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The Impact of Vitamin D in Cancer

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1. Introduction

The relationship between vitamin D and cancer has previously been reported in the literature. A systemic review and meta-analysis of prospective cohort studies revealed that a 20 nmol/L increase in the 25-hydroxyvitamin D₃ (25OHD) levels was associated with an 8% lower mortality in the elderly population (Schöttker et al., 2012). Oncology patients had significantly lower mean serum vitamin D levels than non-cancer primary care patients from the same geographic region (Churilla et al., 2011). In a community oncology experience, vitamin D deficiency is widespread in cancer patients and correlates with advanced stage disease (Churilla et al., 2012). A high prevalent of vitamin D deficiency has been associated with head and neck cancer (Orell-Kotikangas et al., 2011), breast cancer (Crew et al., 2009; Peppone et al., 2012), vulvar cancer (Salehin et al., 2012), prostate cancer (Varsavsky et al., 2011), pancreatic cancer (Wolpin et al., 2011), gastric cancer (Ren et al., 2012), colon and rectal cancer (Tangrea et al., 1997), ovarian cancer (Lefkowitz et al., 1994), oral cavity and esophagus cancers (Lipworth et al., 2009), myelo-proliferative neoplasms and myelo-dysplastic syndromes (Pardanani et al., 2011), multiple myeloma (Ng et al., 2009), non-Hodgkin's lymphoma (Drake et al., 2010), and chronic lymphocytic leukemia (Shamafelt et al., 2011). On the other hand, a serum 25OHD 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). Improving vitamin D status may also help lower the risk of colorectal cancer (Wu et al., 2011a). In a case-control study, a higher vitamin D intake is associated with a lower risk of esophageal squamous cell carcinoma (Launoy et al., 1998). A meta-analysis revealed that an increase of serum 25OHD by 50 nmol/L was associated with a risk reduction of 59% for rectal cancer and 22% for colon cancer (Yin et al., 2009). High 25OHD levels were associated with better prognosis in breast, colon, prostate cancer, and lung cancer relative to patients with lower 25OHD levels (Robsahm et al., 2004; Zhou et al., 2007). In a murine model, dietary vitamin D may play an important role as a preventive agent in andro-

gen-insensitive human prostate tumor growth (Ray et al., 2012). The season in which patients were operated on seemed to have an effect on survival of patients undergoing resection of non-small cell lung cancer (Turna et al., 2012). The survival of patients who had surgery in winter was statistically significantly shorter than that of patients who underwent surgery in the summer. In Australia, prostate cancer mortality rates are inversely correlated with solar radiation exposure (Loke et al., 2011). Dietary vitamin D₃ and calcitriol have been shown to demonstrate equivalent anticancer activity in mouse xenograft models of breast and prostate cancers (Swani et al., 2012). The combination of calcitriol and dietary soy resulted in substantially greater inhibition of tumor growth than the inhibition achieved with either agent alone in a mouse xenograft model of prostate cancer (Wang et al., 2012a). Soy diets alone caused a modest elevation in serum calcitriol. Vitamin D₃ treatment significantly suppressed the viability of gastric cancer and cholangiocarcinoma cells and also had a synergistic effect with other anti-cancer drugs, such as paclitaxel, adriamycin, and vinblastine (Baek et al., 2011). The vitamin D analog, 19-Nor-2 α -(3-hydroxypropyl)-1 α ,25-dihydroxyvitamin D₃, is a potent cell growth regulator with enhanced chemotherapeutic potency in liver cancer cells (Chiang et al., 2011). 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 prevent or delay the progression of recurrence (Palmieri-Sevier et al., 1993). In locally advanced or cutaneous metastatic breast cancer, topical calcipotriol treatment reduced the diameter of treated lesions that contained vitamin D receptor (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 hepatocarcinoma cell apoptosis by 21.4%, and transiently stabilize serum alpha-fetoprotein levels (Dalhoff et al., 2003; Luo et al., 2004; Morris et al., 2002). These findings suggested a relationship between vitamin D and cancer. In this chapter, we will discuss the role of vitamin D in cancer.

2. Genetic factors related to vitamin D and cancer

2.1. The Major Histocompatibility Complex (MHC) class II molecules

The major histocompatibility complex (MHC) class II molecules play an important role in the immune system and are essential in the defense against infection. The human MHC class II molecules are encoded by three different human leukocyte antigen (HLA) isotypes: HLA-DR, -DQ, and -DP. Studies have suggested that several genes within MHC region promote cancer susceptibility. A chimeric DR4 homozygous transgenic mouse line is reported to spontaneously develop diverse hematological malignancies at a high frequency (Raffegerst et al., 2009). Most of these neoplasms were highly similar to those found in human diseases. HLA-DR antigen expression was correlated with the histopathological type and to the degree of cell differentiation in cutaneous squamous cell carcinomas (Garcia-Plata et al., 1993). The DRB1*03 and DR-B1*13 alleles were significantly more frequent in patients with nasopharyngeal carcinoma compared with controls in southern Tunisia (Makni et al., 2010). The DR1 gene is

strongly associated with thyroid carcinoma (Panza et al., 1982). The HLA-DR was also increased in poorly differentiated thyroid carcinoma, especially in the anaplastic type (Lindhorst et al., 2002). The DQA1*0102 and DPB1*0501 alleles were significantly more common in Chinese patients with hepatocellular carcinoma (HCC) (Donaldson et al., 2001). The frequency of DRB1*0404 allele was significantly higher in the gastric cancer group compared with the gastritis group in Koreans (Lee et al., 2009). However, the frequencies of the DRB1*0405 and DQB1*0401 alleles were increased in the Japanese patients with intestinal-type gastric cancer compared with controls (Ando et al., 2009). Somatic mutations affecting HLA class II genes may lead to loss of HLA class II expression due to the formation of microsatellites in unstable colorectal carcinomas (Michel et al., 2010). The DRB1*15 allele and the haplotype DRB1*15 DQB1*0602 were associated with human papillomavirus (HPV)-16 positive invasive cervical cancer in Mexican women (Hernández-Hernández et al., 2009). The DRB1*0410 allele was the susceptibility allele in Japanese patients with testicular germ cell carcinoma (Ozdemir et al., 1997). Furthermore, the frequencies of the DRB1*09 and DQB1*03 alleles were increased in patients with non-Hodgkin's lymphoma and diffuse large B cell lymphoma compared with normal controls (Choi et al., 2008). The frequencies of the DRB1*04 and DRB1*15 alleles were significantly higher in Turkish children with acute leukemia compared with controls (Ozdilli et al., 2010). The DRB1*16 allele was a marker for a significant risk of chronic myelogenous leukemia in Eastern Canada (Naugler and Liwski, 2009). The DRB1*04 and DRB5 alleles are associated with disease progression in Iranian patients with chronic lymphocytic leukemia (Hojattat-Farsangi et al., 2008). On the other hand, calcitriol is known to stimulate phagocytosis and suppress MHC class II antigen expression in human mononuclear phagocytes (Tokuda et al., 1992 & 1996), thereby preventing antigen-specific T cell proliferation. In addition, calcitriol exerts effects that opposes the effect of IL-4 on MHC class II antigen expression in human monocytes (Xu et al., 1993) and specifically modulates human monocyte phenotype and function by altering HLA-DR antigen expression and antigen presentation, while leaving lytic function intact (Rigby et al., 1990). Calcitriol also decreases interferon- γ -induced HLA-DR antigen expression in normal and transformed human keratinocytes (Tamaki et al., 1990-1991 & Tone et al., 1991) and reduces the levels of HLA-DR mRNA in cultured epithelial tumor cell lines (Tone et al., 1993). In addition, 1 α -calcidol significantly modulates the expression of HLA-DR in human peripheral blood monocytes (Scherberich et al., 2005). These findings suggest that calcitriol may have an effect on cancer by suppressing the expression of MHC class II antigens.

2.2. Vitamin D Receptor (VDR)

The expression of VDR in a variety of cell lines, coupled with increased evidence of VDR involvement in cell differentiation, inhibition of cellular proliferation and angiogenesis in many tumor types, suggest that vitamin D plays a role in cancer (Luong and Nguyen, 2010 & Luong and Nguyễn, 2012). VDR ablation is associated with ductal ectasia of the primary mammary ducts, loss of secondary and tertiary branches and atrophy of the mammary fat pad (Welsh et al., 2011). Breast cancer patients with high VDR expression showed significant better in progression-free survival and overall survival than patients with moderate/negative VDR expression scores (Ditch et al., 2012). 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. The anti-carcinogenic potential of vitamin D might be mediated by *VDR* expression. The association between plasma 25OHD levels and colorectal adenoma was modified by the *TaqI* polymorphism of the *VDR* gene (Yamaji et al., 2011). There is a significant association between single nucleotide polymorphisms (SNPs) in the *VDR* gene and vitamin D intake in African Americans with colorectal cancer (Kupfer et al., 2011). The *BsmI* polymorphism of the *VDR* gene also modified the association between dietary vitamin D intake and breast cancer (Rollison et al., 2012). The *AA* genotype of *VDR* is reported to be associated with colorectal cancer, with a stronger association in female patients (Mahmoudi et al., 2012). The *FokI* and *BsmI* genotypes of *VDR* gene are implicated in the pathogenesis of renal cell carcinoma (RCC) in a North Indian population (Arjumand et al., 2012). Altered *VDR* expression was associated with RCC carcinogenesis via the expression of epithelial Ca^{2+} channel transient receptor potential vanilloid subfamily 5 and 6 (TRPV5/6) (Wu et al., 2011b). There is a significant association between shorter progression-free survival time in patients with head and neck squamous cell carcinoma and the *FokI TT* genotype, as well as the *Cdx2-FoxI-ApaI* haplotype (Hama et al., 2011). In Spanish children, osteosarcoma patients showed a significantly higher frequency of the *Ff* genotype of the *FokI VDR* gene than the control group (Ruza et al., 2003). In a German population, the *AaTtBb* genotype of the *VDR* gene is associated with basal cell carcinoma risk, whereas the *aaTTbb* genotype is found at a high frequency in both basal cell carcinomas and cutaneous squamous cell carcinomas compared with controls (Köststner et al., 2012). In a systematic review, *TaqI*, *BsmI* and *FokI* polymorphisms of the *VDR* gene were found to be associated with malignant melanoma (Denzer et al., 2011). Furthermore, the presence of specific *VDR BsmI* and *TaqI* alleles was associated with a higher C-reactive protein (CRP) level in cancer patients with cachectic syndrome (Punzi et al., 2012). In another prospective study, plasma 25OHD levels and common variation among several vitamin D-related genes (*CYP27A1*, *CYP2R1*, *CYP27B1*, *CYP24A1*, *GC*, *RXRA*, and *VDR*) were associated with lethal prostate cancer risk (Shui et al., 2012). Slattery et al. (2009) examined genetic variants that are linked to the pathway that contribute to colon cancer. They revealed that *FoxI VDR* polymorphism was associated with CpG Island methylator phenotype (CIMP) positive/Ki-ras mutated tumors, whereas the Poly A and *Cdx2 VDR* polymorphisms were associated only with Ki-ras mutated tumors.

2.3. MicroRNA (miRNA)

MiRNAs are endogenous noncoding RNAs that regulate gene expression through the translational repression or degradation of target mRNA (Bartel, 2004). Aberrant miRNA expression has been well characterized in cancer (Lu et al., 2005). Circulating miRNAs are suggested to be diagnostic and prognostic markers in breast cancer (Cortez et al., 2012). Circulating miRNA-125b expression is associated with chemotherapeutic resistance of breast cancer (Wang et al., 2012b). Several miRNAs are found to share 125b complementarity with a sequence in the 3'-untranslated region of human *VDR* mRNA. The overexpression miRNA-125b significantly decreased the endogenous *VDR* protein level in human breast adenocarcinoma cells lines (MCF-7) to 40% of the control (Mohri et al., 2009). This miRNA is down-regulated in cancer

tissue and causes high CYP24 protein expression, which catalyzes the inactivation of calcitriol (Komagata et al., 2009). Stress induced by serum starvation caused significant alteration in the expression of multiple miRNAs including miRNA-182, but calcitriol effectively reversed this alteration in breast epithelial cells (Peng et al., 2010). Vitamin D₃ up-regulated protein 1 (VDUP1) is regulated by miRNA-17-5p at the post-transcriptional levels in senescent fibroblasts (Zhuo et al., 2010). VDUP1 expression is increased in cancer cells (Takahashi et al., 2002; Dutta et al., 2005). In melanoma cell lines, the endogenous VDR mRNA level is inversely associated with expression of miRNA-125b (Essa et al., 2010), and calcitriol also reduced the miRNA-27b expression in these cell lines. In human colon cells, calcitriol induced miRNA-22 and may contribute to its antitumor action against this neoplasm (Alvarez-Diaz et al., 2012). Fifteen miRNAs are also differentially regulated by calcitriol in prostate cancer cells (LNCaP) (Wang et al., 2011a). Furthermore, calcitriol regulated miRNA-32 and miRNA-181 expressions in human myeloid leukemia cells (Gocek et al., 2011; Zimmerman et al., 2011; Wang et al., 2009a).

2.4. Renin-Angiotensin System (RAS)

The primary function of the renin-angiotensin system (RAS) is to maintain fluid homeostasis and regulate blood pressure. The angiotensin converting enzyme (ACE) is a key enzyme in the RAS and converts angiotensin (AT) I to the potent vasoconstrictor AT II (Johnston, 1994). The local RAS may influence tissue angiogenesis, cellular proliferation, apoptosis, and inflammation (Deshayes and Nahmias, 2005). Epidemiological and experimental studies suggested that the RAS may contribute to the paracrine regulation of tumor growth. The renin levels are elevated in patients with liver cirrhosis and HCC and positively correlated with α -fetoprotein (Lotfy et al., 2010). The over-expression of ACE is reported in extrahepatic cholangiocarcinoma (Beyazit et al., 2011), leukemic myeloid blast cells (Aksu et al., 2006), and macrophages in the lymph nodes of Hodgkin's disease patients (Koca et al., 2007). The AT II receptors were also expressed in all human gastric cancer lines (Huang et al., 2008), pre-malignant and malignant prostate cells (Louis et al., 2007), human lung cancer xenografts (Feng et al., 2011a), and ovarian cancer (Ino et al., 2006). The RAS mutation in codon 61 was the most common genetic alteration in poorly differentiated thyroid carcinomas (Volante et al., 2009). The ACE *I/D* polymorphism is a possible target for developing genetic markers for breast cancer in Brazilian women (Alves Corrêa et al., 2009). The ACE *I/D* polymorphisms play an important role in breast cancer risk and disease-free survival in Caucasian postmenopausal women (González-Zuloeta Ladd et al., 2012). Carriers of the high-activity *DD* genotype had an increased risk of breast cancer compared with low activity *II/ID* genotype carriers (van der Knaap et al., 2008). The *DD* genotype was associated with patients with an aggressive stage of prostate cancer (Wang et al., 2011b). ACE2 expression was decreased in non-small-cell lung cancer and pancreatic ductal adenocarcinoma in which AT II levels were higher than those in controls (Feng et al., 2010; Zhou et al., 2009). ACE2 has been suggested as a potential molecular target for pancreatic cancer therapy (Zhou et al., 2011). The AT II concentration in gastric cancer region was significantly higher than those of normal region (Kinoshita et al., 2009). Furthermore, AT II receptor blockers (ARB) suppress the cell proliferation effects of AT II in breast cancer cells (Du et al., 2012). The addition of ACE inhibitor or ARB to platinum-based first line chemotherapy contributed to prolong survival in patients with advanced lung cancer (Wilop

et al., 2009) and affected the prognosis of advanced pancreatic cancer patients receiving gemcitabine (Nakai et al., 2010). The RAS inhibitors also improved the outcome of sunitinib treatment in metastatic renal cell carcinoma (Keizman et al., 2011). On the other hand, the administration of ACE inhibitors in patients with the ACE *DD* genotype has been shown to decrease the level of calcitriol required (Pérez-Castrillón et al., 2006). In a hypertensive Turkish population, the presence of the ACE *D* allele, which correlates negatively with serum 25OHD levels, is linked to a higher left ventricular mass index value and elevated ambulatory blood pressure measurements (Kulah et al., 2007). In addition, genetic disruption of the *VDR* gene resulted in overstimulation of the RAS with increased renin and angiotensin II production, which lead to high blood pressure and cardiac hypertrophy. However, treatment with captopril reduced cardiac hypertrophy in *VDR*-knockout mice (Xiang et al., 2005), suggesting that calcitriol may function as an endocrine suppressor of renin biosynthesis. Moreover, calcitriol suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin core promoter (Yuan et al., 2007) and decreases ACE activity in bovine endothelial cells (Higiwara et al., 1988).

