Overlap of Vitamin D and Cholesterol, Triglyceride and High Density Lipoprotein in Prostate Cancer Patients (with Metabolic Syndrome)

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Abstract

Prostate cancer PCa represents a heterogeneous disease with different degrees of aggressiveness, patterns of metastasis and response to therapy (Vesovic, 2005) It occur from a complex etiology that include both exogenous (diet, environment, etc.) and endogenous (hormonal imbalance, family history) factors. Our attempt designed to know the overlap of vitamin D and lipid profile in prostate cancer patients and its relationship in incidence and progression of PCa .Data showed high prostate specific antigen PSA in Pca patients compared with control subject (33.01±6.01, 2.93±0, 62) ng/ml respectively .decline in vitamin D level in Pca patients compared with control subject (17.34 ± 1.15, 26.42 ± 1.05 ±) mg/dl respectively. Significant difference ($p \leq 0.05$) in triglyceride level compared with control subject (129.63± 8.99, 101.26± 3.50) mg/dl respectively, no Significant difference ($p > 0.05$) in HDL and cholesterol levels in PCa patients compared with control group .Weak Negative correlation between Vitamin D with cholesterol (-0.24) **.**Correlation between vitamin D and high density lipoprotein, triglyceride undetectable.

Key words:-prostate cancer, vitamin D, lipids, mechanism

الخلاصة

يعتبر سرطان البروستات من الامرا ض مختلفة المنشا مع الاختلاف في الشده وطريقة الانتقال داخل الجسم والاستجابه للعلاج (Vesovic, 2005) 0 ويحدث للاسباب خارجيه (طعام ،بيئه)وداخليه (عدم التوازن الهرموني و التاريخ العائلي)؟صممت التجربه لمعرفه تاثير فيتامين(د) وتحليل الدهون في مرضى سرطان البروستات وعلاقتهم بالاصابه وسير المرض. ارتفاع في مستوى مستضد البروستات الخاص في المرضى المصابين بسرطان البروستات مقارنه مع مجموعة السيطره (2.93.0.62, 33.01±6.01) ng/mlعلى التوالي .نقص في مستوى فيتامين(د) في مرضى سرطان البروستات مقارنه مع مجموعة 17.34.15, 26.42±1.05) mg/dlعلى التوالي .لايوجد فرق معنوي($p > 0.05$) في مستوى الكوليستيرول في مجموعة المصابين بسرطان البروستات مقارنه مع مجموعة السيطره(4.96 ±159.74, 9.18 ±184.47) mg/dl وكذلك الدهون عالية الكثافه (1.20 ±38.15, 6.01 ±35.09 .) يوجد فرق معنوي بمستوى ($p \leq 0.05$)بين الدهون الثلاثيه في مجموعة المصابين بسرطان البروستات مقارنه مع مجموعة السيطره (3.50± 101.26, 8.99±129.63) mg/dl .ارتباط سالب ضعيف بين فيتامين(د) والكوليسترول($r=-0.24$)والعلاقه بين فيتامين (د) والدهون عالية الكثافه والدهون الثلاثيه غير ملموس .

الكلمات المفتاحية: سرطان البروستات، فيتامين د، اللبيدات، تقنية.

Introduction

The data of National Health and Nutrition Examination Survey (NHANES) showed that Vitamin D insufficiency is a general public health problem, especially for elderly and minority populations (Zadshir *et al*., 2005). In both low and high1, 25-dihydroxyvitamin D levels were concurrent with an increased risk of prostate cancer (PCa) (Tuohimaa *et al*., 2004) .Low levels of 1, 25-dihydroxyvitamin D related with an increased fear for earlier exposure to prostate cancer with high aggressive development of PCa, particularly before the andropause (Li *et al*., 2007). The PCa risk was highest between younger men (<52 years) with low serum 1, 25-dihydroxyvitamin D (Ahonen *et al*., 2000). high vitamin D level might lead to vitamin D resistance by increased inactivation thought enhanced expression of 24-

