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Vitamin D and Cancer

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1. Introduction

Vitamin D has been known as a regulator of bone and mineral metabolism by regulation of calcium absorption in the gut and reabsorption by the kidney, which is mediated by the vitamin D receptor (*VDR*). The expression of *VDR* in a variety of cell lines coupled with increased evidence of *VDR* involvement in cell differentiation and inhibition of cellular proliferation suggests that vitamin D plays a role in many diseases. A meta-analysis of randomized controlled trials demonstrated that intake of vitamin D supplements was associated with a significant 7% reduction in mortality from any causes (Autier & Gandini, 2007). A serum 25-hydroxyvitamin D₃ (25OHD₃) concentration of 25 nmol/l was associated with a 17% reduction in incidence of cancer, a 29% reduction in total cancer mortality, and a 45% reduction in digestive system cancer mortality (Giovannucci et al., 2006). A low serum 25OHD₃ was prospectively associated with an increased risk of fatal cancer in patients referred to coronary angiography (Pilz et al., 2008).

Alphacalcidol, a vitamin D analogue, has been demonstrated significant antitumor activity in patients with low-grade non-Hodgkin's lymphoma of the follicular, small-cleaved cell type (Raina et al., 1991). In patient with parathyroid cancer, vitamin D has been shown to avert or delay the progression of recurrence (Palmieri-Sevier et al., 1993). In locally advanced or cutaneous metastatic breast cancer, topical calcipotriol treatment reduced in the diameter of treated lesions that contained *VDR* (Bower et al., 1991). In a clinical trial, high-dose calcitriol decreased Prostatic-specific antigen (PSA) levels by 50% and reduced thrombosis in prostate cancer patients (Beer et al., 2003 & 2006). In hepatocellular carcinoma, calcitriol and its analogs have been reported to reduce tumor volume, increase apoptosis of hepatocarcinoma cells by 21.4%, and transient stabilization of the serum alpha-fetoprotein levels (Dalhoff et al., 2003; Luo et al., 2004; Morris et al., 2002).

Calcitriol additively or synergistically potentiates the antitumor of other types of chemotherapeutic agents. Calcitriol enhances cellular sensitivity of human colon cancer cells to 5-fluorouracil (Liu et al., 2010). Combination of calcitriol and cytarabine prolonged remission in elderly patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) (Slapak et al., 1992; Ferrero, et al., 2004). In a prospective study, a combination of active vitamin D and α -interferon has shown to be effective in patients with metastatic renal cell carcinoma (Obara et al., 2008). Calcitriol promotes the anti-proliferative effects of gemcitabine and cisplatin in human bladder cancer models (Ma et al., 2010), and also potentiates antitumor activity of paclitaxel and docetaxel (Hershberger et al., 2001; Ting et al. 2007). A phase II study showed that high-dose calcitriol with docetaxel may increase

time to progression in patients with incurable pancreatic cancer when compared with docetaxel monotherapy (Blanke, 2009).

2. Risk factors for the development of both vitamin D deficiency and cancer

It has been noted that vitamin D and cancer share many of the same risk factors, including both environmental (air pollution, geographic and seasonal) and genetic risk factors.

2.1 Environmental factors

Changes in the environment, such as those caused by air pollution, geographic and seasonal factors, may cause diseases that contribute to the development of both vitamin D deficiency and cancer.