2.5. Toll-Like Receptor (TLR)

Toll-like receptors (TLRs) are a group of glycoproteins that functions as surface trans-membrane receptors and are involved in the innate immune responses to exogenous pathogenic microorganisms. Substantial evidence exists for an important role of TLRs in the pathogenesis and outcomes of cancer. TLR2 expression was significantly higher in sporadic colorectal cancerous tissue than in non-cancerous tissue (Nihon-Yanagi et al., 2012). The TLR5 play an important role in tumor progression of gastric cancer (Song et al., 2011). The TLR7 and TLR9 showed high expression in laryngeal carcinoma cells (Shikora et al., 2010). The over-expression of TLR9 was reported oral squamous cell carcinoma (Min et al., 2011), esophageal squamous cell carcinoma (Takala et al., 2011), and breast cancer cells (Qiu et al., 2011; Sandholm et al., 2012). The expression levels of TLR1, TLR2, TLR4, TLR5, TLR6, TLR8, and TLR10 are significantly higher in the human renal carcinoma cell line (780-6) than those in normal renal cell (HK-2) line (Yu et al., 2011). Chronic lymphocytic leukemia cells express all TLRs expressed by normal activated B cells, with a high expression of TLR9 and CD180 and an intermediate expression of TLR1, TLR6, and TLR10 (Arvaniti et al., 2011). The TLR4 polymorphisms are reported in patients with the risk of prostate cancer (Kim et al., 2012), head and neck squamous cell carcinomas (Bergmann et al., 2011), HCC (Minmin et al., 2011), and colon cancer (Eyking et al., 2011). Furthermore, multiple SNPs in TLR2 and TLR4 were associated with colon cancer survival (Slattery et al., 2012). On the other hand, vitamin D deficiency increases the expression of hepatic mRNA levels of TLR2, TLR4, and TLR9 in obese rats (Roth et al., 2011). However, calcitriol suppresses the expression of TLR2 and TLR4 protein and mRNA in human monocytes and triggers hypo-responsiveness to pathogen-associated molecular patterns (Sadeghi et al., 2006). Calcitriol has also been shown to down-regulate intracellular TLR2, TLR4 and TLR9 expression in human monocytes (Dickie et al., 2010). TLR activation results in the expression of the *VDR* and 1α -vitamin D hydroxylase in human monocytes (Liu et al., 2006). Additionally, calcitriol can cause the vitamin D-induced expression of cathelicidin in bronchial epithelial cells (Yim et al., 2007) and may enhance the production of cathelicidin LL-37 (Rivas-Santiago et al., 2008). The addition of a *VDR* antagonist has also

been shown to inhibit the induction of cathelicidin mRNA by more than 80%, thereby reducing the protein expression of this antimicrobial agent by approximately 70% (Yim et al., 2007). Cathelicidin was abundant in tumor-infiltrating NK1.1⁺ cells in mice. Cathelicidin knockout mice (*Camp*^{-/-}) permitted faster tumor growth than wild type controls; NK cells derived from *Camp*^{-/-} mice showed impaired cytotoxic activity toward tumor targets compared with wild-type mice (Büchau et al., 2010). The human cathelicidin LL-37, which inhibits gastric cancer cell proliferation, is down-regulated in gastric adenocarcinomas (Wu et al., 2010). Gastrointestinal cancer cells lacked LL-37 expression; Cathelicidin expression is modulated by histone-deacetylase (HDAC) inhibitors in various gastrointestinal cells, including gastric and hepatocellular cells (Schauer et al., 2004). HDAC inhibitors enhance the acetylation of core proteins, which is linked to the formation of transcriptionally active chromatin in various cells. The expression of the LL-37/hCAP-18 gene was also reduced in some leukemia cells (Yang et al., 2003). In patients with acute myeloid leukemia, there was a marked reduction of LL-37/hCAP-18 expression in the peripheral blood compared with the level in healthy donors (An et al., 2005). In myeloid cells, cathelicidin gene is a direct target of the VDR and is strongly up-regulated by calcitriol (Gombart et al., 2005). The combination of TLR ligands (CpG oligodeoxynucleotides, CpG-ODN) LL-37 generated significantly better therapeutic tumor effects and enhanced survival in murine ovarian tumor-bearing mice compared with CpG-ODN or LL-37 alone (Chuang et al., 2009).

3. Role of vitamin D and its analog in cancer

3.1. The bacillus Calmette-Guerin (BCG) vaccination

The BCG vaccine was developed to provide protection against tuberculosis and has also been demonstrated to offer protection against cancer. The combination of BCG and ionizing radiation resulted in the induction of autophagy in colon cancer cells (Yuk et al., 2010). Intravesical BCG therapy has been demonstrated to reduce the recurrence rate and the risk of progression to muscle-invasive disease in patients with superficial bladder tumors (Herr et al., 1988). The BCG vaccination significantly prolongs the survival of patients with a malignant melanoma after initial surgical removed (Kölmel et al., 2005) and improved survival rates in patients with resected lung cancer (Repin, 1992). BCG inoculation delayed the tumor growth and prolonged the survival time in nude mice with leukemia (Wang et al., 2011c). BCG vaccination reduced the risk of lymphomas in a Danish population (Villumsen et al., 2009) and demonstrated to reduce the mortality, morbidity, and frequency of myeloic and chronic leukemia in children (Ambrosch et al., 1981). On the other hand, BCG-vaccinated infants are almost 6 times more likely to have sufficient vitamin D concentrations than unvaccinated infants 3 months after BCG vaccination, and this association remains strong even after adjusting for season, ethnic group and sex (Lalor et al., 2011). Among the vaccinated group, there was also a strong inverse correlation between the IFN- γ response to *M. tuberculosis* PPD and vitamin D concentration; infants with higher vitamin D concentrations had lower IFN- γ responses. Similarly, tuberculosis in cattle usually presents with a rapid transient increase in serum calcitriol within the first two weeks following infection (Rhodes et al., 2003). 1,25OHD-positive mononuclear cells were later identified in all of the tuberculous granulomas. During

tuberculosis infection, alveolar macrophage-produced calcitriol plays a beneficial role by limiting inflammation-mediated tissue injury, potentiating NO production by stimulated monocytes/macrophages, inhibiting INF- γ production by stimulated CD4⁺ cells, and suppressing the growth of *M. tuberculosis* (Ametaj et al., 1996; Rockett et al., 1998).

3.2. Matrix Metalloproteinase (MMPs)

MMPs are proteolytic enzymes responsible for extracellular matrix remodeling and the regulation of leukocyte migration through the extracellular matrix, which is an important step in inflammatory and infectious pathophysiology. MMPs are produced by many cell types including lymphocytes, granulocytes, astrocytes and activated macrophages. The MMP-1 expression is linked to sarcoma cell invasion (Garamszegi et al., 2011). MMP-2 expression is increased in gastric cancer cells (Partyka et al., 2012) and colorectal cancer (Dong et al., 2011). MMP-9 is expressed in many cancer cells, such as those associated with non-small-cell lung cancer (Peng et al., 2012), ovarian cancer invasion and metastasis (Zhang et al., 2011a), glioblastoma multiforme (Yan et al., 2011), and adamantinous craniopharyndioma (Xia et al., 2011). The MMP-2 and MMP-9 secreted by leukemic cells increase the permeability of blood brain barrier of the CNS by disrupting tight junction proteins (Feng et al., 2011b). In gastric cancer, MMP-2 and MMP-9 play an important role in tumor invasion and metastasis (Parsons et al., 1998). The risks for the development of hypophyseal adenoma and cervical neoplasia are greater in patients with MMP-1 polymorphisms (Altaş et al., 2010; Tee et al., 2012) than those with the wild-type allele. The MMP-2 polymorphism contributed to prostate cancer susceptibility in North India (Srivastava et al., 2012) and to the clinical outcome of Chinese patients with non-small cell lung cancer treated with first-line, platinum-based chemotherapy (Zhao et al., 2011). The MMP-7 polymorphisms are associated with esophageal squamous cell carcinoma and colorectal cancers (Manzoor et al., 2011; Dziki et al., 2011). The SPNs in the MMP-2 and MMP-9 region are associated with susceptibility to head and neck squamous cell carcinoma in an Indian population (Chaudhary et al., 2011). The SNPs of genes encoding MMPs (-1, -2, -3, -7, -8, -9, -12, -13, and -21) are related to breast cancer risk, progression, and survival (Wieczorek et al., 2012). Based on meta-analysis studies, the MMP-2 allele (-1306T) is a protective factor for digestive cancer risk (Zhang and Ren, 2011), the MMP-9 polymorphism is associated with a lower risk of colorectal cancer (Zhang et al., 2012a), and polymorphisms in the promoter regions of MMP-1, -3, -7, and -9 are associated with metastasis in some cancers (Liu et al., 2012). On the other hand, VDR-knock-out mice were shown to have an influx of inflammatory cells, phospho-acetylation of NF- κ B, and up-regulated expression of MMP-2, MMP-9, and MMP-12 in the lung (Sundar et al., 2011). The VDR *TaqI* polymorphism is associated with decreased production of TIMP-1, a natural inhibitor of MMP-9 (Timms et al., 2002). In addition, calcitriol modulates tissue MMP expression under experimental conditions (Dean et al., 1996), down-regulates MMP-9 levels in keratinocytes, and may attenuate the deleterious effects of excessive TNF- α -induced proteolytic activity associated with cutaneous inflammation (Bahar-Shang et al., 2010). Calcitriol decreased the invasive properties of breast carcinoma cells and decreased MMP-9 levels in association with the increased levels of the tissue inhibitor of MMP-1 activity (Koli and Keshi-Oja, 2000). Calcitriol also inhibits endometrial cancer cell growth and is associated with decreased MMP-2 and MMP-9 expression

(Nguyen et al., 2011). Moreover, calciferol, calcitriol, and vitamin D analogs decreased MMP-2 and MMP-9 activities and inhibited prostate cancer cell invasion (Tokar and Webber, 2005; Schartz et al., 1997; Iglesias-Gato et al., 2011; Stio et al., 2011). A vitamin D analog has also been reported to reduce the expression of MMP-2, MMP-9, vascular endothelial growth factor (VEGF) and PTH-related peptide in Lewis lung carcinoma cells (Nakagawa et al., 2005). Taken together, these studies suggest that calcitriol may play an important role in the pathological processes in cancer by down-regulating the level of MMPs and regulating the level of TIMPs.

3.3. Wnt/ β -catenin

The Wnt/ β -catenin signaling pathway plays a pivotal role in the regulation of cell growth, cell development and the differentiation of normal stem cells. Wnt/ β -catenin signaling is implicated in many human cancers, including gastrointestinal cancer, gastric cancer, colon cancer, melanoma, HCC, endometrial carcinoma, ovarian carcinoma, cervical cancer, papillary thyroid carcinoma, renal cell carcinoma, prostate cancer, parathyroid carcinoma, and hematological malignancies (White et al., 2012; Nuñez et al., 2011; Polakis, 2000; Li et al., 2012; Yoshioka et al., 2012; Guturi et al., 2012; Bulut et al., 2011; Gilber-Sirieix et al., 2011; Ueno et al., 2011; Svedlund et al., 2010; Ge and Wang, 2010). Calcitriol inhibits β -catenin transcriptional activity by promoting VDR binding to β -catenin and the induction of E-cadherin expression (Palmer et al., 2001). Paricalcitol, a vitamin D analog, suppressed β -catenin-mediated gene transcription and ameliorated proteinuria and kidney injury in adriamycin nephropathy (He et al., 2011). Most VDR variants fail to activate the vitamin D-responsive promoter and also fail to bind β -catenin or regulate its activity (Byers and Shah, 2007). VDR depletion enhances Wnt/ β -catenin signaling and the tumor burden in colon cancer (Larriba et al., 2011). The action of calcitriol on colon carcinoma cells depends on the dual action of VDR as a transcription factor and a nongenomic activator of RhoA-ROCK and p38MAPK-MSK1, which are required for the inhibition of the Wnt/ β -catenin signaling pathway and cell proliferation (Ordóñez-Morán et al., 2008). The *DICKKOFF-4* gene induces a malignant phenotype, promotes tumor cell invasion, and angiogenesis in colon cancer cells and is repressed by calcitriol (Pendás-Franco et al., 2008a); whereas *DICKKOFF-1* gene acts as a tumor suppressor in human colon cells and is up-regulated by calcitriol (Aguilera et al., 2007; Pendás-Franco et al., 2008b). The transcription factor TCF-4 acts as transcriptional repressor in breast and colorectal cancer cell growth. The TCF-4 and β -catenin binding partner are indirect targets of the VDR pathway. In the VDR knockout mouse, TCF-4 is decreased in the mammary gland when compared with a wild-type mouse. In addition, calcitriol increases TCF-4 RNA and protein levels in several human colorectal cancer cell lines (Beildeck et al., 2009). Furthermore, the Snail1 gene is associated with gastric cancer, melanoma, breast cancer, HCC, and colon carcinoma. Calcitriol inhibits the Wnt/ β -catenin signaling pathway and is abrogated by Snail1 in human colon cancer cells (Larriba et al., 2007).

3.4. The Mitogen-Activated Protein Kinase (MAPK) pathways

The MAPK pathways provide a key link between the membrane bound receptors that receive these cues and changes in the pattern of gene expression, including the extracellular signal-regulated kinase (ERK) cascade, the stress activated protein kinases/c-jun N-terminal kinase

(SAPK/JNK) cascade, and the p38MAPK/RK/HOG cascade (Hipskind and Bilbe, 1998). In human colon cancer cells, calcitriol increases cytosolic Ca^{2+} concentration and transiently activates RhoA-ROCK, and then activates the p38MAPK-MSK signaling pathway (Ordóñez-Morán et al., 2008). In breast cancer cells, the MARK (JNK and p38) signaling pathway involved in calcitriol-induced breast cell death (Brosseau et al., 2010) and potentiated the cytotoxic action of calcitriol and $\text{TNF-}\alpha$ (Weitsman, et al., 2004). In murine squamous cell carcinoma cells, vitamin D induced apoptosis and selective induction of caspase-dependent MEK cleavage (McGuire et al., 2001). In an ovarian cancer animal model, vitamin D induced cell death and is mediated by the p38MAPK signaling pathway (Lange et al., 2010). In human promyeloblastic leukemia cells (HL60), vitamin D derivatives had anti-proliferative activity and activated MAPK signaling pathways (Ji et al., 2002). In human acute myeloid leukemia cells, calcitriol-induced differentiation is enhanced by the activation of MAPK signaling pathways (Zhang et al., 2011b).