hydroxylase(Tuohimaa *et al*.,2004) vitamin D reduces the incidence of many forms of cancer by inhibiting tumor angiogenesis, (Iseki *et al*., 1999; Mantell *et al*., 2000) stimulating adherence of cells (Palmer *et al*., 2001) and promote intercellular communication over gap junctions (Fujioka *et al*., 2000) that ways strengthening the inhibition of proliferation that occurs from tight physical contact with close cells within a tissue (contact inhibition). 1,25(OH) 2D enhances pulsatile release of ionized calcium from intracellular, including the endoplasmic reticulum, induces terminal differentiation and apoptosis (Campbell *et al*., 1997; Garland *et al*.,2006). Cholesterol is an important role player in tumoriogenesis as a neutral lipid within the lipid bilayer of all cells and plays an important role in signaling from the cell surface to various subcellular compartments. It is collected in detergent-resistant membrane domains called lipid rafts. Lipid rafts in turn serve as membrane platforms for signal transduction mechanisms that promote tumor cell growth inhibits apoptotic signals and actively stimulates other malignant cellular behaviors (Freeman and Solomon, 2004). Survival mechanism of PCa cells is entirely processed through specialized membrane microdomains that are dependent on cholesterol for signal transduction. Studies refer that majority of patients suffering from PCa have high levels of total serum cholesterol (Maqura *et al*., 2008; Mittal *et al*., 2011). Survival mechanism of PCa cells is entirely processed through specialized membrane microdomains that are dependent on cholesterol for signal transduction. Studies (Lim *et al*., 2007; Kotani *et al*.,2013 ; Chen *et al*.,2009) refer that majority of patients suffering from PCa havehigh levels of total serum cholesterol (Maqura *et al*., 2008; Mittal *et al*., 2011). Hypercholesterolemia in prostate tumor cell membranes results in the gathering of raft domains. This process inhibits positive regulators of oncogenic signaling within rafts, while maintaining negative regulators in the liquid-disordered membrane fraction (Hui-ming, 2008). The mevalonate pathway, which leads to cholesterol synthesis, plays a key role in controlling cell proliferation by generating farnesyl and geranyl intermediates, These isoprenoids covalently alteration and so modulate the biological activity of signal transducing proteins (Singh *et al*., 2003). Besides raised serum total cholesterol, mean LDL levels increased to some extent as a result of its enhanced ability to oxidation in PCa. Malondialdehyde (MDA) is an endogenous genotoxic product of enzymatic and oxygen radical-induced lipid peroxidation may cross-link DNA on the same and opposite strands via adenine and cytosine and contributes to carcinogenecity and mutagenecity in mammalian cells (Niedernhofer, 2003). Therefore, it can be concluded that elevated plasma cholesterol levels can be a risk for PCa.

Material and methods

Blood was collected from (50) PCa patients and (40) healthy aged between 50-≥70 years subjects by 5 ml syringe and vacuolated in jell and clot activator test tube (Jordan).

Centrifugation by (genex /USA) of the blood 3000 round for 5 minutes to obtain the serum after 45 minuts.

Accent 200 chol diagnostic kits for determination of total cholesterol concentration (pz COMARY/Poland) by using (mindray automated /Germany)

Accent 200 HDL diagnostic kits for determination of total cholesterol concentration (pz COMARY/Poland) by using (mindray automated /Germany)

Accent 200 triglyceride diagnostic kits for determination of total cholesterol concentration (pz COMARY/Poland) by using (mindray automated /Germany)

PSAkits (biomerieux,france) for detection of total prostate specific antigen level by minVIDAS(USA).
Vit D kits (biomerieux,france) for detection of total vitamin D level by minVIDAS(USA)

Data Analysis

The analyses were performed using the statistical package for social (SPSS) version 16(ANOVA),(P≤0.05) between prostate cancer patients group and control group and within patients group (Elston and Johonson, 2008).