2.1.1 Air pollution factors

Atmospheric pollution has been suggested to be a cause of reduced vitamin D synthesis in the skin. In Australia, some authors demonstrated a large difference in vitamin D synthesis between an urban canyon (urbanized environment with tall building) and a typical suburban area (~2.5 km away from urban area) (Kinley et al., 2010). Increased atmospheric pollution may be related to haze from industrial and vehicle sources and lead to decrease in absorption of ultraviolet-B (UVB) photons, thereby reducing the cutaneous vitamin D synthesis (Mimms, 1996; Hollick, 1995). In another study, some reported that the higher atmospheric pollution, the lower the amount of UVB light reaching ground level (Agarwal et al., 2002). They also showed that children living in areas of high atmospheric pollution are at risk of developing vitamin D deficiency rickets. In a study Belgian postmenopausal women who participated in outdoor activities during the summer, urban inhabitants were reported to have an increased prevalence of vitamin D deficiency compared with rural inhabitants (Manicourt & Devogelaer, 2008). In a cross sectional study, living in a polluted area plays a significant independent role in vitamin D deficiency (Hosseini et al., 2010). Similarly, cancer mortality rates (esophagus, stomach, colon-rectum, liver, lung, breast, and bladder) in 263 counties in all Provinces of China were inversely associated with solar UVB exposure by using the National Central Cancer Registries (NCCR) of China, satellite measurements of cloud-adjusted ambient UVB intensity that were obtained from the NASA Goddard Space Flight Center Data Archive Center database, and the Geographic Information System (GIS) methods (Chen et al., 2010). Cancer incidence rates (esophagus, stomach, colon-rectum, and cervix) in 30 counties were inversely correlated with ambient UVB exposure. Lung cancer mortality has been shown the strongest inverse correlation with an estimated 12% fall per 10 mW/(nm m²) increase in UVB irradiance even adjusted for smoking. These associations were similar to those observed in a number of populations of European origin.

2.1.2 Geographic factors

The relationship between the geographical variation of colon cancer mortality rates and vitamin D related to UVB was first proposed in 1980 (Garland & Garland, 1980). The authors showed that the colon mortality rates are highest in the Northeast and lowest in the Southwest of the United States from 1950 - 1969 and was correlated to the annual hours of sunshine. It has been observed that with each 10 degrees distance from equator, there is a

progressive decrease in UVB radiation exposure (Diffey, 1991). Solar UVB is the primary source of vitamin D for most people living on Earth. Nuclear submarine crewmen who were not exposed to UVB for 3 months showed a decrease in an already low circulating 25OHD₃ level from 13.7 to 7.9 ng/ml (Garland & Garland, 1980). Grant determined that 14 types of cancer (bladder, breast, colon, endometrial, esophageal, gallbladder, gastric, ovarian, pancreatic, rectal, renal and vulvar cancer and both Hodgkin's and non-Hodgkin's lymphoma) had mortality rates inversely correlated with solar UVB levels (Grant, 2009). During the cold weather, latitude was found to determine levels of vitamin D-producing UV radiation. As latitude increase, vitamin D producing UV radiation decreases dramatically and may inhibit vitamin D synthesis in humans (Kimlin et al., 2007).

2.1.3 Seasonal factors

Seasonal variations of 25OHD₃ were reported either in southern and northern latitudes (Oliveri et al., 1993; Stryd et al., 1979). Another study confirmed and quantified the relatively large seasonal fluctuations in circulating 25OHD₃ levels in association with summer sun exposure among outdoor workers. Their median serum 25OHD₃ levels decreased from 122 nmol/L in late summer to 74 nmol/L in late winter (Barger-Lux & Heany, 2002). Similarly, a seasonal pattern has been noticed in many cancers with the highest in the winter and springs – including lung cancer, brain tumors, parathyroid tumor, non-Hodgkin's lymphoma, Hodgkin's lymphoma, childhood leukemia/lymphoma, monocytic leukemia, breast cancer, thyroid cancer, bladder carcinoma, and cervical cancer. In the summer and autumn season, certain cancers (breast, colon, prostate, Hodgkin's lymphoma, and lung) have a better survival rates than during other seasons (Luong & Nguyen, 2010).

2.2 Genetic factors

Genetic studies provide an excellent opportunity to link molecular variations with epidemiological data. DNA sequences variations such as polymorphisms have modest and subtle biological effects. Receptors play a crucial role in the regulation of cellular function, and small changes in their structure can influence intracellular signal transduction pathways.