3.5. The Prostaglandins (PGs)

Prostaglandins (PGs) play a role in inflammatory processes, and cyclooxygenase (COX) participates in the conversion of arachidonic acid in PGs. A variety studies have shown that prostaglandin signaling stimulates cancer cell growth and cancer progression. The regulation of PG metabolism and biological actions contribute to its anti-proliferation effects in prostate cells and calcitriol has been reported to regulate the expression of several key genes involved in the PG pathway, resulting in decreased PG synthesis (Moreno et al., 2005). The expression of the COX-2 gene is significantly increased in human gastric adenocarcinoma tissues compared with adjuvant normal gastric mucosal specimens (Ristimäki et al., 1997). There is inversely association between elevated COX-2 levels and decreased VDR expression in patients with breast and ovarian cancers compared with healthy women (Cordes et al., 2012). Calcitriol differentiated the human leukemic cell line (HL-60) and metabolized exogenous arachidonic acid to both COX products (predominantly thromboxane B_2 and PG E_2) and lipoxygenase products, including leukotriene B_4 (Stenson et al., 1988). In a mouse xenograft model of prostate cancer, the combination of calcitriol and dietary soy enhanced calcitriol activity in regulating target gene expression and increased the suppression of PG synthesis and signaling, such as COX-2, 15-hydroxyprostaglandin dehydrogenase (15-PGDH), and PG receptors. (Wang et al., 2012a). Calcitriol and its analogs have also been shown to selectively inhibit the activity of COX-2 (Aparna et al., 2008), and an inverse correlation exists between the expression of PG-metabolizing enzymes and reduced VDR expression in malignant breast cell lines (Thill et al., 2012). Taken together, these findings suggest that vitamin D may play a role in modulating the inflammatory process in cancer.

3.6. Oxidative stress

Reactive oxygen species (ROS) play a major role in various cell-signaling pathways. ROS activates various transcription factors and increases in the expression of proteins that control cellular transformation, tumor cell survival, tumor cell proliferation and invasion, angiogenesis, and metastasis. ROS has an important role in the initiation and progression of many cancers (Gupta et al., 2012; Marra et al., 2011; Zhang et al., 2011c; Wang et al., 2011c; Rogalska et al., 2011; Gupta-

Elera et al., 2012). Single nucleotide polymorphisms of antioxidant defense genes may significantly modify the functional activity of the encoded proteins. Women with genetic variability in the iron-related oxidative stress pathways may be at increased risk of post-menopausal breast cancer (Hong et al., 2007). The *ala* variant of superoxide dismutase (SOD) is associated with a moderately increased risk of prostate cancer (Woodson et al., 2003). Based on meta-analysis studies, manganese SOD (MnSOD) polymorphisms may contribute to cancer development (Val-9Ala) (Wang et al., 2009b), prostate cancer susceptibility (Val-16Ala) (Mao et al., 2010), but not to breast cancer susceptibility (Val-16Ala) (Ma et al., 2010a). Calcitriol can also protect nonmalignant prostate cells from oxidative stress-induced cell death through the prevention of reactive oxygen species (ROS)-induced cellular injuries (Bao et al., 2008). Vitamin D metabolites and vitamin D analogs have been reported to induce lipoxygenase mRNA expression, lipoxygenase activity and ROS in a human bone cell line (Somjen et al., 2011). Vitamin D can also reduce the extent of lipid peroxidation and induce SOD activity in the hepatic anti-oxidant system of rats (Sarda et al., 1996). Moreover, the activation of macrophage 1α -hydroxylase results in an increase in $1,25\text{OHD}$, which inhibits iNOS expression and reduces nitric oxide (NO) production by LPS-stimulated macrophages (Chang et al., 2004). This calcitriol production by macrophages may provide protection against the oxidative injuries caused by the NO burst. Calcitriol is known to inhibit LPS-induced immune activation in human endothelial cells (Equil et al., 2005), and calcitriol has also been shown to enhance intracellular glutathione pools and significantly reduce the nitrite production induced by the LPS (Garcion et al., 1999). Furthermore, overproduction of ROS induces DNA damage and leads to carcinogenesis. In the mouse colon, there was an inverse relationship between VDR levels and colon hyperproliferation; the expression of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, significantly increased with complete loss of VDR (Kállay et al., 2002). Vitamin D decrease 8-OHdG by 22% in the normal human colorectal mucosa (Fedirko et al., 2012). Calcitriol contributes to a reduction of the DNA intensify replication stress in lymphocytes (Halicka et al., 2012). In addition, vitamin D_3 up-regulated protein 1 (VDUP1) is a regular for redox signaling and stress-mediated diseases (Chun et al., 2006). Taken together, these findings suggest that vitamin D modulates oxidative stress in cancer.

4. The use of vitamin D in cancer treatment

A number of clinical trials have used vitamin D_3 and calcitriol alone or in combination with anti-tumor agents. Most preclinical suggest that that the optimal anti-tumor effect of calcitriol and other analogs is seen with the administration of high dose calcitriol on intermittent schedule. A small number of single agent trials utilizing vitamin D_3 and calcitriol have been conducted with limited success.

4.1. Vitamin D_3 trials

Fifteen patients were given 2,000 IU (50 microg) of cholecalciferol daily and monitored prospectively every 2-3 mo. There was a statistically significant decrease in the rate of PSA rise after administration of cholecalciferol compared with that before cholecalciferol. The median PSA doubling time increased from 14.3 months prior to commencing cholecalciferol to 25

months after commencing cholecalciferol. Fourteen of 15 patients had a prolongation of PSA doubling time after commencing cholecalciferol (Woo et al., 2005). Breast cancer patients with bone metastases received 10,000 IU of vitamin D₃ daily for 4 months. There was a significant reduction in the number of sites of pain (Amir et al., 2010). Arlet al. (2012) reported on an unexpected observation of a spectacular 13-month remission of chronic lymphocytic leukemia after the administration of cholecalciferol in an elderly patient. Dietary vitamin D₃ and calcitriol have been shown to demonstrate equivalent anticancer activity in mouse xenograft models of breast and prostate cancers (Swani et al., 2012).

4.2. Calcitriol trials – Single agent

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 hepatocarcinoma cell apoptosis by 21.4%, and transiently stabilize serum alpha-fetoprotein levels (Dalhoff et al., 2003; Luo et al., 2004; Morris et al., 2002). The vitamin D analog, 19-Nor-2 α -(3-hydroxypropyl)-1 α ,25-dihydroxyvitamin D₃, is a potent cell growth regulator with enhanced chemotherapeutic potency in liver cancer cells (Chiang et al., 2011). 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 prevent or delay the progression of recurrence (Palmieri-Sevier et al., 1993). Treatment with paricalcitol inhibited gastric cancer cell growth and peritoneal metastatic gastric cancer volume was significantly lower in paricalcitol treated mice (Park et al., 2012). Calcitriol treatment of breast cancer cell lines led to significantly fewer inflammatory breast cancer experimental metastases as compared to control (Hillyer et al., 2012).

4.3. Calcitriol trials – In combination

Calcitriol additively or synergistically potentiates the antitumor effect 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). A renal cell carcinoma patient with multiple bone metastases that were almost completely resolved after treatment with vitamin D and interferon- α (Fujioka et al., 1988). 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., 2010b), 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). Vitamin D₃ treatment significantly suppressed the viability of gastric cancer and cholangiocarcinoma cells and also had a synergistic effect with other anti-cancer drugs, such as paclitaxel, adriamycin, and vinblastine (Baek et al., 2011). In locally

advanced or cutaneous metastatic breast cancer, topical calcipotriol treatment reduced the diameter of treated lesions that contained vitamin D receptor (VDR) (Bower et al., 1991). Calcitriol potentiates both carboplatin and cisplatin-mediated growth inhibition in breast and prostate cancer cell lines (Cho et al., 1991; Moffatt et al., 1999). Tamoxifen and calcitriol or its analog used together to enhance growth inhibition in breast cancer cells than either agent alone (Vink-van Wijngaarden et al., 1994). Calcitriol sensitizes breast cancer cells to doxorubicin through the inhibition of the expression and activity of cytoplasmic antioxidant enzyme (Ravid et al., 1999). Calcitriol may increase cisplatin sensitivity in chemotherapy-resistant testicular germ cell cancer-derived cell lines (Jørgensen et al., 2012). Combination of retinoic acid and vitamin D analog exert synergistic growth inhibition and apoptosis induction on hepatocellular cancers cells (Zhang et al., 2012b). The combination of calcitriol and dietary soy resulted in substantially greater inhibition of tumor growth than the inhibition achieved with either agent alone in a mouse xenograft model of prostate cancer (Wang et al., 2012a).

5. Conclusion

Vitamin D has a role in the prevention and treatment of cancer. Genetic studies have provided the opportunity to determine what proteins link vitamin D to the pathology of cancer. Vitamin D also exerts its effect on cancer via non-genomic mechanisms. As a result, it is imperative that vitamin D levels in patients with cancer be followed. Many studies use the relationship between serum PTH and 25OHD to define the normal range of serum 25OHD. According to the report on Dietary Reference Intakes for vitamin D and calcium by the Institute of Medicine (IOM), persons are at risk of deficiency at serum 25OHD levels less than 30 nmol/L. Saliba et al. (2011) suggested that a 25OHD threshold of 50 nmol/L is sufficient for PTH suppression and prevention of secondary hyperparathyroidism in persons with normal renal function. 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; Charalam-popoulos et al., 2010). Some authors proposed that, in patients with normal calcium levels, the serum 25OHD₃ levels should be stored to > 55 ng/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.

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References

- [1] Aguilera, O, Peña, C, García, J. M, Larriba, M. J, Ordóñez-morán, P, Navarro, D, & Barbáchano, A. López de Silanes I, Ballestar E, Fraga MF, Esteller M, Gamallo C, Bonilla F, González-Sancho JM, Muñoz A. The Wnt antagonist DICKKOPF-1 gene is induced by 1alpha,25-dihydroxyvitamin D₃ associated to the differentiation of human colon cancer cells. *Carcinogenesis*. (2007). Sep;; 28(9), 1877-84.
- [2] Aksu, S, Beyazit, Y, Haznedaroglu, I. C, Canpinar, H, Kekilli, M, Uner, A, Sayinalp, N, Büyükasik, Y, Goker, H, & Ozcebe, O. I. Over-expression of angiotensin-converting enzyme (CD 143) on leukemic blasts as a clue for the activated local bone marrow RAS in AML. *Leuk Lymphoma*. (2006). May;; 47(5), 891-6.
- [3] Ambrosch, F, Wiedermann, G, Krepler, P, Kundi, M, & Ambrosch, P. Effect of BCG vaccination of the newborn infant on the incidence and course of juvenile leukemias]. *Fortschr Med*. (1981). Sep 17;Article in German], 99(35), 1389-93.
- [4] Ametaj, B, Beitz, D, Reihardt, T, & Nonnecke, B. (1996). dihydroxyvitamin D₃ inhibits secretion of interferon-gamma by mitogen- and antigen-stimulated bovine mononuclear leukocytes. *Vet Immunol Immunopathol*. 52, 77-90., 1, 25.
- [5] Amir, E, Simmons, C. E, Freedman, O. C, Dranitsaris, G, Cole, D. E, Vieth, R, Ooi, W. S, & Clemons, M. A phase 2 trial exploring the effects of high-dose (10,000 IU/day) vitamin D₃ in breast cancer patients with bone metastases. *Cancer*. (2010). Jan 15;; 116(2), 284-91.
- [6] An, L. L, Ma, X. T, Yang, Y. H, Lin, Y. M, Song, Y. H, & Wu, K. F. Marked reduction of LL-37/hCAP-18, an antimicrobial peptide, in patients with acute myeloid leukemia. *Int J Hematol*. (2005). Jan;; 81(1), 45-7.
- [7] Ando, T, Ishikawa, T, Kato, H, Yoshida, N, Naito, Y, Kokura, S, Yagi, N, Takagi, T, Handa, O, Kitawaki, J, Nakamura, N, Hasegawa, G, Fukui, M, Imamoto, E, Nakamura, C, Oyamada, H, Isozaki, Y, Matsumoto, N, Nagao, Y, Okita, M, Nakajima, Y, Kurokawa, M, Nukina, M, Ohta, M, Mizuno, S, Ogata, M, Obayashi, H, Park, H, Kitagawa, Y, Nakano, K, & Yoshikawa, T. Synergistic effect of HLA class II loci and cytokine gene polymorphisms on the risk of gastric cancer in Japanese patients with *Helicobacter pylori* infection. *Int J Cancer*. (2009). Dec 1;; 125(11), 2595-602.
- [8] Altas, M, Bayrak, O. F, Ayan, E, Bolukbasi, F, Silav, G, Coskun, K. K, Culha, M, Sahin, F, Sevli, S, & Elmaci, I. The effect of polymorphisms in the promoter region of the MMP-1 gene on the occurrence and invasiveness of hypophyseal adenoma. *Acta Neurochir (Wien)*. (2010). Sep;; 152(9), 1611-7.
- [9] Alvarez-díaz, S, Valle, N, Ferrer-mayorga, G, Lombardía, L, Herrera, M, Domínguez, O, Segura, M. F, Bonilla, F, Hernando, E, & Muñoz, A. MicroRNA-22 is induced by vitamin D and contributes to its antiproliferative, antimigratory and gene regulatory effects in colon cancer cells. *Hum Mol Genet*. (2012). May 15;; 21(10), 2157-65.

- [10] Alves Corrêa SA, Ribeiro de Noronha SM, Nogueira-de-Souza NC, Valleta de Carvalho C, Massad Costa AM, Juvenal Linhares J, Vieira Gomes MT, Guerreiro da Silva ID. Association between the angiotensin-converting enzyme (insertion/deletion) and angiotensin II type 1 receptor (A1166C) polymorphisms and breast cancer among Brazilian women. *J Renin Angiotensin Aldosterone Syst.* (2009). Mar;; 10(1), 51-8.
- [11] Arjumand, W, Ahmad, S. T, Seth, A, Saini, A. K, & Sultana, S. Vitamin D receptor FokI and BsmI gene polymorphism and its association with grade and stage of renal cell carcinoma in North Indian population. *Tumour Biol.* (2012). Feb;; 33(1), 23-31.
- [12] Arlet, J. B, Callens, C, Hermine, O, Darnige, L, Macintyre, E, Pouchot, J, & Capron, L. Chronic lymphocytic leukaemia responsive to vitamin D administration. *Br J Haematol.* (2012). Jan;; 156(1), 148-9.
- [13] Arvaniti, E, Ntoufa, S, Papakonstantinou, N, Touloumenidou, T, Laoutaris, N, Anagnostopoulos, A, Lamnissou, K, Caligaris-cappio, F, Stamatopoulos, K, Ghia, P, Muzio, M, & Belessi, C. Toll-like receptor signaling pathway in chronic lymphocytic leukemia: distinct gene expression profiles of potential pathogenic significance in specific subsets of patients. *Haematologica.* (2011). Nov;; 96(11), 1644-52.
- [14] Baek, S, Lee, Y. S, Shim, H. E, Yoon, S, Baek, S. Y, Kim, B. S, Oh, S. O, & Vitamin, D. regulates cell viability in gastric cancer and cholangiocarcinoma. *Anat Cell Biol.* (2011). Sep;; 44(3), 204-9.
- [15] Bahar-shany, K, Ravid, A, & Koren, R. Upregulation of MMP-production by TNF α in keratinocytes and its attenuation by vitamin D. *J Cell Physiol.* (2010). , 222, 729-37.
- [16] Bao, B. Y, Ting, H. J, Hsu, J. W, & Lee, Y. F. Protective role of 1 α -dihydroxyvitamin D₃ against oxidative stress in nonmalignant human prostate epithelial cells. *Int J Cancer.* (2008). , 122, 2699-706.
- [17] Bartel, D. P. (2004). MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell.* , 116, 281-297.
- [18] BeerTM; Lemmon, D; Lowe, BA; et al. ((2003). High-dose weekly oral calcitriol in patients with a rising PSA after prostatectomy or radiation for prostate carcinoma. *Cancer.* , 97, 1217-1224.
- [19] BeerTM; Venner, PM; Ryan, CW; et al. ((2006). High dose calcitriol may reduce thrombosis in cancer patients. *Br J Hematol.* , 135, 392-394.
- [20] Beildeck, M. E, Islam, M, Shah, S, Welsh, J, & Byers, S. W. Control of TCF-4 expression by VDR and vitamin D in the mouse mammary gland and colorectal cancer cell lines. *PLoS One.* (2009). Nov 17;4(11):e7872.
- [21] Bell, N. H, Shaw, S, & Turner, R. T. Evidence that 1,25-dihydroxyvitamin D₃ inhibits the hepatic production of 25-hydroxyvitamin D in man. *J Clin Invest.* (1984). , 74, 1540-1544.