Results

Table (1) Prostate specific antigen, vitamin D, cholesterol, triglyceride and high density lipoprotein levels in prostate cancer patients and control group.

Test	Prostate cancer patients with metabolic syndrome group /mean ±SE	Control group Mean ±SE
PSA (ng/ml)	33.09 ± 6.01 b	2.93 ± 0.26 a
vitamin D (ng/ml))	17.34 ± 1.15 b	26.42 ± 1.05 a
high density lipoprotein (mg/dl)	35.61 ± 0.85 a	38.15 ± 1.20 a
Triglyceride (mg/dl)	129.63± 8.99 b	101.26± 3.50 a
Cholesterol (mg/dl)	184.47 ± 9.18 a	159.74± 4.96 a

Deferent letters indicate significant difference (p≤0.05).

There is significant difference (p≤0.05) in prostate specific antigen between PCa patients group and control group (33.09±6.01, 2.93±0.26)ng/ml respectively (Table-1). There is significant difference (p≤0.05) in vitamin D level between PCa patients group and control group (17.34±1.15, 26.42±1.05)mg/dl respectively (Table-1).
There is no significant difference (p>0.05) in cholesterol level between PCa patients group and control group (184.47±9.18, 159.74±4.96)mg/dl respectively (Table-1).
There is significant difference (p≤≤0.05) in triglyceride level between PCa patients group and control group (129.63±8.99, 101.26±3.50)mg/dl respectively (Table-1).
There is no significant difference (p>0.05) in high density lipoprotein level between PCa patients group and control group (35.61±0.85, 38.15±1.20) mg/dl respectively (table-1).There is very weak negative correlation vitamin D with cholesterol (r=-0.24) in prostate cancer patients (figure -1).The correlation between Vit D and triglyceride (r=-0.07), HDL(r=o.o49), is undetectable in prostate cancer patients (figure 2 and 3).

