited as an alternative to the UVB–vitamin D-cancer hypothesis. The relatively low phosphorus content and low phosphorus availability in tropical and subtropical soil, and the low phosphorus content of related subtropical and tropical crops, provide a hypothetical mediating factor which links the association of low latitude with reduced cancer incidence, Fig. 2.

This novel latitude–phosphorus-cancer hypothesis is consistent with evidence of a rise in non-communicable diseases in populations of Pacific Islanders as their traditional diet of tropical food items has been replaced with imported food from northern latitudes [65]. Unfortunately, most of the Pacific Island region lacks historical records from long-established cancer registries [66], and it has not been possible to observe longitudinal changes in cancer incidence associated with historical changes in the traditional Pacific Islander diet. Modern dietary interventions based on the Pacific Islander traditional diet should be investigated for cancer prevention.

In conclusion, the evidence in this mini-review supports findings that vitamin D supplementation does not play a direct protective role against cancer. The two novel cancer hypotheses presented in this mini-review, the vitamin D–hyperphosphatemia-cancer hypothesis and the latitude–phosphorus-cancer hypothesis, are proposed as

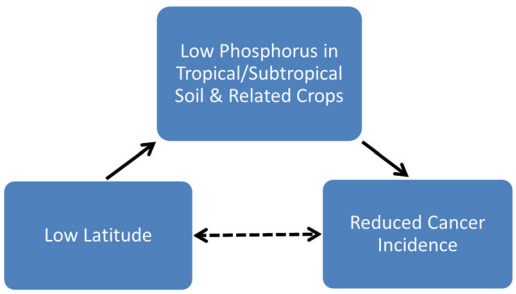

Fig. 2 Latitude-phosphorus-cancer hypothesis. At low latitude, tropical and subtropical soil and crops are lower in phosphorus compared to temperate regions, which is hypothesized to reduce cancer incidence associated with lower latitudes (dotted arrow)

guides for further investigation of controversies surrounding vitamin D and cancer.

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by the author.