- [22] Bergmann, C, Bachmann, H. S, Bankfalvi, A, Lotfi, R, Pütter, C, Wild, C. A, Schuler, P. J, Greve, J, Hoffmann, T. K, Lang, S, Scherag, A, & Lehnerdt, G. F. Toll-like receptor 4 single-nucleotide polymorphisms Asp299Gly and Thr399Ile in head and neck squamous cell carcinomas. *J Transl Med.* (2011). Aug 21;9:139.
- [23] Beyazit, Y, Purnak, T, Suvak, B, Kurt, M, Sayilir, A, Turhan, T, Tas, A, Torun, S, Celik, T, Ibis, M, & Haznedaroglu, I. C. Increased ACE in extrahepatic cholangiocarcinoma as a clue for activated RAS in biliary neoplasms. *Clin Res Hepatol Gastroenterol.* (2011). Oct;; 35(10), 644-9.
- [24] BlankeCD; Beer, TM; Todd; et al. ((2009). Phase II study of calcitriol-enhanced docetaxel in patients with previously untreated metastatic or locally advanced pancreatic cancer. *Investigational New Drugs.* , 27(4), 374-378.
- [25] BowerM; Colston, KW; Stein, RC; et al. ((1991). Topical calcipotriol treatment in advanced breast cancer. *Lancet.* , 337(8743), 701-702.
- [26] Brosseau, C. M, Pirianov, G, & Colston, K. W. Involvement of stress activated protein kinases (JNK and in 1,25 dihydroxyvitamin D₃-induced breast cell death. *Steroids.* (2010). Dec 12;75(13-14):1082-8., 38.
- [27] Büchau, A. S, Morizane, S, Trowbridge, J, Schaubert, J, Kotol, P, Bui, J. D, & Gallo, R. L. The host defense peptide cathelicidin is required for NK cell-mediated suppression of tumor growth. *J Immunol.* (2010). Jan 1;, 184(1), 369-78.
- [28] Bulut, G, Fallen, S, Beauchamp, E. M, Drebing, L. E, Sun, J, Berry, D. L, Kallakury, B, Crum, C. P, Toretsky, J. A, Schlegel, R, & Üren, A. Beta-catenin accelerates human papilloma virus type-16 mediated cervical carcinogenesis in transgenic mice. *PLoS One.* (2011). e27243.
- [29] Byers, S, Shah, S, & Vitamin, D. and the regulation of Wnt/beta-catenin signaling and innate immunity in colorectal cancer. *Nutr Rev.* (2007). Aug;65(8 Pt 2):S, 118-20.
- [30] Chang, J, Kuo, M, Kuo, H, Hwang, S, Tsai, J, et al. alpha,25-hydroxyvitamin D₃ regulates inducible nitric oxide synthase messenger RNA expression and nitric oxide release in macrophage-like RAW 264.7 cells. *J Lab Clin Med.* (2004). , 143, 14-22.
- [31] Charalampopoulos A; Charalabopoulos, A; Batistatou, A; et al. ((2010). Parathormone and 1,25(OH)₂D₃ but not 25(OH)D₃ serum levels, in an inverse correlation, reveal an association with advanced stages of colorectal cancer. *Clin Exp Med.* , 10, 69-72.
- [32] Chaudhary, A. K, Pandya, S, Mehrotra, R, Singh, M, & Singh, M. Role of functional polymorphism of matrix metalloproteinase-2 (-1306 C/T and -168 G/T) and MMP-9 (-1562 C/T) promoter in oral submucous fibrosis and head and neck squamous cell carcinoma in an Indian population. *Biomarkers.* (2011). Nov;; 16(7), 577-86.
- [33] Chiang, K. C, Yeh, C. N, Chen, H. Y, Lee, J. M, Juang, H. H, Chen, M. F, Takano, M, Kittaka, A, & Chen, T. C. Nor-2α-(3-hydroxypropyl)-1α,25-dihydroxyvitamin D₃

(MART-10) is a potent cell growth regulator with enhanced chemotherapeutic potency in liver cancer cells. *Steroids*. (2011). Dec 11; 76(13), 1513-9.

- [34] Cho, Y. L, Christensen, C, Saunders, D. E, Lawrence, W. D, Deppe, G, Malviya, V. K, & Malone, J. M. Combined effects of 1,25-dihydroxyvitamin D₃ and platinum drugs on the growth of MCF-7 cells. *Cancer Res*. (1991). Jun 1; 51(11), 2848-53.
- [35] Choi, H. B, Roh, S. Y, Choi, E. J, Yoon, H. Y, Kim, S. Y, Hong, Y. S, Kim, D. W, & Kim, T. G. Association of HLA alleles with non-Hodgkin's lymphoma in Korean population. *Int J Hematol*. (2008). Mar; 87(2), 203-9.
- [36] Chuang, C. M, Monie, A, Wu, A, Mao, C. P, & Hung, C. F. Treatment with LL-37 peptide enhances antitumor effects induced by CpG oligodeoxynucleotides against ovarian cancer. *Hum Gene Ther*. (2009). Apr; 20(4), 303-13.
- [37] Chung, J. W, Jeon, J. H, Yoon, S. R, & Choi, I. Vitamin D upregulated protein 1 (VDUP1) is a regulator for redox signaling and stress-mediated diseases. *J Dermatol*. (2006). Oct; 33(10), 662-9.
- [38] Churilla, T. M, Lesko, S. L, Brereton, H. D, Klem, M, Donnelly, P. E, & Peters, C. A. Serum vitamin D levels among patients in a clinical oncology practice compared to primary care patients in the same community: a case-control study. *BMJ Open*. (2011). Dec 19;1(2):e000397.
- [39] Churilla, T. M, Brereton, H. D, Klem, M, & Peters, C. A. Vitamin D Deficiency Is Widespread in Cancer Patients and Correlates With Advanced Stage Disease: A Community Oncology Experience. *Nutr Cancer*. (2012). Mar 27. [Epub ahead of print]
- [40] Cordes, T, Hoellen, F, Dittmer, C, Salehin, D, Kümmel, S, Friedrich, M, Köster, F, Becker, S, Diedrich, K, & Thill, M. Correlation of prostaglandin metabolizing enzymes and serum PGE₂ levels with vitamin D receptor and serum 25(OH)₂D₃ levels in breast and ovarian cancer. *Anticancer Res*. (2012). Jan; 32(1), 351-7.
- [41] Cortez, M. A, Welsh, J. W, & Calin, G. A. Circulating MicroRNAs as Noninvasive Biomarkers in Breast Cancer. *Recent Results Cancer Res*. (2012). , 195, 151-61.
- [42] Crew, K. D, Shane, E, Cremers, S, McMahon, D. J, Irani, D, & Hershman, D. L. High prevalence of vitamin D deficiency despite supplementation in premenopausal women with breast cancer undergoing adjuvant chemotherapy. *J Clin Oncol*. (2009). May 1; 27(13), 2151-6.
- [43] Dalhoff K; Dancey, J; Astrup, L; et al. ((2003). A phase II study of the vitamin D analogue Seocalcitol in patients with inoperable hepatocellular carcinoma. *Br J Cancer*. , 89, 252-257.
- [44] Dean, D. D, Schwartz, Z, Schmitz, J, Muniz, O. E, Lu, Y, et al. Vitamin D regulation of metalloproteinase activity in matrix vesicles. *Connect Tissue Res*. (1996). , 35, 331-6.

- [45] Denzer, N, Vogt, T, & Reichrath, J. Vitamin D receptor (VDR) polymorphisms and skin cancer: A systematic review. *Dermatoendocrinol.* (2011). Jul;; 3(3), 205-10.
- [46] Deshayes, F, & Nahmias, C. Angiotensin receptors: a new role in cancer? *Trends Endocrinol Metab.* (2005). Sep;; 16(7), 293-9.
- [47] Dickie, L, Church, L, Coulthard, L, Mathews, R, Emery, P, & Mcdermott, M. Vitamin D downregulates intracellular toll-like receptor 9 expression and toll-like receptor 9-induced IL-6 production in human monocytes. *Rheumatol.* (2010). , 48, 1466-71.
- [48] Ditsch, N, Toth, B, Mayr, D, Lenhard, M, Gallwas, J, Weissenbacher, T, Dannecker, C, Friese, K, & Jeschke, U. The association between vitamin D receptor expression and prolonged overall survival in breast cancer. *J Histochem Cytochem.* (2012). Feb;; 60(2), 121-9.
- [49] Donaldson, P. T, Ho, S, Williams, R, & Johnson, P. J. HLA class II alleles in Chinese patients with hepatocellular carcinoma. *Liver.* (2001). Apr;; 21(2), 143-8.
- [50] Dong, W, Li, H, Zhang, Y, Yang, H, Guo, M, Li, L, & Liu, T. Matrix metalloproteinase 2 promotes cell growth and invasion in colorectal cancer. *Acta Biochim Biophys Sin (Shanghai).* (2011). Nov;; 43(11), 840-8.
- [51] Drake, M. T, Maurer, M. J, Link, B. K, Habermann, T. M, Ansell, S. M, Micallef, I. N, Kelly, J. L, Macon, W. R, Nowakowski, G. S, Inwards, D. J, Johnston, P. B, Singh, R. J, Allmer, C, Slager, S. L, Weiner, G. J, Witzig, T. E, & Cerhan, J. R. Vitamin D insufficiency and prognosis in non-Hodgkin's lymphoma. *J Clin Oncol.* (2010). Sep 20;; 28(27), 4191-8.
- [52] Du, N, Feng, J, Hu, L. J, Sun, X, Sun, H. B, Zhao, Y, Yang, Y. P, & Ren, H. Angiotensin II receptor type 1 blockers suppress the cell proliferation effects of angiotensin II in breast cancer cells by inhibiting AT1R signaling. *Oncol Rep.* (2012). Jun;; 27(6), 1893-903.
- [53] Dziki, L, Przybyłowska, K, Majsterek, I, Trzcinski, R, & Sygut, M. A. A. G Polymorphism of the MMP-7 Gene Promoter Region in Colorectal Cancer. *Pol Przegl Chir.* (2011). Nov 1;; 83(11), 622-6.
- [54] Equils, O, Naiki, Y, Shapiro, A. M, Michelsen, K, Lu, D, et al. hydroxyvitamin D₃ inhibits liposaccharide-induced immune activation in human endothelial cells. *Clin Exp Immunol.* (2005). , 143, 58-64.
- [55] Essa, S, Denzer, N, Mahlknecht, U, Klein, R, Collnot, E. M, Tilgen, W, & Reichrath, J. VDR microRNA expression and epigenetic silencing of vitamin D signaling in melanoma cells. *J Steroid Biochem Mol Biol.* (2010). Jul;121(1-2):110-3.
- [56] Essa, S, Reichrath, S, Mahlknecht, U, Montenarh, M, Vogt, T, & Reichrath, J. Signature of VDR miRNAs and epigenetic modulation of vitamin D signaling in melanoma cell lines. *Anticancer Res.* (2012). Jan;; 32(1), 383-9.

- [57] Eyking, A, Ey, B, Rünzi, M, Roig, A. I, Reis, H, Schmid, K. W, Gerken, G, Podolsky, D. K, & Cario, E. Toll-like receptor 4 variant D299G induces features of neoplastic progression in Caco-2 intestinal cells and is associated with advanced human colon cancer. *Gastroenterology*. (2011). Dec;; 141(6), 2154-65.
- [58] Fedirko, V, Bostick, R. M, Flanders, W. D, Long, Q, Shaukat, A, Rutherford, R. E, Daniel, C. R, Cohen, V, & Dash, C. Effects of vitamin D and calcium supplementation on markers of apoptosis in normal colon mucosa: a randomized, double-blind, placebo-controlled clinical trial. *Cancer Prev Res (Phila)*. (2009). Mar;; 2(3), 213-23.
- [59] Feng, Y, Wan, H, Liu, J, Zhang, R, Ma, Q, Han, B, Xiang, Y, Che, J, Cao, H, Fei, X, & Qiu, W. The angiotensin-converting enzyme 2 in tumor growth and tumor-associated angiogenesis in non-small cell lung cancer. *Oncol Rep*. (2010). Apr;; 23(4), 941-8.
- [60] Feng, Y, Ni, L, Wan, H, Fan, L, Fei, X, Ma, Q, Gao, B, Xiang, Y, Che, J, & Li, Q. Overexpression of ACE2 produces antitumor effects via inhibition of angiogenesis and tumor cell invasion in vivo and in vitro. *Oncol Rep*. (2011). a Nov;; 26(5), 1157-64.
- [61] Feng, S, Cen, J, Huang, Y, Shen, H, Yao, L, Wang, Y, & Chen, Z. Matrix metalloproteinase-2 and-9 secreted by leukemic cells increase the permeability of blood-brain barrier by disrupting tight junction proteins. *PLoS One*. (2011b). e20599.
- [62] Ferrero, D, Campa, E, Dellacasa, C, et al. (2004). Differentiating agents + low-dose chemotherapy in the management of old/poor prognosis patients with acute myeloid leukemia or myelodysplastic syndrome. *Haematologica*. , 89, 619-620.
- [63] Fujioka, T, Hasegawa, M, Ishikura, K, Matsushita, Y, Sato, M, & Tanji, S. Inhibition of tumor growth and angiogenesis by vitamin D₃ agents in murine renal cell carcinoma. *J Urol*. (1998). , 160, 247-51.
- [64] Garamszegi, N, Garamszegi, S. P, & Scully, S. P. Matrix metalloproteinase-1 contribution to sarcoma cell invasion. *J Cell Mol Med*. (2011). Jul 31. doi:j.x. [Epub ahead of print], 1582-4934.
- [65] García-plata, D, Mozos, E, Carrasco, L, & Solana, R. HLA molecule expression in cutaneous squamous cell carcinomas: an immunopathological study and clinical-immunohistopathological correlations. *Histol Histopathol*. (1993). Apr;; 8(2), 219-26.
- [66] Garcion, E, Sindji, L, Leblondel, G, Brachet, P, & Darcy, F. hydroxyvitamin D₃ regulates the synthesis of γ -glutamyl transpeptidase and glutathione levels in rat primary astrocytes. *J Neurochem*. (1999). , 73, 859-66.
- [67] GarlandCF; Grant, WB; Mohr, SB; et al. ((2007). What is the dose-response relationship between vitamin D and cancer risk? *Nutr Rev*. Pt.2, , 65(8), S91-S95.
- [68] Ge, X, & Wang, X. Role of Wnt canonical pathway in hematological malignancies. *J Hematol Oncol*. (2010). Sep 15;3:33
- [69] Gilbert-sirieix, M, Makoukji, J, Kimura, S, Talbot, M, Caillou, B, Massaad, C, & Massaad-massade, L. Wnt/ β -catenin signaling pathway is a direct enhancer of thyroid