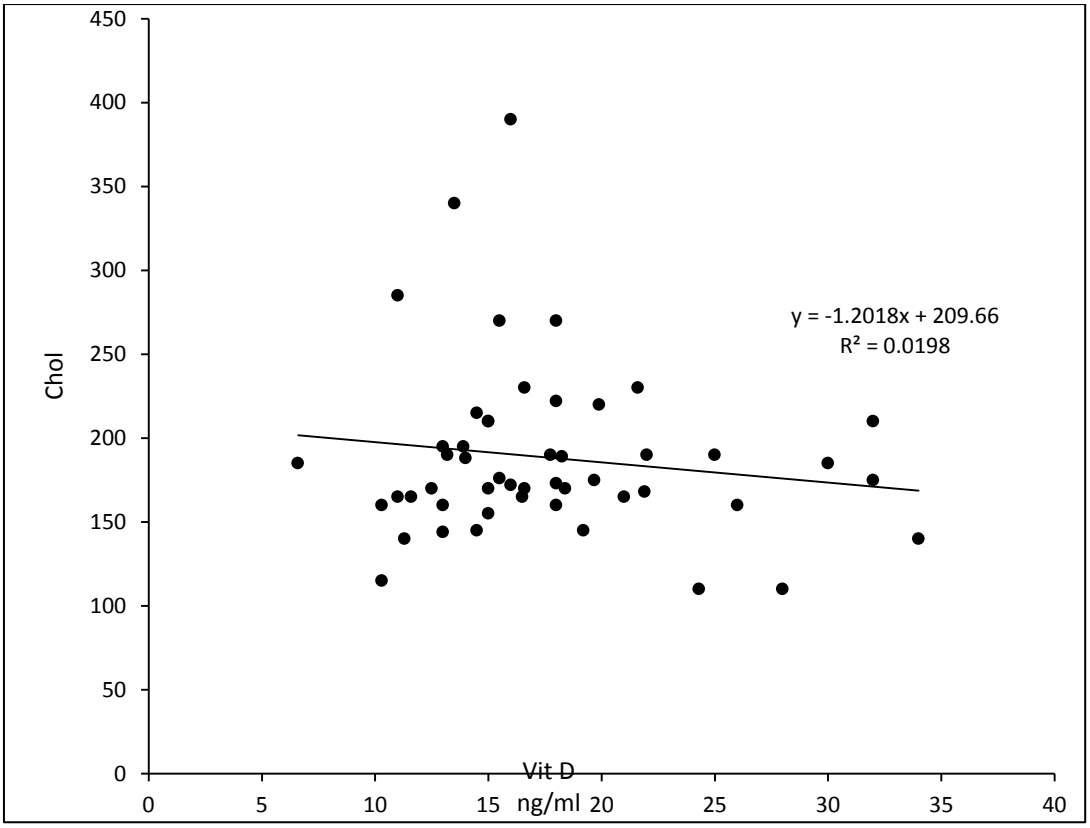

Figure (1) weak negative correlation between vitamin D and cholesterol in prostate Cancer patients.

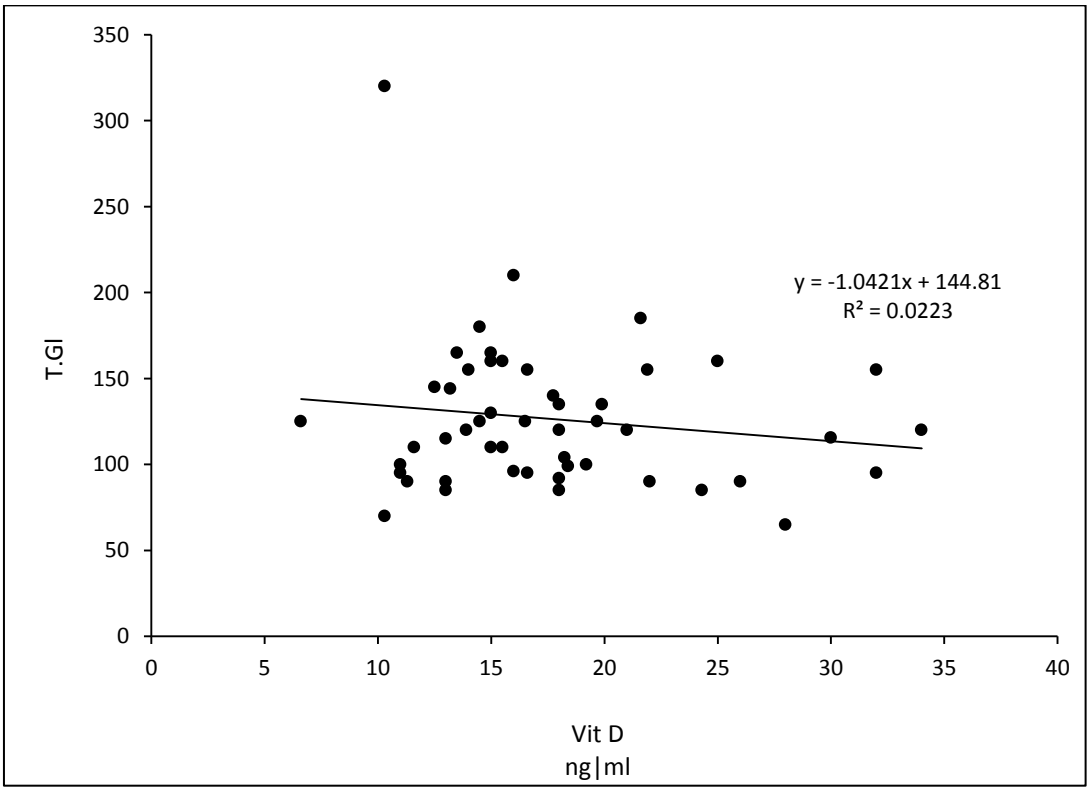

Figure (2) weak negative correlation between Vit D and triglyceride in prostate cancer patients