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References

1. D.D. Bikle, Vitamin D and cancer: the promise not yet fulfilled. Endocrine **46**(1), 29–38 (2014)
2. J.E. Manson, N.R. Cook, I.-M. Lee, W. Christen, S.S. Bassuk, S. Mora, H. Gibson, D. Gordon, T. Copeland, D. D'Agostino, Vitamin D supplements and prevention of cancer and cardiovascular disease. New Engl. J. Med. **380**(1), 33–44 (2019)
3. R. Scragg, K.-T. Khaw, L. Toop, J. Sluyter, C.M. Lawes, D. Waayer, E. Giovannucci, C.A. Camargo, Monthly high-dose vitamin D supplementation and cancer risk: a post hoc analysis of the vitamin D assessment randomized clinical trial. JAMA Oncol. **4**(11), e182178–e182178 (2018)
4. N. Keum, D. Lee, D. Greenwood, J. Manson, E. Giovannucci, Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. Ann. Oncol **30**, 733–743 (2019)
5. Z.-H. Hu, J.E. Connett, J.-M. Yuan, K.E. Anderson, Role of survivor bias in pancreatic cancer case-control studies. Ann. Epidemiol. **26**(1), 50–56 (2016)
6. J. Lappe, P. Watson, D. Travers-Gustafson, R. Recker, C. Garland, E. Gorham, K. Baggerly, S.L. McDonnell, Effect of vitamin D and calcium supplementation on cancer incidence in older women: a randomized clinical trial. Jama **317**(12), 1234–1243 (2017)
7. X. Wu, W. Hu, L. Lu, Y. Zhao, Y. Zhou, Z. Xiao, L. Zhang, H. Zhang, X. Li, W. Li, Repurposing vitamin D for treatment of human malignancies via targeting tumor microenvironment. Acta. Pharma. Sinica. B. **9**, 203–219 (2018)
8. Y. Omura, D. Lu, M.K. Jones, A. Nihrane, H. Duvvi, D. Yapor, Y. Shimotsuura, M. Ohki, Optimal dose of vitamin D3 400 IU for Average adults has a significant anti-cancer effect, while widely used 2000 IU or higher promotes cancer: marked reduction of taurine & 1α, 25 (OH) 2D3 was found in various cancer tissues and oral intake of optimal dose of taurine 175 mg for average adults, rather than 500 mg, was found to be a new potentially safe and more effective method of cancer treatment. Acupunct. electro-Ther. Res. **41**(1), 39–60 (2016)
9. M. Haznadar, K.W. Krausz, E. Margono, C.M. Diehl, E.D. Bowman, S.K. Manna, A.I. Robles, B.M. Ryan, F.J. Gonzalez, C. C. Harris, Inverse association of vitamin D3 levels with lung cancer mediated by genetic variation. Cancer Med. **7**(6), 2764–2775 (2018)
10. T.L. Gomes, R.C. Fernandes, L.L. Vieira, R.M. Schincaglia, J.F. Mota, M.S. Nóbrega, C. Pichard, G.D. Pimentel, Low vitamin D at ICU admission is associated with cancer, infections, acute respiratory insufficiency, and liver failure. Nutrition **60**, 235–240 (2019)
11. S. Hossain, M.A. Beydoun, H.A. Beydoun, X. Chen, A.B. Zonderman, R.J. Wood, Vitamin D and breast cancer: a systematic review and meta-analysis of observational studies. Clin. Nutr. ESPEN. **30**, 170–184 (2019)
12. D. Muller, A. Hodge, A. Fanidi, D. Albanes, X. Mai, X. Shu, S. Weinstein, T. Larose, X. Zhang, J. Han, No association between circulating concentrations of vitamin D and risk of lung cancer: an analysis in 20 prospective studies in the Lung Cancer Cohort Consortium (LC3). Ann. Oncol. **29**(6), 1468–1475 (2018)