- transcription factor-1 in humanpapillary thyroid carcinoma cells. PLoS One. (2011). e22280.
- [70] Giovannucci E; Liu, Y; Rimm, EB; et al. ((2008). Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst. , 98, 451-459.
- [71] Gocek, E, Wang, X, Liu, X, Liu, C. G, & Studzinski, G. P. MicroRNA-32 upregulation by 1,25-dihydroxyvitamin D₃ in human myeloid leukemia cells leads to Bim targeting and inhibition of AraC-induced apoptosis. Cancer Res. (2011). Oct 1,, 71(19), 6230-9.
- [72] Gombart, A. F, Borregaard, N, & Koeffler, H. P. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D₃. FASEB J. (2005). Jul,, 19(9), 1067-77.
- [73] González-Zuloeta Ladd AM, Arias Vásquez A, Sayed-Tabatabaei FA, Coebergh JW, Hofman A, Njajou O, Stricker B, van Duijn C. Angiotensin-converting enzyme gene insertion/deletion polymorphism and breast cancer risk. Cancer Epidemiol Biomarkers Prev. (2005). Sep,, 14(9), 2143-6.
- [74] Gupta, S. C, Hevia, D, Patchva, S, Park, B, Koh, W, & Aggarwal, B. B. Upsides and Downsides of Reactive Oxygen Species for Cancer: The Roles of Reactive Oxygen Species in Tumorigenesis, Prevention, and Therapy. Antioxid Redox Signal. (2012). Jan 16. [Epub ahead of print]
- [75] Gupta-elera, G, Garrett, A. R, Robison, R. A, & Neill, O. KL. The role of oxidative stress in prostate cancer. Eur J Cancer Prev. (2012). , 21, 155-62.
- [76] Guturi, K. K, Mandal, T, Chatterjee, A, Sarkar, M, Bhattacharya, S, Chatterjee, U, & Ghosh, M. K. Mechanism of β -catenin mediated transcriptional regulation of EGFR expression in GSK3 β inactivated prostate cancer cells. J Biol Chem. (2012). Apr 5. [Epub ahead of print]
- [77] Hama, T, Norizoe, C, Suga, H, Mimura, T, Kato, T, Moriyama, H, & Urashima, M. Prognostic significance of vitamin D receptor polymorphisms in head and neck squamous cell carcinoma. PLoS One. (2011). e29634.
- [78] Halicka, H. D, Zhao, H, Li, J, Traganos, F, Studzinski, G. P, & Darzynkiewicz, Z. Attenuation of constitutive DNA damage signaling by dihydroxyvitamin D₃. Aging (Albany NY). (2012). Apr 11. [Epub ahead of print], 1, 25.
- [79] He, W, Kang, Y. S, Dai, C, & Liu, Y. Blockade of Wnt/ β -catenin signaling by paricalcitol ameliorates proteinuria and kidney injury. J Am Soc Nephrol. (2011). Jan,, 22(1), 90-103.
- [80] Hernández-hernández, D. M, Cerda-flores, R. M, Juárez-cedillo, T, Granados-arriola, J, Vargas-alarcón, G, Apresa-garcía, T, Alvarado-cabrero, I, García-carrancá, A, Salce-

- do-vargas, M, & Mohar-betancourt, A. Human leukocyte antigens I and II haplotypes associated with human papillomavirus 16-positive invasive cervical cancer in Mexican women. *Int J Gynecol Cancer*. (2009). Aug; 19(6), 1099-106.
- [81] Herr, H. W, Laudone, V. P, Badalament, R. A, Oettgen, H. F, Sogani, P. C, Freedman, B. D, & Melamed, M. R. Whitmore WF Jr. Bacillus Calmette-Guérin therapy alters the progression of superficial bladder cancer. *J Clin Oncol*. (1988). Sep; 6(9), 1450-5.
- [82] Hershberger PA; Yu, WD; Modzelewski, RA; et al. ((2001). Calcitriol (1,25-dihydroxy-cholecalciferol) enhances paclitaxel antitumor activity in vitro and in vivo and accelerates paclitaxel-induced apoptosis. *Clin Cancer Res*. , 7, 1043-1051.
- [83] Higashimura, H, Furuhashi, H, Nakaya, K, & Nakamura, Y. Effects of vitamin D₃ and related compounds on angiotensin converting activity of endothelial cells and on release of plasminogen activator from them. *Chem Pharm Bull*. (1988). , 36, 4858-64.
- [84] Hillyer, R. L, Sirinvasin, P, Joglekar, M, Sikes, R. A, Van Golen, K. L, & Nohe, A. Differential effects of vitamin D treatment on inflammatory and non-inflammatory breast cancer cell lines. *Clin Exp Metastasis*. (2012). Dec; 29(8), 971-9.
- [85] Hipskind, R. A, & Bilbe, G. MAP kinase signaling cascades and gene expression in osteoblasts. *Front Biosci*. (1998). Aug 1;3:d, 804-16.
- [86] Hojjat-farsangi, M, Jeddi-tehrani, M, Amirzargar, A. A, Razavi, S. M, Sharifian, R. A, Rabbani, H, & Shokri, F. Human leukocyte antigen class II allele association to disease progression in Iranian patients with chronic lymphocytic leukemia. *Hum Immunol*. (2008). Oct; 69(10), 666-74.
- [87] Hong, C. C, Ambrosone, C. B, Ahn, J, Choi, J. Y, McCullough, M. L, Stevens, V. L, et al. Genetic variability in iron-related oxidative stress pathways (Nrf2, NQO1, NOS3, and HO-1), iron intake, and risk of postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev*. (2007). , 16, 1784-94.
- [88] Huang, W, Yu, L. F, Zhong, J, Qiao, M. M, Jiang, F. X, Du, F, Tian, X. L, & Wu, Y. L. Angiotensin II type 1 receptor expression in human gastric cancer and induces MMP2 and MMP9 expression in MKN-28 cells. *Dig Dis Sci*. (2008). Jan; 53(1), 163-8.
- [89] Ino, K, Shibata, K, Kajiyama, H, Yamamoto, E, Nagasaka, T, Nawa, A, Nomura, S, & Kikkawa, F. Angiotensin II type 1 receptor expression in ovarian cancer and its correlation with tumour angiogenesis and patient survival. *Br J Cancer*. (2006). Feb 27; 94(4), 552-60.
- [90] Iglesias-gato, D, Zheng, S, Flanagan, J. N, Jiang, L, Kittaka, A, Sakaki, T, Yamamoto, K, Itoh, T, Lebrasseur, N. K, Norstedt, G, & Chen, T. C. Substitution at carbon 2 of nor-1 α ,25-dihydroxyvitamin D₃ with 3-hydroxypropyl group generates an analogue with enhanced chemotherapeutic potency in PC-3 prostate cancer cells. *J Steroid Biochem Mol Biol*. (2011). Nov;127(3-5):269-75., 19.

- [91] Ji, Y, Kutner, A, Verstuyf, A, Verlinden, L, & Studzinski, G. P. Derivatives of vitamins D₂ and D₃ activate three MAPK pathways and upregulate pRb expression in differentiating HL60 cells. *Cell Cycle*. (2002). Nov-Dec; 1(6), 410-5.
- [92] Johnston, C. I. Tissue angiotensin converting enzyme in cardiac and vascular hypertrophy, repair, and remodeling. *Hypertension*. (1994). , 23, 258-68.
- [93] Jørgensen, A. Blomberg Jensen M, Nielsen JE, Juul A, Rajpert-De Meyts E. Influence of vitamin D on cisplatin sensitivity in testicular germ cell cancer-derived cell lines and in a NTERA2 xenograft model. *J Steroid Biochem Mol Biol*. (2012). Oct 23. pii: S0960-0760(12)00208-7. doi:jsbmb.2012.10.008. [Epub ahead of print]
- [94] Kállay, E, Bareis, P, Bajna, E, Kriwanek, S, Bonner, E, Toyokuni, S, & Cross, H. S. Vitamin D receptor activity and prevention of colonic hyperproliferation and oxidative stress. *Food Chem Toxicol*. (2002). Aug; 40(8), 1191-6.
- [95] Keizman, D, Huang, P, Eisenberger, M. A, Pili, R, Kim, J. J, Antonarakis, E. S, Hammers, H, & Carducci, M. A. Angiotensin system inhibitors and outcome of sunitinib treatment in patients with metastatic renal cell carcinoma: a retrospective examination. *Eur J Cancer*. (2011). Sep; 47(13), 1955-61.
- [96] Kim, H. J, Bae, J. S, Chang, I. H, Kim, K. D, Lee, J, Shin, H. D, Lee, J. Y, Kim, W. J, Kim, W, & Myung, S. C. Sequence variants of toll-like receptor 4 (TLR4) and the risk of prostate cancer in Korean men. *World J Urol*. (2012). Apr; 30(2), 225-32.
- [97] Kinoshita, J, Fushida, S, Harada, S, Yagi, Y, Fujita, H, Kinami, S, Ninomiya, I, Fujimura, T, Kayahara, M, Yashiro, M, Hirakawa, K, & Ohta, T. Local angiotensin II-generation in human gastric cancer: correlation with tumor progression through the activation of ERK1/2, NF-kappaB and survivin. *Int J Oncol*. (2009). Jun; 34(6), 1573-82.
- [98] Koca, E, Haznedaroglu, I. C, Uner, A, Sayinalp, N, Saglam, A. E, Goker, H, & Ozcebe, O. I. Angiotensin-converting enzyme expression of the lymphoma-associated macrophages in the lymph nodes of Hodgkin's disease. *J Natl Med Assoc*. (2007). Nov; 99(11):1243-4, 1246-7.
- [99] Kölmel, K. F, Grange, J. M, Krone, B, Mastrangelo, G, Rossi, C. R, Henz, B. M, Seebacher, C, Botev, I. N, Niin, M, Lambert, D, Shafir, R, Kokoschka, E. M, Kleeberg, U. R, Gefeller, O, & Pfahlberg, A. Prior immunisation of patients with malignant melanoma with vaccinia or BCG is associated with better survival. An European Organization for Research and Treatment of Cancer cohort study on 542 patients. *Eur J Cancer*. (2005). Jan; 41(1), 118-25.
- [100] Komagata, S, Nakajima, M, Takagi, S, Mohri, T, Taniya, T, & Yokoi, T. Human CYP24 catalyzing the inactivation of calcitriol is post-transcriptionally regulated by miR-125b. *Mol Pharmacol*. (2009). Oct; 76(4), 702-9.

- [101] Koli, K, & Keski-oja, J. Alpha, 25-dihydroxyvitamin D and its analogues down-regulate cell invasion-associated proteases in cultured malignant cells. *Cell Growth Differ.* (2000). Apr;, 11(4), 221-9.
- [102] Köstner, K, Denzer, N, Koreng, M, Reichrath, S, Gräber, S, Klein, R, Tilgen, W, Vogt, T, & Reichrath, J. Association of genetic variants of the vitamin D receptor (VDR) with cutaneous squamous cell carcinomas (SCC) and basal cell carcinomas (BCC): a pilot study in a German population. *Anticancer Res.* (2012). Jan;, 32(1), 327-33.
- [103] Kulah, E, Dursun, A, Aktunc, E, Acikgoz, S, Aydin, M, et al. Effects of angiotensin-converting enzyme gene polymorphism and serum vitamin D levels on ambulatory blood pressure measurement and left ventricular mass in Turkish hypertensive population. *Blood Press Monit.* (2007). , 12, 207-13.
- [104] Kupfer, S. S, Anderson, J. R, Ludvik, A. E, Hooker, S, Skol, A, Kittles, R. A, Keku, T. O, Sandler, R. S, Ruiz-ponte, C, Castellvi-bel, S, Castells, A, Carracedo, A, & Ellis, N. A. Genetic associations in the vitamin D receptor and colorectal cancer in African Americans and Caucasians. *PLoS One.* (2011). e26123.
- [105] Ma, X, Chen, C, Xiong, H, Fan, J, Li, Y, Lin, H, et al. No association between SOD2 Val16Ala polymorphism and breast cancer susceptibility: a meta-analysis based on 9,710 cases and 11,041 controls. *Breast Cancer Res Treat.* (2010a). , 122, 509-14.
- [106] Ma Y; Yu, WD; Trump, DL; et al. ((2010b). Enhances antitumor activity of gemcitabine and cisplatin in human bladder cancer models. *Cancer.* , 116, 3294-3303.
- [107] Mahmoudi, T, Arkani, M, Karimi, K, Safaei, A, Rostami, F, Arbabi, E, Pourhoseingholi, M. A, Mohebbi, S. R, Nikzamir, A, Romani, S, Almasi, S, Abbaszadeh, M, Vafaei, M, & Zali, M. R. The-4817 G>A (rs2238136) variant of the vitamin D receptor gene: a probable risk factor for colorectal cancer. *Mol Biol Rep.* (2012). May;, 39(5), 5277-82.
- [108] Makni, H, & Daoud, J. Ben Salah H, Mahfoudh N, Haddar O, Karray H, Boudawara T, Ghorbel A, Khabir A, Frikha M. HLA association with nasopharyngeal carcinoma in southern Tunisia. *Mol Biol Rep.* (2010). Jun;, 37(5), 2533-9.
- [109] Malik, M. A, Sharma, K. L, Zargar, S. A, & Mittal, B. Association of matrix metalloproteinase-7 (-181A>G) polymorphism with risk of esophageal squamous cell carcinoma in Kashmir Valley. *Saudi J Gastroenterol.* (2011). Sep-Oct;, 17(5), 301-6.
- [110] Mao, C, Qiu, L. X, Zhan, P, Xue, K, Ding, H, Du, F. B, et al. MnSOD Val16Ala polymorphism and prostate cancer susceptibility: a meta-analysis involving 8,962 subjects. *J Cancer Res Clin Oncol.* (2010). , 136, 975-9.
- [111] Marra, M, Sordelli, I. M, Lombardi, A, Lamberti, M, Tarantino, L, Giudice, A, et al. Molecular targets and oxidative stress biomarkers in hepatocellular carcinoma: an overview. *J Transl Med.* (2011).

- [112] McGuire, T. F, Trump, D. L, & Johnson, C. S. Vitamin D induced apoptosis of murine squamous cell carcinoma cells. Selective induction of caspase-dependent MEK cleavage and up-regulation of MEKK-1. *J Biol Chem.* (2001). Jul 13;; 276(28), 26365-73.
- [113] Michel, S, Linnebacher, M, Alcaniz, J, Voss, M, Wagner, R, Dippold, W, & Becker, C. von Knebel Doeberitz M, Ferrone S, Kloor M. Lack of HLA class II antigen expression in microsatellite unstable colorectal carcinomas is caused by mutations in HLA class II regulatory genes. *Int J Cancer.* (2010). Aug 15;; 127(4), 889-98.
- [114] Min, R, Zun, Z, Siyi, L, Wenjun, Y, Lizheng, W, & Chenping, Z. Increased expression of Toll-like receptor-9 has close relation with tumour cell proliferation in oral squamous cell carcinoma. *Arch Oral Biol.* (2011). Sep;; 56(9), 877-84.
- [115] Minmin, S, Xiaoqian, X, Hao, C, Baiyong, S, Xiaying, D, Junjie, X, Xi, Z, Jianquan, Z, & Songyao, J. Single nucleotide polymorphisms of Toll-like receptor 4 decrease the risk of development of hepatocellular carcinoma. *PLoS One.* (2011). Apr 29;6(4):e19466.
- [116] Moffatt, K. A, Johannes, W. U, & Miller, G. J. α Dihydroxyvitamin D₃ and platinum drugs act synergistically to inhibit the growth of prostate cancer cell lines. *Clin Cancer Res.* (1999). Mar;; 5(3), 695-703.
- [117] Mohri, T, Nakajima, M, Takagi, S, Komagata, S, & Yokoi, T. MicroRNA regulates human vitamin D receptor. *Int J Cancer.* (2009). Sep 15;; 125(6), 1328-33.
- [118] Moreno, J, Krishnan, A. V, Swami, S, Nonn, L, Peehl, D. M, & Feldman, D. Regulation of prostaglandin metabolism by calcitriol attenuates growth stimulation in prostate cancer cells. *Cancer Res.* (2005). Sep 1;; 65(17), 7917-25.
- [119] Morris DL; Jourdan, JL; Finlay, I; et al. ((2002). Hepatic intra-arterial injection of 1,25-dihydroxyvitamin D₃ in lipiodol: pilot study in patients with hepatocellular carcinoma. *Int J Oncol.* , 21, 901-906.
- [120] Nuñez, F, Bravo, S, Cruzat, F, Montecino, M, & De Ferrari, G. V. Wnt/ β -catenin signaling enhances cyclooxygenase-2 (COX2) transcriptional activity in gastric cancer cells. *PLoS One.* (2011). Apr 6;6(4):e18562.
- [121] Nakagawa, K, Sasaki, Y, Kato, S, Kubodera, N, & Okano, T. Oxa-1 α ,25-dihydroxyvitamin D₃ inhibits metastasis and angiogenesis in lung cancer. *Carcinogenesis.* (2005). , 26, 1044-54.
- [122] Nakai, Y, Isayama, H, Ijichi, H, Sasaki, T, Sasahira, N, Hirano, K, Kogure, H, Kawakubo, K, Yagioka, H, Yashima, Y, Mizuno, S, Yamamoto, K, Arizumi, T, Togawa, O, Matsubara, S, Tsujino, T, Tateishi, K, Tada, M, Omata, M, & Koike, K. Inhibition of renin-angiotensin system affects prognosis of advanced pancreatic cancer receiving gemcitabine. *Br J Cancer.* (2010). Nov 23;; 103(11), 1644-8.
- [123] Naugler, C, & Liwski, R. HLA risk markers for chronic myelogenous leukemia in Eastern Canada. *Leuk Lymphoma.* (2009). Feb;; 50(2), 254-9.