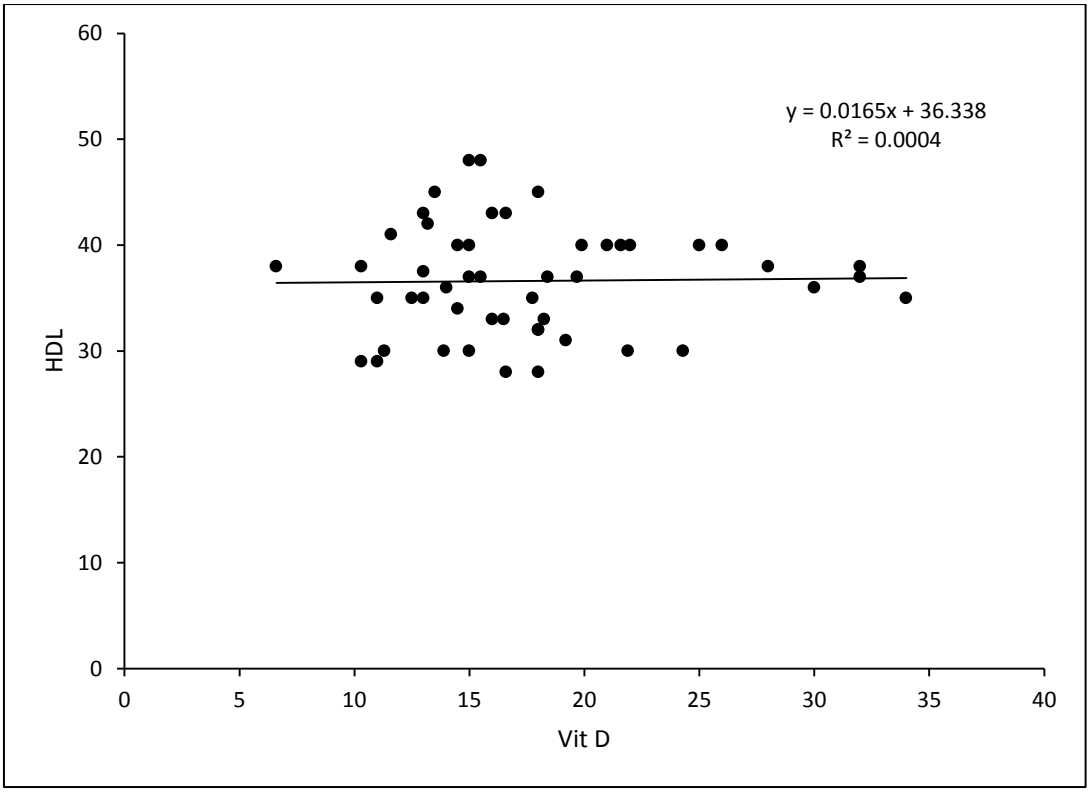

Figure (3) weak positive correlation between Vit D and high density lipoprotein in prostate cancer patients