13. X. Jiang, N.L. Dimou, K. Al-Dabhani, S.J. Lewis, R.M. Martin, P. C. Haycock, M.J. Gunter, T.J. Key, R.A. Eeles, K. Muir, Circulating vitamin D concentrations and risk of breast and prostate cancer: a Mendelian randomization study. Int. J. Epidemiol. (2018). https://doi.org/10.1093/ije/dyy284
14. P. Chandler, D. Tobias, L. Wang, S. Smith-Warner, D. Chasman, L. Rose, E. Giovannucci, J. Buring, P. Ridker, N. Cook, Association between vitamin D genetic risk score and cancer risk in a large cohort of US women. Nutrients **10**(1), 55 (2018)
15. F. Alshahrani, N. Aljohani, Vitamin D: deficiency, sufficiency and toxicity. Nutrients **5**(9), 3605–3616 (2013)
16. D.J. Owens, R. Allison, G.L. Close, Vitamin D and the athlete: current perspectives and new challenges. Sports Med. **48**(1), 3–16 (2018)
17. M.R.I. Young, Y. Xiong, Influence of vitamin D on cancer risk and treatment: why the variability? Trends cancer Res. **13**, 43 (2018)
18. S.-M. Jeon, E.-A. Shin, Exploring vitamin D metabolism and function in cancer. Exp. Mol. Med. **50**(4), 20 (2018)
19. S. Minisola, F. Ferrone, V. Danese, V. Cecchetti, J. Pepe, C. Cipriani, L. Colangelo, Controversies surrounding vitamin D: focus on supplementation and cancer. Int. J. Environ. Res. public health **16**(2), 189 (2019)
20. R.B. Brown, A. Haq, C.F. Stanford, M.S. Razzaque, Vitamin D, Phosphate and Vasculotoxicity. Can. J. Physiol. Pharmacol. **93**, 1077–1082 (2015)
21. R.B. Brown, F. Al Anouti, M.S. Razzaque, Vitamin D supplements: Magic pill or overkill? South East Asia. J. Public Health **5** (2), 1–3 (2015)
22. R.B. Brown, M.S. Razzaque: Chapter 31 - Endocrine Regulation of Phosphate Homeostasis. In: A.K. Singh, G.H. Williams (eds.) Textbook of Nephro-Endocrinology (Second Edition). pp. 539–548. Academic Press, (2018)
23. M. Waterhouse, B. Hope, L. Krause, M. Morrison, M.M. Protani, M. Zakrzewski, R.E. Neale, Vitamin D and the gut microbiome: a systematic review of in vivo studies. Eur. J. Nutr. 1–16 (2018). https://doi.org/10.1007/s00394-018-1842-7
24. P. Lips, Relative value of 25 (OH) D and 1, 25 (OH) 2D measurements. J. Bone Miner. Res. **22**(11), 1668–1671 (2007)
25. A. Webb, B. DeCosta, M. Holick, Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. J. Clin. Endocrinol. Metab. **68**(5), 882–887 (1989)
26. R.B. Brown, M.S. Razzaque, Phosphate toxicity and tumorigenesis. Biochim. Biophys. Acta. Rev. Cancer **1869**(2), 303–309 (2018)
27. R.B. Brown, M.S. Razzaque, Dysregulation of phosphate metabolism and conditions associated with phosphate toxicity. Bonekey reports **4**, 705 (2015)
28. Y. Kuang, J.D. Nagy, J.J. Elser, Biological stoichiometry of tumor dynamics: mathematical models and analysis. Discret. Contin. Dyn. Syst. Ser. B **4**(1), 221–240 (2004)
29. C.D. Papaloucas, M.D. Papaloucas, V. Kouloulias, K. Neanidis, K. Pistevou-Gompaki, J. Kouvaris, A. Zygogianni, K. Mystakidou, A.C. Papaloucas, Measurement of blood phosphorus: a quick and inexpensive method for detection of the existence of cancer in the body. Too good be true, or. Forgot. Knowl. ? Med Hypotheses **82**(1), 24–25 (2014). https://doi.org/10.1016/j.mehy.2013.10.028