- [124] Ng, A. C, Kumar, S. K, Rajkumar, S. V, & Drake, M. T. Impact of vitamin D deficiency on the clinical presentation and prognosis of patients with newly diagnosed multiple myeloma. *Am J Hematol.* (2009). Jul;; 84(7), 397-400.
- [125] Nguyen, H, Ivanova, V. S, Kavandi, L, Rodriguez, G. C, Maxwell, G. L, & Syed, V. Progesterone and 1,25-dihydroxyvitamin D₃ inhibit endometrial cancer cell growth by upregulating semaphorin 3B and semaphorin 3F. *Mol Cancer Res.* (2011). Nov;; 9(11), 1479-92.
- [126] Nihon-yanagi, Y, Terai, K, Murano, T, Matsumoto, T, & Okazumi, S. Tissue expression of Toll-like receptors 2 and 4 in sporadic human colorectal cancer. *Cancer Immunol Immunother.* (2012). Jan;; 61(1), 71-7.
- [127] Lange, T. S, Stuckey, A. R, Robison, K, Kim, K. K, Singh, R. K, Raker, C. A, Brard, L, Lange, T. S, Stuckey, A. R, Robison, K, Kim, K. K, Singh, R. K, Raker, C. A, & Brard, L. Effect of a vitamin D₃ derivative (B3CD) with postulated anti-cancer activity in an ovarian cancer animal model. *Invest New Drugs.* (2010). Oct;; 28(5), 543-53.
- [128] Lalor, M, Floyd, S, Gorak-stolinska, P, Weir, R, Blitz, R, Branson, K, et al. (2011). BCG vaccination: a role for vitamin D? *PLoS ONE.* 6, 216709.
- [129] Larriba, M. J, Valle, N, Pálmer, H. G, Ordóñez-morán, P, Alvarez-díaz, S, Becker, K. F, Gamallo, C, De Herreros, A. G, González-sancho, J. M, & Muñoz, A. The inhibition of Wnt/beta-catenin signalling by 1alpha,25-dihydroxyvitamin D₃ is abrogated by Snail1 in human colon cancer cells. *Endocr Relat Cancer.* (2007). Mar;; 14(1), 141-51.
- [130] Larriba, M. J, Ordóñez-morán, P, Chicote, I, Martín-fernández, G, Puig, I, Muñoz, A, & Pálmer, H. G. Vitamin D receptor deficiency enhances Wnt/ β -catenin signaling and tumor burden in colon cancer. *PLoS One.* (2011). e23524.
- [131] Launoy, G, Milan, C, Day, N. E, Pienkowski, M. P, Gignoux, M, & Faivre, J. Diet and squamous-cell cancer of the oesophagus: a French multicentre case-control study. *Int J Cancer.* (1998). Mar 30;; 76(1), 7-12.
- [132] Lee, H. W, Hahm, K. B, Lee, J. S, Ju, Y. S, Lee, K. M, & Lee, K. W. Association of the human leukocyte antigen class II alleles with chronic atrophic gastritis and gastric carcinoma in Koreans. *J Dig Dis.* (2009). Nov;; 10(4), 265-71.
- [133] Lefkowitz, E. S, & Garland, C. F. Sunlight, vitamin D, and ovarian cancer mortality rates in US women. *Int J Epidemiol.* (1994). Dec;; 23(6), 1133-6.
- [134] Li, Z. Q, Ding, W, Sun, S. J, Li, J, Pan, J, Zhao, C, Wu, W. R, & Si, W. K. Cyr61/CCN1 Is Regulated by Wnt/ β -Catenin Signaling and Plays an Important Role in the Progression of Hepatocellular Carcinoma. *PLoS One.* (2012). e35754.
- [135] Lindhorst, E, Schumm-draeger, P. M, Bojunga, J, Usadel, K. H, & Herrmann, G. Differences in tumor cell proliferation, HLA DR expression and lymphocytic infiltration in various types of thyroid carcinoma. *Exp Clin Endocrinol Diabetes.* (2002). Jan;; 110(1), 27-31.

- [136] Lipworth, L, Rossi, M, Mclaughlin, J. K, Negri, E, Talamini, R, Levi, F, & Franceschi, S. La Vecchia C. Dietary vitamin D and cancers of the oral cavity and esophagus. *Ann Oncol.* (2009). Sep;, 20(9), 1576-81.
- [137] Liu, P. T, Stenger, S, Li, H, Wenzel, L, Tan, B. H, Krutzik, S. R, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science.* (2006). , 311, 1770-3.
- [138] LiuG; Hu, X; Chakrabarty, S; et al. ((2010). Vitamin D mediates its action in human colon carcinoma cells in a calcium-sensing receptor-dependent manner: downregulates malignant cell behavior and the expression of thymidylate synthase and surviving and promotes cellular sensitivity to 5-FU. *Int J Cancer.* , 126, 631-639.
- [139] Liu, D, Duan, W, Guo, H, Xu, X, & Bai, Y. Meta-analysis of associations between polymorphisms in the promoter regions of matrix metalloproteinases and the risk of colorectal cancer. *Int J Colorectal Dis.* (2011). Sep;, 26(9), 1099-105.
- [140] Liu, D, Guo, H, Li, Y, Xu, X, Yang, K, & Bai, Y. Association between polymorphisms in the promoter regions of matrix metalloproteinases (MMPs) and risk of cancer metastasis: a meta-analysis. *PLoS One.* (2012). e31251.
- [141] Loke, T. W, Sevfi, D, & Khadra, M. Prostate cancer incidence in Australia correlates inversely with solar radiation. *BJU Int.* (2011). Nov;108 Suppl , 2, 66-70.
- [142] Lotfy, M. El-Kenawy Ael-M, Abdel-Aziz MM, El-Kady I, Talaat A. Elevated renin levels in patients with liver cirrhosis and hepatocellular carcinoma. *Asian Pac J Cancer Prev.* (2010). , 11(5), 1263-6.
- [143] Louis, S. N, Wang, L, Chow, L, Rezmann, L. A, & Imamura, K. MacGregor DP, Casey D, Catt KJ, Frauman AG, Louis WJ. Appearance of angiotensin II expression in non-basal epithelial cells is an early feature of malignant change in human prostate. *Cancer Detect Prev.* (2007). , 31(5), 391-5.
- [144] Lu, J, Getz, G, Miska, E. A, Alvarez-saavedra, E, Lamb, J, Peck, D, Sweet-cordero, A, Ebert, B. L, Mak, R. H, Ferrando, A. A, Downing, J. R, Jacks, T, Horvitz, H. R, & Golub, T. R. MicroRNA expression profiles classify human cancers. *Nature.* (2005). Jun 9;, 435(7043), 834-8.
- [145] LuoWJ; Chen, JY; Xu, W; et al. ((2004). Effects of vitamin D analogue EB1089 on proliferation and apoptosis of hepatic carcinoma cells. *Zhonghua Yu Fang Yi Xue Za Zhi.* article in Chinese], 38, 415-418.
- [146] Luong, K. V, & Nguyen, L. T. Coexisting hyperparathyroidism and primary hyperparathyroidism with vitamin D-deficient osteomalacia in a Vietnamese immigrant. *Endocrine Practice.* (1996). , 2, 250-254.
- [147] Luong, K, & Nguyen, L. T. The beneficial role of vitamin D and its analogs in cancer treatment and prevention. *Crit Rev Oncol Hematol.* (2010). Mar;, 73(3), 192-201.

- [148] Lương KVQNguyễn LTH. ((2012). Vitamin D and cancer. In “Advanced in Cancer Management”. InTech Publishing Co. January 2012. , 1-16.
- [149] ObaraW; Mizutani, Y; Oyama, C; et al. ((2008). Prospective study of combined treatment with interferon-alpha and active vitamin D₃ for Japanese patients with metastatic renal cell carcinoma. *Int J Urol.* , 15, 794-799.
- [150] Ordóñez-Morán, P, Larriba, MJ, Pálmer, HG, Valero, RA, Barbáchano, A, Duñach, M, de Herreros, AG, Villalobos, C, Berciano, MT, Lafarga, M, & Muñoz, A. 1 mediate vitamin D effects on gene expression, phenotype, and Wnt pathway in colon cancer cells. *J Cell Biol.* 2008 Nov 17;183(4):697-710.
- [151] Orell-kotikangas, H, Schwab, U, Osterlund, P, Saarilahti, K, Mäkitie, O, & Mäkitie, A. A. High prevalence of vitamin D insufficiency in patients with head and neck cancer at diagnosis. *Head Neck.* (2012). Jan 27. doi:hed.21954. [Epub ahead of print]
- [152] Ozdemir, E, Kakehi, Y, Mishina, M, Ogawa, O, Okada, Y, Ozdemir, D, & Yoshida, O. High-resolution HLA-DRB1 and DQB1 genotyping in Japanese patients with testicular germ cell carcinoma. *Br J Cancer.* (1997). , 76(10), 1348-52.
- [153] Ozdilli, K, Oguz, F. S, Anak, S, Kekik, C, Carin, M, & Gedikoglu, G. The frequency of HLA class I and II alleles in Turkish childhood acute leukaemia patients. *J Int Med Res.* (2010). Sep-Oct,, 38(5), 1835-44.
- [154] Panza, N. Del Vecchio L, Maio M, De Felice M, Lombardi G, Minozzi M, Zappacosta S. ong association between an HLA-DR antigen and thyroid carcinoma. *Tissue Antigens.* (1982). Aug,, 20(2), 155-8.
- [155] Pálmer, H. G, González-sancho, J. M, Espada, J, Berciano, M. T, Puig, I, Baulida, J, Quintanilla, M, Cano, A, De Herreros, A. G, Lafarga, M, Muñoz, A, & Vitamin, D. promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of beta-catenin signaling. *J Cell Biol.* (2001). Jul 23,, 154(2), 369-87.
- [156] Palmieri-SevierA; Palmieri, GM; Baumgartner, CJ; Britt, LG. ((1993). Case report: long-term remission of parathyroid cancer: possible relation to vitamin D and calci-triol therapy. *Am J Med Sci.* , 306(5), 309-312.
- [157] Pardanani, A, Drake, M. T, Finke, C, Lasho, T. L, Rozell, S. A, Jimma, T, & Tefferi, A. Vitamin D insufficiency in myeloproliferative neoplasms and myelodysplastic syndromes: clinical correlates and prognostic studies. *Am J Hematol.* (2011). Dec,, 86(12), 1013-6.
- [158] Park, M. R, Lee, J. H, Park, M. S, Hwang, J. E, Shim, H. J, Cho, S. H, Chung, I. J, & Bae, W. K. Suppressive effect of 19-nor-1 α -25-dihydroxyvitamin D₂ on gastric cancer cells and peritoneal metastasis model. *J Korean Med Sci.* (2012). Sep,, 27(9), 1037-43.
- [159] Parsons, S. L, Watson, S. A, Collins, H. M, Griffin, N. R, Clarke, P. A, & Steele, R. J. Gelatinase (MMP-2 and-9) expression in gastrointestinal malignancy. *Br J Cancer.* (1998). Dec,, 78(11), 1495-502.

- [160] Partyka, R, Gonciarz, M, Jalowiecki, P, Kokocinska, D, & Byrczek, T. VEGF and metalloproteinase 2 (MMP 2) expression in gastric cancer tissue. *Med Sci Monit.* (2012). Apr 1;18(4):BR, 130-134.
- [161] Pendás-franco, N, García, J. M, Peña, C, Valle, N, Pálmer, H. G, Heinäniemi, M, Carlberg, C, Jiménez, B, Bonilla, F, Muñoz, A, & González-sancho, J. M. DICKKOPF-4 is induced by TCF/beta-catenin and upregulated in human colon cancer, promotes tumour cell invasion and angiogenesis and is repressed by 1alpha,25-dihydroxyvitamin D₃. *Oncogene.* (2008). a Jul 24; 27(32), 4467-77.
- [162] Pendás-franco, N, Aguilera, O, Pereira, F, González-sancho, J. M, Muñoz, A, & Vitamin, D. and Wnt/beta-catenin pathway in colon cancer: role and regulation of DICKKOPF genes. *Anticancer Res.* (2008). Sep-Oct;28(5A);, 2613-23.
- [163] Peng, X, Vaishnav, A, Murillo, G, Alimirah, F, Torres, K. E, & Mehta, R. G. Protection against cellular stress by 25-hydroxyvitamin D₃ in breast epithelial cells. *J Cell Biochem.* (2010). Aug 15; 110(6), 1324-33.
- [164] Peng, W. J, Zhang, J. Q, Wang, B. X, Pan, H. F, Lu, M. M, Wang, J, Peng, W. J, Zhang, J. Q, Wang, B. X, Pan, H. F, Lu, M. M, & Wang, J. Prognostic value of matrix metalloproteinase 9 expression in patients with non-small cell lung cancer. *Clin Chim Acta.* (2012). Jul 11;413(13-14):1121-6.
- [165] Peppone, L. J, Rickles, A. S, Janelins, M. C, Insalaco, M. R, Skinner, K. A, Peppone, L. J, Rickles, A. S, Janelins, M. C, Insalaco, M. R, & Skinner, K. A. The Association Between Breast Cancer Prognostic Indicators and Serum OH Vitamin D Levels. *Ann Surg Oncol.* (2012). Mar 24. [Epub ahead of print], 25.
- [166] Pérez-castrillón, J. L, Justo, I, Sanz, A, De Luis, D, & Dueñas, A. Effect of angiotensin converting enzyme inhibitors on 1,25(OH)₂ D levels of hypertensive patients. Relationship with ACE polymorphisms. *Horm Metab Res.* (2006). , 38, 812-6.
- [167] Polakis, P. (2000). Wnt signaling and cancer. *Genes Dev* , 14, 1837-1851.
- [168] Punzi, T, Fabris, A, Morucci, G, Biagioni, P, Gulisano, M, & Ruggiero, M. Pacini S. C-reactive protein levels and vitamin d receptor polymorphisms as markers in predicting cachectic syndrome in cancer patients. *Mol Diagn Ther.* (2012). Apr 1; 16(2), 115-24.
- [169] Qiu, J, Shao, S, Yang, G, Shen, Z, & Zhang, Y. Association of Toll like receptor 9 expression with lymph node metastasis in human breast cancer. *Neoplasma.* (2011). , 58(3), 251-5.
- [170] Raffegerst, S. H, Hoelzlwimmer, G, Kunder, S, Mysliwietz, J, Quintanilla-martinez, L, & Schendel, D. J. Diverse hematological malignancies including hodgkin-like lymphomas develop in chimeric MHC class II transgenic mice. *PLoS One.* (2009). Dec 31;4(12):e8539.