Discussion

Reduced PSA level was an important indicator for PCa diagnosis and follow up of the treatment of PCa; the data have showed high level of PSA which indicates they have PCa (Chen., *et al.*, 2009) (table 1).Human prostate cells contain vitamin D receptor (VDR) for 1, 25-dihydroxyvitamin D, the active form of vitamin D to promotion of cell differentiation, apoptosis and Inhibition of cellular proliferation. PCa caused VDR decline in VDR number leading to less expression for 1, 25-hydroxyvitamin D which is converted locally within the prostate to 1, 25-(OH)2 D by 1α- hydroxylase and the activity of this enzyme decreased in cells derived from adenocarcinomas compared with cells derived from normal tissues or benign prostatic hyperplasia (BPH) (Hsu., *et al* 2001) in addition to VDR single Nucleotide polymorphisms (Hendrickson.,*et al* 2011) a Genetic heterogeneity ,all these factors lead to decrease in the level of vitamin D in PCa patients compared with healthy subjects(Donkena and Young, 2011) (table 1).Cholesterol essential component for 7-dehydrocholesterol in the skin is Converted to previtamin D which is then immediately converts by a heat dependent process to vitamin D (Holick, 2010). There is no significant difference ($p>0.05$) in HDLcholesterol and this indicate no effects of prostate cancer upon HDL and cholesterol while significant difference ($p<0.05$) in triglyceride level concerned with high-grade tumor (Chen *et al.*, 2009).)(table 1). There is weak negative correlation between Vit D and cholesterol because The fully active dihydroxylated Vitamin D induce the expression and possess Metabolism of vitamin D leads to decrease level 3-hydroxy-3-methyl-glutaryl-Coenzme A (HMG-CoA) reductase activity and low level of Vit D led to increased level of cholesterol (figure- 1)(Bhattacharyya.,*et al* 2012).

References

Ahonen, M.; Tenkanen, L.; Teppo, L.; Hakama, M and Tuohimaa,P. (2000) Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control, 11:847-52

Campbell, M.; Reddy ,G and Koeffler, H (1997) Vitamin D3 analogs and their 24-oxo metabolites equally inhibit clonal proliferation of a variety of cancer cells but have differing molecular effects. J Cell Biochem, 66(3):413–425.

Chen ,S.; Chen, K.; Alex T.; Chang ,Y.; Howard, H and Chang,L (2009) Correlation Between Pretreatment Serum Biochemical Markers and Treatment Outcome for Prostatic Cancer with Bony Metastasis. J Chin Med Assoc , 72 . 6:301-306

Donkena ,K and Young, Ch. (2011) Vitamin D, Sunlight and Prostate Cancer Risk.doi/10.4061/2011/281863

Freeman,MR and Solomon,KR(2004). Cholesterol and prostate cancer. Cell Biochem, 91:54-69

Fujioka, T.; Suzuki, Y.;Okamoto ,T.;Mastushita, N.; Hasegawa, M. and Omori, S. (2000). Prevention of renal cell carcinoma by active vitamin D3. World J Surg, 24(10):1205–1210

Garland, C.; Garland, F.; Gorham, E.; Lipkin ,M.; Newmark, ,H.; Mohr ,S and Holick, M (2006) The Role of Vitamin D in Cancer Prevention .American Journal of Public Health , 96 (2) 2:252-261

Hendrickson ,W.; Flavin ,R.; Kasperzyk, J.; Fiorentino, M.; Fang F.; Lis R.; Fiore, C.; Penney ,K.; Ma ,Jing.; Kantoff, Ph.; Stampfer, M.; Loda ,M.; Mucci ,L and Giovannucci, E. (2011) Vitamin D Receptor Protein Expression in Tumor Tissue and Prostate Cancer Progression , journal of clinical oncology, 29 .17 :2378-2384

Holick ,M (2010)The vitamin D deficiency pandemic: A forgotten hormone important for health. Public Health Reviews, 32:267-283

Hsu, Ju-Yu.; Feldman ,D.; McNeal ,J and Peehl ,D (2001) Reduced 1a-hydroxylase Activity in Human Prostate Cancer Cells Correlates with Decreased Susceptibility to 25-Hydroxyvitamin D3-induced Growth Inhibition1. Cancer research, 61: 2852–2856

Hui-ming, C (2008).Metabolic syndrome and prostate cancer .ph.D Thesis. johns Hopkins university .USA.