The VDR is expressed and regulated in mammary gland during the reproductive cycle (Zinser & Welsh, 2004). VDR ablation is associated with ductal ectasia of the primary ducts, loss of secondary and tertiary ductal branches and atrophy of the mammary fat pad (Welsh et al., 2011). VDR has also been demonstrated to be lowered in human colorectal adenocarcinoma biopsies (34.5%) than in adjacent normal mucosa (82.5%) (Meggouh et al., 1990). In this colorectal adenocarcinoma, the incidence decreased from right colon (64.7%) to left colon (27.7%), and rectum (15%). Certain allelic variations in the VDR may also be genetic risk factors for developing tumors. There are five important common polymorphisms within the VDR gene region that are likely to exert functional effects on VDR expression. *Cdx2*, located in the promoter region of exon 1, affects the binding ability of VDR and subsequent VDR transcription activity; *Fok1* located in translation start of the exon 2; and three other variants (*Bsm1*, *Apa1* and *Taq1*) located at the 3' end of VDRs that may influence VDR expression by altering the mRNA stability. In a review of the literature, an association of VDR polymorphisms and cancer prognosis are reported to be strongest for prostate cancer (*Fok1* and *Taq1*), breast cancer (*Bsm1*, *Taq1* and *Apa1*), malignant melanoma

(*Bsm1*, *Fok1* and *Taq1*), renal cell carcinoma (*Taq1*), colorectal cancer (*Apa1*, *Fok1*, *Bsm1*, and *Taq1*), epithelial ovarian cancer (*Fok1*), lung cancer (*Taq1*), and oral squamous cell carcinoma (*Taq1*) (Köstner et al., 2009; Mahmoudi et al., 2010; Slattery et al., 2001; Slattery et al., 2006; Taylor et al., 1996; Lundin et al., 1999; Hutchinson et al., 2000; Tamez et al., 2009; Dogan et al., 2009; Bektas-Kayhan et al., 2010). However, other reports are conflicting and the role of *VDR* polymorphisms remains obscure. Their studies revealed no relationship between prostate and breast cancers and *VDR* variants (Ntais et al., 2003; Császák & Abel, 2001; Newcomb et al., 2002; Buyru et al., 2003).

There are numerous potential gene products that are transcriptionally activated by *p53* and are involved in cell cycle arrest or apoptosis (Ko & Prives, 1996). Some authors demonstrated a trend toward lower risk of a *p53* mutation with increased hours of sunshine exposure (Slattery et al., 2010). They also reported specific point mutations of the *p53* gene were associated with the *Fok1* and *Cdx2* *VDR* genotypes. The *p53* is one of the more commonly mutated genes in rectal and pancreatic tumors (Slattery et al., 2009; Slebos et al., 2000). The mutated *p53* gene increases the nuclear accumulation of *VDR*, even in the absence of added vitamin D, and converts vitamin D into an anti-apoptotic agent (Stambolsky et al., 2010).

The cytochrome P₄₅₀ (*CYP*) is responsible for the oxidation, peroxidation, and/or reduction of vitamins, steroids, xenobiotics, and metabolism of drugs. The *CYP27B1* (25-hydroxyvitamin D₃-1 α -hydroxylase) enzyme catalyzes the 1 α -hydroxylation of the 25OHD₃ to 1,25OHD₃, the most active form of vitamin D₃ metabolite. 1 α -hydroxylase is down-regulated early in the neoplastic process of prostatic cancer cells (Chen et al., 2003; Hsu et al., 2001). In another study, the common genotypic variation in *CYP27B1*, however, has little or no effect on overall prostate cancer risk (Holt et al., 2009). The *CYP27B1* mRNA in malignant breast tumors was reported to decrease in comparison with normal mammary tissue (McCarthy et al., 2009). 1 α -hydroxylation levels were found elevated in malignant pancreatic cells and their proliferation is inhibited by prohormone 25OHD₃ (Schwartz et al., 2004). Calcitriol significantly increased the 24-hydroxylase mRNA in the human cervical adenocarcinoma and the human ovarian adenocarcinoma cell lines (Kloss et al., 2010). The *CYP24A1* encodes for the catabolic enzyme 24-hydroxylase and is responsible for inactivating vitamin D metabolites. The *CYP24A1* gene was found to be amplified in breast cancer (Albertson et al., 2000). In prostate cancer mortality, significantly altered risks of recurrence/progression were observed in relation to genotype for two *tagSNPs* (single-nucleotide polymorphisms) of *VDR*, *CYP24A1*, and one *CYP27B1* (Holt et al., 2010); *CYP24A1* expression is inversely correlated with promoter DNA methylation in prostate cancer cell lines (Luo et al., 2010), and its overexpression was also observed to be associated with poorer survival in patients with lung adenocarcinoma (Chen et al., 2011). The gene encoding for *CYP24A1* and *CYP27B1* have been observed to be expressed in colon cancer cells (Anderson et al., 2006; Tangpricha et al., 2001). Variants of *CYP24A1* and *CYP27B1* have also been reported to be associated with risk of distal colon cancer (Dong et al., 2009). There is a deregulation of the vitamin D signaling and metabolic pathways in breast cancer (Lopes et al., 2010). The *VDR* was strongly associated with the estrogen receptor positivity in breast carcinomas. *CYP27B1* expression is slightly lower in invasive carcinomas (44.6%) than in benign lesions (55.8%). In contrast, *CYP24A1* expression was augmented in carcinomas (56% in *in situ* and 53.7% in invasive carcinomas) when compared with that in benign lesions (19%). In another study, however, it has found no difference in the expression of the *VDR*,