30. J.J. Elser, M.M. Kyle, M.S. Smith, J.D. Nagy, Biological stoichiometry in human cancer. PLoS ONE. **2**(10), e1028 (2007)
31. M. D'Arcangelo, O. Brustugun, Y. Xiao, Y. Choi, C. Behrens, L. Solis, Y. Wang, R. Firestein, T. Boyle, M. Lund-Iversen, 194 Prevalence and prognostic significance of sodium-dependent phosphate transporter 2B (NaPi2B) protein expression in non-small cell lung cancer (NSCLC). Ann. Oncol. **25**(suppl 4), iv66–iv67 (2014)
32. D. Ward, A. Griffin, Phosphorus incorporation into nucleic acids and proteins of liver nuclei of normal and azo dye-fed rats. Cancer Res. **15**, 456–461 (1955)
33. H. Jin, C.-X. Xu, H.-T. Lim, S.-J. Park, J.-Y. Shin, Y.-S. Chung, S.-C. Park, S.-H. Chang, H.-J. Youn, K.-H. Lee, High dietary inorganic phosphate increases lung tumorigenesis and alters Akt signaling. Am. J. Respir. Crit. care Med. **179**(1), 59–68 (2009)
34. C.E. Camalier, M.R. Young, G. Bobe, C.M. Perella, N.H. Colburn, G.R. Beck, Elevated phosphate activates N-ras and promotes cell transformation and skin tumorigenesis. Cancer Prev. Res. **3**(3), 359–370 (2010)
35. K.M. Wilson, I.M. Shui, L.A. Mucci, E. Giovannucci, Calcium and phosphorus intake and prostate cancer risk: a 24-y follow-up study. Am. J. Clin. Nutr. **101**, 173–183 (2015)
36. P. Liu, H. Cheng, T.M. Roberts, J.J. Zhao, Targeting the phosphoinositide 3-kinase (PI3K) pathway in cancer. Nat. Rev. Drug Discov. **8**(8), 627 (2009)
37. Y. Lin, K.E. McKinnon, S.W. Ha, G.R. Beck, Inorganic phosphate induces cancer cell mediated angiogenesis dependent on forkhead box protein C2 (FOXC2) regulated osteopontin expression. Mol. Carcinog. **54**(9), 926–934 (2014)
38. A.A. Bobko, T.D. Eubank, B. Driesschaert, I. Dhimitruka, J. Evans, R. Mohammad, E.E. Tchekneva, M.M. Dikov, V.V. Khramtsov, Interstitial inorganic phosphate as a tumor microenvironment marker for tumor progression. Sci. Rep. **7**, 41233 (2017). https://doi.org/10.1038/srep41233
39. J. Chudek, A. Nagy, F. Kokot, A. Podwinski, A. Wiecek, E. Ritz, G. Kovacs, Phosphatemia is related to chromosomal aberrations of parathyroid glands in patients with hyperparathyroidism. J. Nephrol. **20**(2), 164–172 (2007)
40. S. Yamada, M. Tokumoto, N. Tatsumoto, M. Taniguchi, H. Noguchi, T. Nakano, K. Masutani, H. Ooboshi, K. Tsuruya, T. Kitazono, Phosphate overload directly induces systemic inflammation and malnutrition as well as vascular calcification in uremia. Am. J. Physiol.-Ren. Physiol. **306**(12), F1418–F1428 (2014)
41. R.J. Klement, The emerging role of ketogenic diets in cancer treatment. Curr. Opin. Clin. Nutr. Metab. Care **22**(2), 129–134 (2019)
42. F. Bozzetti, B. Zupec-Kania, Toward a cancer-specific diet. Clin. Nutr. **35**(5), 1188–1195 (2016)
43. C.F. Garland, F.C. Garland, Do sunlight and vitamin D reduce the likelihood of colon cancer? Int. J. Epidemiol. **9**(3), 227–231 (1980)
44. I. Savoye, C.M. Olsen, D.C. Whiteman, A. Bijon, L. Wald, L. Dartois, F. Clavel-Chapelon, M.-C. Boutron-Ruault, M. Kvaskoff, Patterns of ultraviolet radiation exposure and skin cancer risk: the E3N-SunExp study. J. Epidemiol. **28**, 27–33 (2017)
45. R. Krause, B. Matulla-Nolte, M. Essers, A. Brown, W. Hopfenmüller, UV radiation and cancer prevention: what is the evidence? Anticancer Res. **26**(4A), 2723–2727 (2006)
46. W.B. Grant, Ecological studies of the UVB–vitamin D–cancer hypothesis. Anticancer Res. **32**(1), 223–236 (2012)
47. B. Lindelöf, B. Krynitz, S. Ayoubi, C. Martschin, D. Wiegleb-Edström, K. Wiklund, Previous extensive sun exposure and subsequent vitamin D production in patients with basal cell carcinoma of the skin, has no protective effect on internal cancers. Eur. J. Cancer **48**(8), 1154–1158 (2012)
48. F. Turati, M. Rossi, C. Pelucchi, F. Levi, C. La Vecchia, Fruit and vegetables and cancer risk: a review of southern European studies. Br. J. Nutr. **113**(S2), S102–S110 (2015)