- [171] Raina V; Cunninham, D; Gilchrist, N; Soukop, M. ((1991). Alphacalcidol is a nontoxic, effective treatment of follicular small-cleaved cell lymphoma. *Br J Cancer.* , 63, 463-465.
- [172] Ray, R, Banks, M, Abuzahra, H, Eddy, V. J, Persons, K. S, Lucia, M. S, Lambert, J. R, & Holick, M. F. Effect of dietary vitamin D and calcium on the growth of androgen-insensitive human prostate tumor in a murine model. *Anticancer Res.* (2012). Mar,, 32(3), 727-31.
- [173] Ravid, A, Rocker, D, Machlenkin, A, Rotem, C, Hochman, A, Kessler-icekson, G, Liberman, U. A, & Koren, R. Dihydroxyvitamin D₃ enhances the susceptibility of breast cancer cells to doxorubicin-induced oxidative damage. *Cancer Res.* (1999). Feb 15,, 59(4), 862-7.
- [174] Ren, C, Qiu, M. Z, Wang, D. S, Luo, H. Y, Zhang, D. S, Wang, Z. Q, Wang, F. H, Li, Y. H, Zhou, Z. W, & Xu, R. H. Prognostic effects of hydroxyvitamin D levels in gastric cancer. *J Transl Med.* (2012). Jan 27;10:16., 25.
- [175] Repin IuMBCG vaccine immunotherapy after radical operations for lung cancer]. *Vestn Khir Im I I Grek.* (1992). Jul-Aug;149(7-8):11-6. [Article in Russian]
- [176] Rhodes, S. G, Terry, L. A, Hope, J, Hewinson, R. G, & Vordermeier, H. M. dihydroxyvitamin D₃ and development of tuberculosis in cattle. *Clin Diagn Lab Immunol.* (2003). Nov,, 10(6), 1129-35.
- [177] Ristimäki, A, Honkanen, N, Jänkälä, H, Sipponen, P, & Härkönen, M. Expression of cyclooxygenase-2 in human gastric carcinoma. *Cancer Res.* (1997). Apr 1,, 57(7), 1276-80.
- [178] Rivas-santiago, B, Hernandez-pando, R, Carranza, C, Juarez, E, Contreras, J. L, et al. Expression of cathelicidin LL-37 during *Mycobacterium tuberculosis* infection in human alveolar macrophages, monocytes, neutrophils, and epithelial cells. *Infect Immunity.* (2008). , 76, 935-41.
- [179] Robsahm, T. E, Tretli, S, Dahlback, A, Moan, J, & Vitamin, D. from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). *Cancer Causes Control.* (2004). Mar,, 15(2), 149-58.
- [180] Rockett, K, Brookes, R, Udalova, I, Vidal, V, Hill, A, & Kwiatkowski, D. (1998). hydroxyvitamin D₃ induces nitric oxide synthase and suppresses growth of *Mycobacterium tuberculosis* in a human macrophage-like cell line. *Infect Immun.* 66, 5314-5321., 1, 25.
- [181] Rogalska, A, Gajek, A, Szwed, M, Józwiak, Z, & Marczak, A. The role of reactive oxygen species in WP 631-induced death of human ovarian cancer cells: a comparison with the effect of doxorubicin. *Toxicol In Vitro.* (2011). , 25, 1712-20.
- [182] Rollison, D. E, Cole, A. L, Tung, K. H, Slattery, M. L, Baumgartner, K. B, Byers, T, Wolff, R. K, & Giuliano, A. R. Vitamin D intake, vitamin D receptor polymorphisms,

and breast cancer risk among women living in the southwestern U.S. *Breast Cancer Res Treat.* (2012). Apr; 132(2), 683-91.

- [183] Roth, C. L, Elfers, C. T, Figlewicz, D. P, Melhorn, S. J, Morton, G. J, et al. Vitamin D deficiency in obese rats exacerbates NAFLD and increases hepatic resistin and toll-like receptor activation. *Hepatology.* (2011). Oct 12. [Epub ahead of print].
- [184] Ruza, E, Sotillo, E, Sierrasesúmaga, L, Azcona, C, & Patiño-garcía, A. Analysis of polymorphisms of the vitamin D receptor, estrogen receptor, and collagen Ialpha1 genes and their relationship with height in children with bone cancer. *J Pediatr Hematol Oncol.* (2003). Oct; 25(10), 780-6.
- [185] Sadeghi, K, Wessner, B, Laggner, U, Ploder, M, Tamandl, D, et al. Vitamin D₃ down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen-associated molecular patterns. *Eur J Immunol.* (2006). , 36, 361-70.
- [186] Sandholm, J, Kauppila, J. H, Pressey, C, Tuomela, J, Jukkola-vuorinen, A, Vaarala, M, Johnson, M. R, Harris, K. W, & Selander, K. S. Estrogen receptor- α and sex steroid hormones regulate Toll-like receptor-9 expression and invasive function in human breast cancer cells. *Breast Cancer Res Treat.* (2012). Apr; 132(2), 411-9.
- [187] Salehin, D, Haugk, C, Thill, M, Cordes, T, William, M, Hemmerlein, B, & Friedrich, M. Serum 25-hydroxyvitamin D levels in patients with vulvar cancer. *Anticancer Res.* (2012). Jan; 32(1), 265-70.
- [188] Saliba, W, Barnett, O, Rennert, H. S, Lavi, I, & Rennert, G. The relationship between serum 25(OH)D and parathyroid hormone levels. *Am J Med.* (2011). , 124, 1165-70.
- [189] Sardar, S, Chakraborty, A, & Chatterjee, M. Comparative effectiveness of vitamin D₃ and dietary vitamin E on peroxidation of lipids and enzymes of the hepatic antioxidant system in Sprague-Dawley rats. *Int J Vitam Nutr Res.* (1996). , 66, 39-45.
- [190] Schaubert, J, Iffland, K, Frisch, S, Kudlich, T, Schmausser, B, Eck, M, Menzel, T, Gostner, A, Lühns, H, & Scheppach, W. Histone-deacetylase inhibitors induce the cathelicidin LL-37 in gastrointestinal cells. *Mol Immunol.* (2004). Jul; 41(9), 847-54.
- [191] Scherberich, J, Kellermeyer, M, Ried, C, & Hartinger, A. alpha-calcidol modulates major human monocyte antigens and toll-like receptors TLR2 and TLR4 in vitro. *Eur J Med Res.* (2005). , 10, 179-82.
- [192] Schöttker, B, Ball, D, Gellert, C, & Brenner, H. Serum hydroxyvitamin D levels and overall mortality. A systematic review and meta-analysis of prospective cohort studies. *Ageing Res Rev.* (2012). Feb 17. [Epub ahead of print], 25.
- [193] Schwartz, G. G, Wang, M. H, Zang, M, Singh, R. K, & Siegal, G. P. alpha,25-Dihydroxyvitamin D (calcitriol) inhibits the invasiveness of human prostate cancer cells. *Cancer Epidemiol Biomarkers Prev.* (1997). Sep; 6(9), 727-32.
- [194] Shanafelt, T. D, Drake, M. T, Maurer, M. J, Allmer, C, Rabe, K. G, Slager, S. L, Weiner, G. J, Call, T. G, Link, B. K, Zent, C. S, Kay, N. E, Hanson, C. A, Witzig, T. E, & Cer-

han, J. R. Vitamin D insufficiency and prognosis in chronic lymphocytic leukemia. *Blood*. (2011). Feb 3;; 117(5), 1492-8.

- [195] Shui, I. M, Mucci, L. A, Kraft, P, Tamimi, R. M, Lindstrom, S, Penney, K. L, Nimmptsch, K, Hollis, B. W, Dupre, N, Platz, E. A, Stampfer, M. J, & Giovannucci, E. Vitamin D-Related Genetic Variation, Plasma Vitamin D, and Risk of Lethal Prostate Cancer: A Prospective Nested Case-Control Study. *J Natl Cancer Inst*. (2012). May 2;; 104(9), 690-699.
- [196] Sikora, J, Frydrychowicz, M, Kaczmarek, M, Brzezicha, B, Mozer-lisewska, I, Szczepanski, M, & Zeromski, J. TLR receptors in laryngeal carcinoma- immunophenotypic, molecular and functional studies. *Folia Histochem Cytobiol*. (2010). Dec;; 48(4), 624-31.
- [197] Skinner, H. G, & Schwartz, G. G. (2009). The relation of serum parathyroid hormone and serum calcium to serum levels of Prostatic-specific antigen: a population-based study. *Cancer Epidemiol Biomarkers Prev*. , 18(11), 2869-2873.
- [198] Slapek, C. A, Desforjes, J. F, Fogaren, T, et al. (1992). Treatment of acute myeloid leukemia in the elderly with low-dose cytarabine, hydroxyurea, and calcitriol. *Am J Hematol*. , 41, 178-183.
- [199] Slattery, M. L, Wolff, R. K, Curtin, K, Fitzpatrick, F, Herrick, J, Potter, J. D, Caan, B. J, & Samowitz, W. S. Colon tumor mutations and epigenetic changes associated with genetic polymorphism: insight into disease pathways. *Mutat Res*. (2009). Jan 15;660(1-2):12-21.
- [200] Slattery, M. L, Herrick, J. S, Bondurant, K. L, & Wolff, R. K. Toll-like receptor genes and their association with colon and rectal cancer development and prognosis. *Int J Cancer*. (2012). Jun 15;; 130(12), 2974-80.
- [201] Somjen, D, Katzburg, S, Grafi-cohen, M, Knoll, E, Sharon, O, & Posner, G. H. Vitamin D metabolites and analogs induce lipoxigenase mRNA expression and as well as reactive oxygen species (ROS) production in human bone cell line. *J Steroid Biochem Mol Biol*. (2011). , 123, 85-9.
- [202] Song, E. J, Kang, M. J, Kim, Y. S, Kim, S. M, Lee, S. E, Kim, C. H, Kim, D. J, & Park, J. H. Flagellin promotes the proliferation of gastric cancer cells via the Toll-like receptor 5. *Int J Mol Med*. (2011). Jul;; 28(1), 115-9.
- [203] Srivastava, P, Lone, T. A, Kapoor, R, & Mittal, R. D. Association of Promoter Polymorphisms in MMP 2 and TIMP2 with Prostate Cancer Susceptibility in North India. *Arch Med Res*. (2012). Feb 25. [Epub ahead of print]
- [204] Stenson, W. F, Teitelbaum, S. L, & Bar-shavit, Z. Arachidonic acid metabolism by a vitamin D₃-differentiated human leukemic cell line. *J Bone Miner Res*. (1988). Oct;; 3(5), 561-71.

- [205] Stio, M, Martinesi, M, Simoni, A, Zuegel, U, Steinmeyer, A, Santi, R, Treves, C, & Nesi, G. The novel vitamin D analog ZK191784 inhibits prostate cancer cell invasion. *Anticancer Res.* (2011). Dec;; 31(12), 4091-8.
- [206] Sundar, I, Hwang, J, Wu, S, Sun, J, & Rahman, I. Deletion of vitamin D receptor leads to premature emphysema/COPD by increased matrix metalloproteinase and lymphoid aggregates formation. *Biochem Biophys Res Commun.* (2011). , 406, 127-33.
- [207] Swami, S, Krishnan, A. V, Wang, J. Y, Jensen, K, Horst, R, Albertelli, M. A, & Feldman, D. Dietary Vitamin D₃ and Dihydroxyvitamin D₃ (Calcitriol) Exhibit Equivalent Anticancer Activity in Mouse Xenograft Models of Breast and Prostate Cancer. *Endocrinology.* (2012). Mar 27. [Epub ahead of print], 1, 25.
- [208] Svedlund, J, Aurén, M, Sundström, M, Dralle, H, Akerström, G, Björklund, P, & Westin, G. Aberrant WNT/ β -catenin signaling in parathyroid carcinoma. *Mol Cancer.* (2010). Nov 15;9:294.
- [209] Takala, H, Kauppila, J. H, Soini, Y, Selander, K. S, Vuopala, K. S, Lehenkari, P. P, Saarnio, J, & Karttunen, T. J. Toll-like receptor 9 is a novel biomarker for esophageal squamous cell dysplasia and squamous cell carcinoma progression. *J Innate Immun.* (2011). , 3(6), 631-8.
- [210] Tamaki, K, Saitoh, A, & Kubota, Y. hydroxyvitamin D₃ decreases the interferon-gamma (IFN-gamma) induced HLA-DR expression but not intercellular adhesion molecule 1 (ICAM-1) on human keratinocytes. *Reg Immunol.* (1990). , 3, 223-7.
- [211] Tangrea, J, Helzlsouer, K, Pietinen, P, Taylor, P, Hollis, B, Virtamo, J, & Albanes, D. Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. *Cancer Causes Control.* (1997). Jul;; 8(4), 615-25.
- [212] Tee, Y. T, Liu, Y. F, Chang, J. T, Yang, S. F, Chen, S. C, Han, C. P, Wang, P. H, & Liao, C. L. Single-Nucleotide Polymorphisms and Haplotypes of Membrane Type 1 Matrix Metalloproteinase in Susceptibility and Clinical Significance of Squamous Cell Neoplasia of Uterine Cervix in Taiwan Women. *Reprod Sci.* (2012). Apr 23. [Epub ahead of print]
- [213] Thill, M, Hoellen, F, Becker, S, Dittmer, C, Fischer, D, et al. Expression of prostaglandin- and vitamin D-metabolising enzymes in benign and malignant breast cells. *Anticancer Res.* (2012). , 32, 367-72.
- [214] Timms, P. M, Mannan, N, Hitman, G. A, Noonan, K, Mills, P. G, et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? *Q J Med.* (2002). , 95, 787-96.
- [215] Ting HJ; Hsu, J; Bao,BY; Lee, YF. ((2007). Docetaxel-induced growth inhibition an apoptosis in androgen indepenent prostate cancer cells are enhanced by 1alpha,25-dihydroxyvitamin D₃. *Cancer Lett.* , 247, 122-129.