CYP27B1, and *CYP24A1* mRNA in breast cancer and non-neoplastic mammary tissue (de Lyra et al., 2006).

Vitamin D binding protein (DBP) is the main transporter of vitamin D in the bloodstream. DBP-macrophage activating factor (DBP-maf) is considered to be deglycosylated DBP in cancer patients causing inability to activate macrophages and a strong inhibitory activity on prostate tumor cells (Rehder et al., 2009; Gregory et al., 2010). DBP-maf acts as a potent anti-angiogenic factor and inhibits tumor growth *in vivo* (Kalkunte et al., 2005). These authors also reported that DBP-maf also inhibited the vascular endothelial growth factor (VEGF) signaling.

3. Role of vitamin D and its analog in cancer

Calcitriol acts mainly via its high affinity receptor *VDR* through a complex network of genomic (transcription and post-transcription), binds to intracellular *VDR*, which subsequently heterodimerizes with another nuclear retinoid X receptor (*RXR*) and non-genomic mechanisms which may indirectly affect gene transcription via the regulation of intracellular signaling pathways that target transcription factors. *VDR* expressed has been detected in a variety of cultured human cell lines. In breast cancer, the protein levels of the *VDR* were elevated in sensitive cell lines upon 1,25OHD₃ treatment, whereas resistant clones were unable to induce *VDR* (Jensen et al., 2002). The authors suggested that the levels of *VDR* in cancer might serve as a prognostic marker in cancer treatment with 1,25OHD₃.

Calcitriol is a potent regulator of cell proliferation, differentiation and apoptosis in a variety of cell types. Calcitriol and its analogs induce apoptosis in tumor cells through the activation of a caspase cascade (Guzey et al., 2002; Weitsman et al., 2003). The caspases have been considered the pivotal executioner of all programmed cell death (Hengartner, 2000). However, calcitriol may induce apoptosis in cancer cells through another novel cascade- and *p53*-independent pathway that can be inhibited by *Bcl-2* (Mathiasen et al., 1999). Calcitriol and its analogs may cause apoptosis in cancer cells directly by increasing intracellular free calcium ([Ca²⁺]_i) (Vandewalle et al., 1995) and indirectly through the activation of a calcium-dependent cysteine protease, *μ-calpain* (Berry et al., 1999; Mathiasen et al., 2002). Furthermore, calcitriol stimulates membrane phospho-inositide breakdown in human colon cancer cell line, causing translocation of protein kinase C to the membrane, and increasing [Ca²⁺]_i by both releasing calcium stores and promoting calcium influx (Wali et al., 1992). Calcitriol and its analogs are potent inducers of both active and latent forms of transforming growth factor beta (TGFβ), which participates in the regulation of cell growth, phenotype, and differentiation in various tissues (Koli & Keski-Oja, 1995; Laiho & Keski-Oja, 1992).