49. F.L. Meyskens, E. Szabo, Diet and cancer: the disconnect between epidemiology and randomized clinical trials. Cancer Epidemiology and Prevention. Biomarkers **14**(6), 1366–1369 (2005)
50. T.M. Gibson, L.M. Ferrucci, J.A. Tangrea, A. Schatzkin, Epidemiological and clinical studies of nutrition. In: Seminars in oncology 2010, vol. 3, pp. 282–296. Elsevier
51. USDA: National Nutrient Database for Standard Reference, Legacy. (2018). https://ndb.nal.usda.gov/ndb/ Accessed March 4 2019
52. S. McClure, A. Chang, E. Selvin, C. Rebholz, L. Appel, Dietary sources of phosphorus among adults in the United States: Results from NHANES 2001–2014. Nutrients **9**(2), 95 (2017)
53. U. Fresán, J. Sabaté, M.A. Martínez-Gonzalez, G. Segovia-Siapco, C. de la Fuente-Arrillaga, M. Bes-Rastrollo, Adherence to the 2015 Dietary Guidelines for Americans and mortality risk in a Mediterranean cohort: The SUN project. Prev. Med. **118**, 317–324 (2019)
54. M. Schulpen, P.H. Peeters, P.A. van den Brandt, Mediterranean diet adherence and risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. Gastric Cancer **22**, 663–674 (2019)
55. W.J. Witlox, F.H. van Osch, M. Brinkman, S. Jochems, M.E. Goossens, E. Weiderpass, E. White, P.A. van den Brandt, G.G. Giles, R.L. Milne, An inverse association between the Mediterranean diet and bladder cancer risk: a pooled analysis of 13 cohort studies. Eur. J. Nutr. (2019). https://doi.org/10.1007/s00394-019-01907-8
56. A. Castelló, P. Amiano, N.F. de Larrea, V. Martín, M.H. Alonso, G. Castaño-Vinyals, B. Pérez-Gómez, R. Olmedo-Requena, M. Guevara, G. Fernandez-Tardon, Low adherence to the western and high adherence to the mediterranean dietary patterns could prevent colorectal cancer. Eur. J. Nutr. **58**(4), 1495–1505 (2019). https://doi.org/10.1007/s00394-018-1674-5
57. L. Schneider, L.J. Su, L. Arab, J.T. Bensen, L. Farnan, E.T. Fontham, L. Song, J. Hussey, A.T. Merchant, J.L. Mohler, Dietary patterns based on the Mediterranean diet and DASH diet are inversely associated with high aggressive prostate cancer in PCaP. Ann. Epidemiol. **29**, 16–22. e11 (2019)
58. F. Turati, G. Carioli, F. Bravi, M. Ferraroni, D. Serraino, M. Montella, A. Giacosa, F. Toffolutti, E. Negri, F. Levi, Mediterranean diet and breast cancer risk. Nutrients **10**(3), 326 (2018)
59. A. Hodge, J. Bassett, N. Shivappa, J. Hébert, D. English, G. Giles, G. Severi, Dietary inflammatory index, Mediterranean diet score, and lung cancer: a prospective study. Cancer Causes Control **27**(7), 907–917 (2016)
60. Y. Mahamat-Saleh, I. Cervenka, I. Savoye, M.-C. Boutron-Ruault, M. Kvaskoff, Mediterranean dietary pattern and skin cancer risk: a prospective cohort study in French women. Rev. d.'Épidémiologie et. de. St.é Publique **66**, S272 (2018)
61. L. Schwingshackl, C. Schwedhelm, C. Galbete, G. Hoffmann, Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis. Nutrients **9**(10), 1063 (2017)
62. C. Zhang, H. Tian, J. Liu, S. Wang, M. Liu, S. Pan, X. Shi, Pools and distributions of soil phosphorus in China. Global Biogeochem. Cycles **19**(1), 1–8 (2005)
63. X. Liu, W. Meng, G. Liang, K. Li, W. Xu, L. Huang, J. Yan, Available phosphorus in forest soil increases with soil nitrogen but not total phosphorus: evidence from subtropical forests and a pot experiment. PloS ONE **9**(2), e88070 (2014)
64. Brazil nut. (2009). http://www.newworldencyclopedia.org/p/index.php?title=Brazil_nut&oldid=905997
65. J. Parry, Pacific islanders pay heavy price for abandoning traditional diet. World Health Organization. Bull. World Health Organ. **88**(7), 484 (2010)
66. M.A. Moore, F. Baumann, S. Foliaki, M.T. Goodman, R. Haddock, R. Maraka, J. Koroivueta, D. Roder, T. Vinit, H.J. Whippy, Cancer epidemiology in the pacific islands-past, present and future. Asian Pac. J. cancer Prev.: APJCP **11**(0 2), 99 (2010)