- [216] Tokar, E. J, & Webber, M. M. Cholecalciferol (vitamin D₃) inhibits growth and invasion by up-regulating nuclear receptors and 25-hydroxylase (CYP27A1) in human prostate cancer cells. *Clin Exp Metastasis*. (2005). , 22(3), 275-84.
- [217] Tokuda, N, Mizuki, N, Kasahara, M, & Levy, R. B. hydroxyvitamin D₃ down-regulation of HLA-DR on human peripheral blood monocytes. *Immunol*. (1992). , 75, 349-54.
- [218] Tokuda, N, & Levy, R. hydroxyvitamin D₃ stimulates phagocytosis but suppresses HLA-DR and CD13 antigen expression in human mononuclear phagocytes. *Proc Soc Exp Biol Med*. (1996). , 211, 244-50.
- [219] Tone, T, Eto, H, Katsuoka, K, Nishioka, K, & Nishiyama, S. Suppression of gamma-interferon induced HLA-DR antigen expression on normal and transformed keratinocytes by 1,25 (OH)₂ vitamin D₃. *Nippon Hifuka Gakkai Zasshi*. (1991). Article in Japanese], 101, 519-25.
- [220] Tone, T, Eto, H, Katou, T, Otani, F, & Nishiyama, S. Alpha,25-dihydroxyvitamin D modulation of HLA-DR mRNA induced by gamma-interferon in cultured epithelial tumor cell lines. *J Dermatol*. (1993). , 20, 581-4.
- [221] Turna, A, Pekçolaklar, A, Metin, M, Yaylim, I, & Gurses, A. The effect of season of operation on the survival of patients with resected non-small cell lung cancer. *Interact Cardiovasc Thorac Surg*. (2012). Feb;, 14(2), 151-5.
- [222] Ueno, K, Hirata, H, Majid, S, Chen, Y, Zaman, M. S, Tabatabai, Z. L, Hinoda, Y, & Dahiya, R. Wnt antagonist DICKKOPF-3 (Dkk-3) induces apoptosis in human renal cell carcinoma. *Mol Carcinog*. (2011). Jun;, 50(6), 449-57.
- [223] Wang, X, Gocek, E, Liu, C. G, & Studzinski, G. P. MicroRNAs181 regulate the expression of 27Kip1in human myeloid leukemia cells induced to differentiate by 1,25-dihydroxyvitamin D₃. *Cell Cycle*. (2009). a Mar 1;8(5):736-41.
- [224] Wang, S, Wang, F, Shi, X, Dai, J, Peng, Y, Guo, X, et al. Association between manganese superoxide dismutase (MnSOD) Val-9Ala polymorphism and cancer risk- A meta-analysis. *Eur J Cancer*. (2009b). , 45, 2874-81.
- [225] Wang, H. C, & Choudhary, S. Reactive oxygen species-mediated therapeutic control of bladder cancer. *Nat Rev Urol*. (2011). , 8, 608-16.
- [226] Wang, W. L, Chatterjee, N, Chittur, S. V, Welsh, J, & Tenniswood, M. P. Effects of 1α, 25 dihydroxyvitamin D₃ and testosterone on miRNA and mRNA expression in LNCaP cells. *Mol Cancer*. (2011). a May 18;10:58.
- [227] Wang, S, Wang, X, Wu, J, Lin, Y, Chen, H, Zheng, X, Zhou, C, & Xie, L. Association of vitamin D receptor gene polymorphism and calcium urolithiasis in the Chinese Han population. *Urol Res*. (2011). b Nov 25. [Epub ahead of print]

- [228] Wang, Y. Y, Wang, L. Z, & Sun, L. R. Antitumor effect of BCG on growth of transplanted human myeloid leukemia HL-60 cells in nude mice]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. (2011). c Jun;, 19(3), 725-9.
- [229] Wang, J. Y, Swami, S, Krishnan, A. V, & Feldman, D. Combination of calcitriol and dietary soy exhibits enhanced anticancer activity and increased hypercalcemic toxicity in a mouse xenograft model of prostate cancer. *Prostate*. (2012). a Mar 27. doi:pros. 22516. [Epub ahead of print]
- [230] Wang, H, Tan, G, Dong, L, Cheng, L, Li, K, Wang, Z, & Luo, H. Circulating MiR-125b as a Marker Predicting Chemoresistance in Breast Cancer. *PLoS One*. (2012b). e34210.
- [231] Weitsman, G. E, Ravid, A, Liberman, U. A, & Koren, R. The role of MAP kinase in the synergistic cytotoxic action of calcitriol and TNF-alpha in human breast cancer cells. *J Steroid Biochem Mol Biol*. (2004). May;89-90(1-5):361-4., 38.
- [232] Welsh, J, Zinser, L. N, Miannecki-morton, L, Martin, J, Waltz, S. E, James, H, & Zinser, G. M. Age-related changes in the epithelial and stromal compartments of the mammary gland in normocalcemic mice lacking the vitamin D₃ receptor. *PLoS One*. (2011). Jan 26;6(1):e16479
- [233] White, B. D, Chien, A. J, & Dawson, D. W. Dysregulation of Wnt/ β -catenin signaling in gastrointestinal cancers. *Gastroenterology*. (2012). Feb;, 142(2), 219-32.
- [234] Wieczorek, E, Reszka, E, Gromadzinska, J, & Wasowicz, W. Genetic polymorphism of matrix metalloproteinases in breast cancer. *Neoplasma*. (2012). , 59(3), 237-47.
- [235] Wilop, S, Von Hobe, S, Crysandt, M, Esser, A, Osieka, R, & Jost, E. Impact of angiotensin I converting enzyme inhibitors and angiotensin II type 1 receptor blockers on survival in patients with advanced non-small-cell lung cancer undergoing first-line platinum-based chemotherapy. *J Cancer Res Clin Oncol*. (2009). Oct;, 135(10), 1429-35.
- [236] Wolpin, B. M, Ng, K, Bao, Y, Kraft, P, Stampfer, M. J, Michaud, D. S, Ma, J, Buring, J. E, Sesso, H. D, Lee, I. M, Rifai, N, Cochrane, B. B, Wactawski-wende, J, Chlebowski, R. T, Willett, W. C, Manson, J. E, Giovannucci, E. L, & Fuchs, C. S. Plasma 25-hydroxyvitamin D and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*. (2012). Jan;, 21(1), 82-91.
- [237] Woo, T. C, Choo, R, Jamieson, M, Chander, S, & Vieth, R. Pilot study: potential role of vitamin D (Cholecalciferol) in patients with PSA relapse after definitive therapy. *Nutr Cancer*. (2005). , 51(1), 32-6.
- [238] Woodson, K, Tangrea, J. A, Lehman, T. A, Modali, R, Taylor, K. M, Snyder, K, et al. Manganese superoxide dismutase (MnSOD) polymorphism, alpha-tocopherol supplementation and prostate cancer risk in the alpha-tocopherol, beta-carotene cancer prevention study (Finland). *Cancer Causes Control*. (2003). , 14, 513-8.
- [239] Wu, W. K, Sung, J. J, To, K. F, Yu, L, Li, H. T, Li, Z. J, Chu, K. M, Yu, J, & Cho, C. H. The host defense peptide LL-37 activates the tumor-suppressing bone morphogenetic

protein signaling via inhibition of proteasome in gastric cancer cells. *J Cell Physiol.* (2010). Apr; 223(1), 178-86.

- [240] Wu, K, Feskanich, D, Fuchs, C. S, Chan, A. T, Willett, W. C, Hollis, B. W, Pollak, M. N, & Giovannucci, E. Interactions between plasma levels of hydroxyvitamin D, insulin-like growth factor (IGF)-1 and C-peptide with risk of colorectal cancer. *PLoS One.* (2011a). e28520., 25.
- [241] Wu, Y, Miyamoto, T, Li, K, Nakagomi, H, Sawada, N, Kira, S, Kobayashi, H, Zakohji, H, Tsuchida, T, Fukazawa, M, Araki, I, & Takeda, M. Decreased expression of the epithelial Ca²⁺ channel TRPV5 and TRPV6 in human renal cell carcinoma associated with vitamin D receptor. *J Urol.* (2011b). Dec; 186(6), 2419-25.
- [242] Yamaji, T, Iwasaki, M, Sasazuki, S, Sakamoto, H, Yoshida, T, & Tsugane, S. Association between plasma 25-hydroxyvitamin D and colorectal adenoma according to dietary calcium intake and vitamin D receptor polymorphism. *Am J Epidemiol.* (2012). Feb 1; 175(3), 236-44.
- [243] Yan, W, Zhang, W, Sun, L, Liu, Y, You, G, Wang, Y, Kang, C, You, Y, & Jiang, T. Identification of MMP-9 specific microRNA expression profile as potential targets of anti-invasion therapy in glioblastoma multiforme. *Brain Res.* (2011). Sep 9; 1411, 108-15.
- [244] Yang, Y. H, Zheng, G. G, Li, G, Zhang, B, Song, Y. H, & Wu, K. F. Expression of LL-37/hCAP-18 gene in human leukemia cells. *Leuk Res.* (2003). Oct; 27(10), 947-50.
- [245] Yim, S, Dhawan, P, Ragunath, C, Christakos, S, & Diamond, G. Induction of cathelicidin in normal and CF bronchial epithelial cells by 1,25-dihydroxyvitamin D₃. *J Cys Fibros.* (2007). , 6, 403-410.
- [246] Yin, L, Grandi, N, Raum, E, Haug, U, Arndt, V, & Brenner, H. Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. *Aliment Pharmacol Ther.* (2009). Jul 1; 30(2), 113-25.
- [247] Yoshioka, S, King, M. L, Ran, S, & Okuda, H. MacLean JA 2nd, McAsey ME, Sugino N, Brard L, Watabe K, Hayashi K. WNT7A regulates tumor growth and progression in ovarian cancer through the WNT/ β -catenin pathway. *Mol Cancer Res.* (2012). Mar; 10(3), 469-82.
- [248] Yu, H, Xu, S. S, Cheng, Q. Q, He, L. M, & Li, Z. Expression and clinical significance of Toll-like receptors in human renal carcinoma cell 786-0 and normal renal cell HK-2]. *Zhonghua Yi Xue Za Zhi.* (2011). Jan 11;Article in Chinese], 91(2), 129-31.
- [249] Yuan, W, Pan, W, Kong, J, Zheng, W, Szeto, F, et al. dihydroxyvitamin D₃ suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. *J Biol Chem.* (2007). , 282, 29821-30.
- [250] Yuk, J. M, Shin, D. M, Song, K. S, Lim, K, Kim, K. H, Lee, S. H, Kim, J. M, Lee, J. S, Paik, T. H, Kim, J. S, & Jo, E. K. *Bacillus calmette-guerin* cell wall cytoskeleton enhan-

- ces colon cancer radiosensitivity through autophagy. *Autophagy*. (2010). Jan;; 6(1), 46-60.
- [251] Xia, Z, Liu, W, Li, S, Jia, G, Zhang, Y, Li, C, Ma, Z, Tian, J, & Gong, J. Expression of matrix metalloproteinase-9, type IV collagen and vascular endothelial growth factor in adamantinous craniopharyngioma. *Neurochem Res*. (2011). Dec;; 36(12), 2346-51.
- [252] Xiang, W, Kong, J, Chen, S, Cao, L, Qiao, G, et al. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. *Am J Phys Endocrinol Met*. (2005). E, 125-32.
- [253] Xu, H, Soruri, A, Gieseler, R. K, & Peters, J. H. dihydroxyvitamin D₃ exerts opposing effects to IL-4 on MHC class-II antigen expression, accessory activity, and phagocytosis of human monocytes. *Scand J Immunol*. (1993). , 38, 535-60.
- [254] Zhao, X, Wang, X, Wu, W, Gao, Z, Wu, J, Garfield, D. H, Wang, H, Wang, J, Qian, J, Li, H, Jin, L, Li, Q, Han, B, Lu, D, & Bai, C. Matrix metalloproteinase-2 polymorphisms and clinical outcome of Chinese patients with nonsmall cell lung cancer treated with first-line, platinum-based chemotherapy. *Cancer*. (2011). Nov 9. doi:cncr.26669. [Epub ahead of print]
- [255] Zhang, L. Y, & Ren, K. W. Meta-analysis of MMP2-1306T allele as a protective factor in digestive cancer. *Arch Med Res*. (2011). Apr;; 42(3), 239-43.
- [256] Zhang, W, Yang, H. C, Wang, Q, Yang, Z. J, Chen, H, Wang, S. M, Pan, Z. M, Tang, B. J, Li, Q. Q, & Li, L. Clinical value of combined detection of serum matrix metalloproteinase-9, heparanase, and cathepsin for determining ovarian cancer invasion and metastasis. *Anticancer Res*. (2011). a Oct;; 31(10), 3423-8.
- [257] Zhang, J, Harrison, J. S, & Studzinski, G. P. Isoforms of gamma and delta contribute to differentiation of human AML cells induced by 1,25-dihydroxyvitamin D₃. *Exp Cell Res*. (2011). b Jan 1;317(1):117-30., 38MAPK.
- [258] Zhang, Q, Ma, Y, Cheng, Y. F, Li, W. J, Zhang, Z, & Chen, S. Y. Involvement of reactive oxygen species in 2-methoxyestradiol-induced apoptosis in human neuroblastoma cells. *Cancer Lett*. (2011c). , 313, 201-10.
- [259] Zhang, L. F, Mi, Y. Y, Cao, Q, Wang, W, Qin, C, Wei, J. F, Zhou, Y. J, Li, Y. F, Tang, M, Liu, W. M, Zhang, W, & Zou, J. G. Update analysis of studies on the MMP-9-1562 C>T polymorphism and cancer risk. *Mol Biol Rep*. (2012). a Apr;; 39(4), 3435-41.
- [260] Zhang, J, Zhang, H, Zhang, X, & Yu, Z. Synergistic effect of retinoic acid and vitamin D analog EBinduced apoptosis of hepatocellular cancer cells. *Cytotechnology*. (2012). b Oct 16. [Epub ahead of print], 1089.
- [261] Zhou, W, Heist, R. S, Liu, G, Asomaning, K, Neuberg, D. S, Hollis, B. W, Wain, J. C, Lynch, T. J, Giovannucci, E, Su, L, & Christiani, D. C. Circulating 25-hydroxyvitamin D levels predict survival in early-stage non-small-cell lung cancer patients. *J Clin Oncol*. (2007). Feb 10;; 25(5), 479-85.

- [262] Zhou, L, Zhang, R, Yao, W, Wang, J, Qian, A, Qiao, M, Zhang, Y, & Yuan, Y. Decreased expression of angiotensin-converting enzyme 2 in pancreatic ductal adenocarcinoma is associated with tumor progression. *Tohoku J Exp Med.* (2009). Feb;; 217(2), 123-31.
- [263] Zhou, L, Zhang, R, Zhang, L, Yao, W, Li, J, & Yuan, Y. Angiotensin-converting enzyme 2 acts as a potential molecular target for pancreatic cancer therapy. *Cancer Lett.* (2011). Aug 1;; 307(1), 18-25.
- [264] Zhuo de X, Niu XH, Chen YC, Xin DQ, Guo YL, Mao ZB. Vitamin D₃ up-regulated protein 1(VDUP1) is regulated by FOXO3A and miR-17-5p at the transcriptional and post-transcriptional levels, respectively, in senescent fibroblasts. *J Biol Chem.* (2010). Oct 8;; 285(41), 31491-501.
- [265] Zimmerman, E. I, Dollins, C. M, Crawford, M, Grant, S, Nana-sinkam, S. P, Richards, K. L, Hammond, S. M, & Graves, L. M. Lyn kinase-dependent regulation of miR181 and myeloid cell leukemia-1 expression: implications for drug resistance in myelogenous leukemia. *Mol Pharmacol.* (2010). Nov;; 78(5), 811-7.
- [266] Van Der Knaap, R, Siemes, C, Coebergh, J. W, Van Duijn, C. M, Hofman, A, & Stricker, B. H. Renin-angiotensin system inhibitors, angiotensin I-converting enzyme gene insertion/deletion polymorphism, and cancer: the Rotterdam Study. *Cancer.* (2008). Feb 15;; 112(4), 748-57.
- [267] Varsavsky, M, Reyes-garcía, R, Cortés-berdonces, M, García-martin, A, Rozas-moreno, P, & Muñoz-torres, M. Serum 25 OH vitamin D concentrations and calcium intake are low in patients with prostate cancer. *Endocrinol Nutr.* (2011). Nov;; 58(9), 487-91.
- [268] Vink-van Wijngaarden T, Pols HA, Buurman CJ, van den Bemd GJ, Dorssers LC, Birkenhäger JC, van Leeuwen JP. Inhibition of breast cancer cell growth by combined treatment with vitamin D₃ analogues and tamoxifen. *Cancer Res.* (1994). Nov 1;; 54(21), 5711-7.
- [269] Villumsen, M, Sørup, S, Jess, T, Ravn, H, Relander, T, Baker, J. L, Benn, C. S, Sørensen, T. I, Aaby, P, & Roth, A. Risk of lymphoma and leukaemia after bacille Calmette-Guérin and smallpox vaccination: a Danish case-cohort study. *Vaccine.* (2009). Nov 16;; 27(49), 6950-8.
- [270] Volante, M, Rapa, I, Gandhi, M, Bussolati, G, Giachino, D, Papotti, M, & Nikiforov, Y. E. RAS mutations are the predominant molecular alteration in poorly differentiated thyroid carcinomas and bear prognostic impact. *J Clin Endocrinol Metab.* (2009). Dec;; 94(12), 4735-41.