Calcitriol has been shown to mediate a G₂/M cell cycle progression and induce cell death in a number of cancer cell lines via direct induction of *GADD45a*, which is a DNA-induced and *p53*-regulated gene that plays an essential role in cell cycle control and DNA repair (Jiang et al., 2003; Akutsu et al., 2001). By contrast, the anti-proliferative functions of *VDR* are associated at the G₀/G₁ stage of the cell cycle, coupled with upregulation of a number of cell cycle inhibitors, kinase inhibitors *p21^(waf1/cip1)* (Saramäki et al., 2006). However, paricalcitol arrested in G₁/G₀ phases and G₂/M phases in leukemia cell lines, in G₁G₀ in myeloma cells, and induced the expression of *p21^(waf1/cip1)* and *p27^(Kip1)*, and down-regulation of *p45^{SKP2}* (Wang et al., 1996; Munker et al., 1996; Jiang et al., 1994; Lin et al., 2003).

Angiogenesis has been suggested as an indicator of neoplastic transformation. Calcitriol has been reported a potent inhibitor of tumor cell-induced angiogenesis (Shokravi et al., 1995; Majewski et al., 1996). Calcitriol inhibits hypoxia inducible factor-1(HIF-1)/VEGF pathway

in human cancer cells (Ben-Shoshan et al., 2007). Increased levels of HIF-1 activity are often associated with increased tumor aggressiveness, therapeutic resistance, and mortality (Semenza, 2003). VEGF stimulates endothelial cells to proliferate, migrate, and organize into capillary beds (Polverini et al., 2002). DBP-maf inhibited VEGF signaling by decreasing VEGF-mediated phosphorylation of VEGFR-2 and ERK1/2, a downstream target of the VEGF signaling cascade (Kalkunte et al., 2005). Calcitriol and its analogs have been demonstrated to inhibit tumor invasion and metastasis by reducing the expression of serine proteinases, metalloproteinases (MMP-2 and MMP-9), VEGF and parathyroid hormone related peptide (*PTHrP*) in lung carcinoma cell lines (LLC-GFP cells) (Nakagawa et al., 2005a). The metastatic growth of LLC-GFP cells was remarkably reduced in response to calcitriol (Nakagawa et al., 2005b).

Calcitriol and its analogs induced the expression of tumor suppressor gene *PTEN* (phosphatase and tensin homolog deleted on chromosome 10) (Liu et al., 2005; Kumagai et al., 2003). Overexpression of *VDR* stimulated the activity of *PTEN* promoter and also enhances the *PTEN* protein level (Pan et al., 2009). The *PTEN* phosphatase can block phosphoinositide 3-kinase/AKT (PI3K/Akt) signaling pathway, which contribute to both cell death and the inhibition of cell proliferation (Cantley & Neel, 1999). *PTEN* mutations have been found in many human cancers (Tamura et al., 1999). In colon cancer cells, calcitriol and its analogs increase the expression of *E-cadherin*, a transmembrane protein located in intercellular adherent junctions, which make cells more adherent to each other (Pálmer et al., 2001). Loss of *E-cadherin* expression is a common even during the transition from adenoma to carcinoma (Perl et al., 1998). *E-cadherin* is a tumor suppressor gene, and its decrease in expression is associated with poor prognosis in patients with prostate cancer (Umbas et al., 1994). Vitamin D also suppresses *tenascin-C*, which promotes growth, invasion, and angiogenesis during tumorigenesis (González-Sancho et al., 1998).

The induction of ornithine decarboxylase (ODC) may be an essential process in the mechanism of tumor promotion (O'Brien et al., 1975), and calcitriol has been reported to inhibit tumor promoter-induced ODC expression in the skin, stomach, colon, and liver in animals (Hashiba et al., 1987). Calcitriol, however, did not induce epidermal ODC activity, but inhibited the induction of ODC by the tumor promoters 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and teleocidin, suggesting that it is an anti-promoter rather than a promoter in mouse skin carcinogenesis (Chida et al., 1984).

Calcitriol has been reported to regulate the transcription of the tumor necrosis factor alpha (TNF- α) without affecting translation in leukemia cell line (Steffen et al., 1988), may increase the sensitivity of cancer cells to TNF- α and potentiates the cytotoxic effect of the cytokine (Yacobi et al., 1996), which is an important factor in immunological anti-cancer therapy. TNF- α potentiates the effect of 1,25OHD₃ in inducing of differentiation of human myeloid cell lines (Trinchieri et al., 1987).