Iseki, K.; Tatsuta, M.; Uehara, H.; Yano, H.; Sakai, N. and Ishiguro, S(1999) Inhibition of angiogenesis as a mechanism for inhibition by 1alphahydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 of colon carcinogenesis induced by azoxymethane in Wistar rats. Int J Cancer, 81(5):730–733

Mantell, D.; Owens, P.; Bundred , N.; Mawer , E and Canfield, A(2000) alpha,25-dihydroxyvitamin D(3) inhibits angiogenesis in vitro and in vivo. Circ Res, 87(3):214–220.

Kotani, K.; Sekine ,Y.; Ishikawa ,S.; Ikpot, I.; Suzuki, K and Remaley, A (2013) High-Density Lipoprotein and Prostate Cancer: An Overview. J Epidemiol, 23(5):313-319

Li, H.; Stampfer, M.; Hollis, B.; Mucci , LA.;Gaziano , JM.; Hunter, D.; Giovannucci, EL and Ma ,J (2007) A Prospective Study of Plasma Vitamin D Metabolites, Vitamin D Receptor Polymorphisms, and Prostate Cancer. PLoS Medicine, 4:103

Lim ,U.;Gayles ,T.; Katki, HA.; Stolzenberg-Solomon, R.;Weinstein, SJ.; Pietinen, P.;Taylor, PR.; Virtamo, J and Albanes, D(2007) Serum high-density lipoprotein cholesterol and risk of non-hodgkin lymphoma. Cancer Res, 67: 5569-74

Mgura,L.;Blanchard,R.;Hope,B.;Beal.JR.;Schwartz,GG and Sahmoune AE.(2008) Hypercholesterimia and prostate cancer :A hospital-based case –contreol study .cancer cases control,19:1259-1266

Mittal, A.; Sathian, B.;Chandrasekharan ,N.; Lekhi,A.;Kumar,Sand Yadav,S.K.(2011) Role of Hypercholesterolemia in Prostate Cancer-Case Control Study from Manipal Teaching Hospital Pokhara, Nepal. Asian Pacific Journal of Cancer Prevention, 12:1905-1907

Niedernhofer**,** LJ.; Daniels, JS.; Rouzer, CA.; Greene, RE and Marnett, LJ. (2003). Malondialdehyde, a product of lipid peroxidation, is mutagenic in human cells. J Biol Chem, 278: 31426-33

Pálmer, HG.; González-Sancho, JM.;Espada J.; Berciano, MT.; Puig, I.; Baulida, J.;Quintanilla, M.; Cano, A.;de Herreros, AG.; Lafarga, M. and Muñoz A. (2001). Vitamin D (3) promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of beta-catenin signaling. Cell Biol, 154(2):369–87.

Fujioka,T.;Suzuki,Y.;Okamoto,T.;Mastushita,N.;Hasegawa,M.andOmori,S.(200). Prevention of renal cell carcinoma by active vitamin D3. World J Surg, 24(10):1205–1210

Singh,RP.;Kumar,R and Kapur, N. (2003). Molecular regulation of cholesterol biosynthesis: Implications in carcinogenesis. J Environ Pathol Toxicol Oncol, 22: 75-92.

Tuohimaa, P.; Tenkanen, L.; Ahonen, M,; Lumme, S.;Jellum, E.; Hallmans, G.; Stattin, P.; Harvei, S.; Hakulinen, T.; Luostarinen, T.; Dillner, J.; Lehtinen, M and Hakama, M. (2004). both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int J Cancer, 108: 104-8.

Vesovic, Z (2005) Molecular genetic of prostate cancer:association of the candidate genes CYP17 and MSR1.ph.D thesis. Faculty of Medicine, University of Ulm.

Zadshir, A.; Tareen, N.;Pan ,D.; Ris, K and Martins, D. (2005). the prevalence of hypovitaminosis D among US adults: Data from the NHANES III. Ethn Dis, 15, 97-101.

Elston, R.; Johonson, W (2008).Basic Biostatistics for Genetics and Epidemiology ,A practical Approach .1 Edt.wiley

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