Prostaglandins (PGs) have been shown to play a role in the development and progression of many cancers. Calcitriol has been reported to regulate the expression of several key genes involved in the PG pathway causing a decrease in PG synthesis (Moreno et al., 2005). Cyclooxygenase (COX) participates in the conversion of arachidonic acid to PGs. COX-2 has been reported to increase in various malignancies (van Rees et al., 2001; Ristimäki et al., 2002). Calcitriol and its analogs decreased expression of COX-2 in colon cancer cells (Kumagai et al., 2003). Selective COX-2 inhibitor reduces the polyp in patients with familial adenomatous polyposis (Steinbach et al., 2000). 15-hydroxy-prostaglandin dehydrogenase (15-PGDH) is the enzyme that catalyzes the conversion of PGs to their corresponding 15-

keto derivatives; 15-PGDH has been demonstrated as an oncogene antagonist and plays a tumor-suppressive role in colon cancer (Yan et al., 2004). Calcitriol increases 15-PGDH mRNA and protein expression in various prostate cancer cells (Moreno et al., 2005). Calcitriol has also found to regulate COX-2 and 15-PGDH expression in other cells (Pichaud et al., 1997; Aparna et al., 2008). Calcitriol and its analogs can significantly decrease intestinal tumor load in *Apc^{Min}* mice (Huerta et al., 2002). Vitamin D and its metabolites have been known to inhibit cell proliferation in human rectal mucosa and a colon cancer cell line (Thomas et al., 1992).

The human peroxisome proliferator-activated receptor delta (*PPAR δ*) and *VDR* signaling pathways regulate a multiple of genes that are of importance for a multiple of cellular functions including cell proliferation, cell differentiation, immune response and apoptosis. The provided link between *VDR* and *PPAR* may play an important role in treatment in prostate cancer and melanoma (Peehl & Feldman, 2004; Sertznig et al., 2009). *PPAR δ* expression was reported to be increased by 1.5–3.2-fold after a 3-h stimulation of breast and prostate cancer cell lines with 1,25OHD₃ (Dunlop et al., 2005). *PPAR δ* has been reported to regulate lung cancer cell growth (Fukumoto et al., 2005) and it also may attenuate colon and skin carcinogenesis (Hartman et al., 2004; Marin et al., 2006; Kim et al., 2004). In addition, *PPAR δ* deficiency does not suppress intestinal tumorigenesis in *Apc^{Min/+}* mice (Reed et al., 2004).

Hypercalcemia is a common complication of paraneoplastic syndromes and is a contributor to the morbidity of cancer patients; in most cases, hypercalcemia is mediated by *PTHrP*. The *PTHrP* production has been suppressed by 1,25OHD₃ and its analogs in cancer cell line via down-regulation and suppression of epidermal growth factor (EGF)-induced *PTHrP* gene expression (Kremer et al., 1996; Kunakornsawat et al., 2002; Fazon et al., 1998). Calcitonin has been known to secrete in response to high calcium level and C cell of the human medullary carcinoma and was suppressed by calcitriol (Telenius-Berg et al., 1975; Zabel & Dietel, 1991).

4. Conclusion

Vitamin D certainly has a role in the prevention and treatment of cancer. It is necessary to check serum 25OHD₃ and parathyroid hormone (PTH) status in cancer patients. Serum levels of PTH have been reported to correlate with PSA levels and colorectal cancer (Skinner & Schwartz, 2009; Charalampopoulos et al., 2010). Some authors proposed that, in patients with normal calcium levels, the serum 25OHD₃ levels should be stored to > 55ng/ml in cancer patients (colon, breast, and ovary) (Garland et al., 2007). Calcitriol, 1,25OHD₃, is best used for cancer treatment, because of its active form of vitamin D₃ metabolite, suppression of PTH levels (acted as cellular growth factor), and their receptors presented in most of human cells. However, monitor of serum 25OHD₃ after taking calcitriol is not necessary because calcitriol inhibits the production of serum 25OHD₃ by the liver (Bell et al., 1984; Luong & Nguyen, 1996). The main limitation to the clinical widespread evolution of 1,25OHD₃ is its hypercalcemic side-effects.

5. References

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