

**STUDY OF HOMEOSTASIS MODEL ASSESSMENT OF INSULIN RESISTANCE, DYSLIPIDEMIA, ANTIOXIDANT VITAMINS STATUS, SERUM CALCIUM, PHOSPHATE AND PROSTATE SPECIFIC ANTIGEN IN PROSTATE CANCER.****M.KRISHNAMMA, S.PRASANTH VARDHAN, J.N.NAIDU AND M.PRASAD NAIDU****Biochemistry Dept, Narayana Medical College and Hospital, Nellore-524003, Andhra Pradesh, India.***ABSTRACT**

The Incidence of Prostate Cancer is increasing day by day all over the world. At present the Incidence is about 5 per 1, 00,000 in India. There is strong evidence that genetic and environmental factors play in important role in pathophysiology, of prostatic cancer. In this study HOMA-IR, serum Calcium, Phosphate, Lipid profile, PSA and antioxidant vitamins were estimated. Age matched 50 Prostate cancer cases and 50 controls included in the study. The insulin resistance in all cases and control groups evaluated by estimating fasting blood glucose and insulin levels, by using HOMA IR Formula. Antioxidant vitamins estimated by HPLC, Serum Calcium, Phosphate, lipid profile and Prostate specific antigen by enzymatic kits using Autoanalyzers. In the present study, the values of HOMA-IR, serum Calcium and PSA are ($p < 0.05$) significantly increased than in controls. The Serum alfa tocopherol and ascorbic acid values in cases significantly reduced ($p < 0.05$) than in controls. The growing of prostate cancer is a multifactorial. Insulin resistance, antioxidant vitamins status, hyper calcimeia and dyslipidemia play an important role in pathogenesis of prostate cancer.

KEYWORDS: HOMA-IRDyslipidemia, Insulin Resistance, Antioxidant Vitamin, Hyperglycemia.**M.PRASAD NAIDU**Biochemistry Dept, Narayana Medical College and Hospital,
Nellore-524003, Andhra Pradesh, India.

*Corresponding author

INTRODUCTION

The prostate is located in the pelvis and is surrounded by the rectum, bladder, the periprostatic and dorsal venous plexus and the urinary sphincter.¹ The development of prostate cancer is multi step process.² Several molecular etiological pathways have been suggested for prostate cancer.³ Androgen transactivation pathways clearly have received the greatest attention; others have the focus of increasing research activity.⁴ An increased risk of disease has been reported among subjects obesity or body mass^{5,6} Hyperinsulinemia, in affected individuals, may promote cancer, as insulin can exert its oncogenic potential via abnormal stimulation of multiple cellular signaling cascades, enhancing growth factor dependent cell proliferation and/or by directly affecting cell metabolism.⁷ There is an increased risk among individuals with elevated serum levels of insulin like growth factor,. Some studies have shown that the metabolic syndrome characterized by central obesity insulin resistance, high serum glucose levels and dyslipidemia may play a role in Prostate cancer.⁸ Insulin increases the bioactivity of IGF-I by enhancing hepatic IGF-I synthesis and by reducing hepatic protein production of the insulin-like growth factor binding proteins 1 (IGFBP-1) and 2 (IGFBP-2).⁹ Therefore, although insulin can directly induce tumor growth, many of its mitogenic and antiapoptotic effects are operating through the IGFI system, as reported in individuals with high levels of circulating IGF-I, in which an increased risk of developing certain types of tumors, in particular breast and prostate cancers.¹⁰ The antioxidant α tocopherol (vit E) and selenium may also reduce the risk¹¹ both genetic and environmental factors have been implicated in the etiology of prostate cancer. Several molecular etiological pathways have been suggested for prostate cancer – androgen transactivation pathways, vitamin D metabolism, insulin like growth factor signaling pathways and chemical carcinogenic pathways¹² Insulin resistance is associated with a higher risk of prostate cancer among men and that insulin sensitivity is associated with a

reduced risk of prostate cancer among men¹³. Association between prostate cancer risk and oxidative stress has been well recognized. There is considerable evidence suggesting oxidative stress contributes to etiology and pathogenesis of prostate cancer¹⁴. PSA had been found to correlate with pathological states of tumor extension and metastasis. Advanced pathological stages are associated with higher PSA levels in the serum¹⁵. Elevated fasting plasma insulin and other components of the metabolic syndrome were associated with greater prostate cancer mortality with clinical stage T2-3 prostate cancer¹⁶. Previous studies have hypothesized that catecholamine's might have a tropic effect on the growth of prostate cells by slowing down the apoptotic process suggesting a link between hyperinsulinemia and the development of prostate cancer¹⁷. Diabetes mellitus duration is inversely correlated with the risk of prostate cancer¹⁸. DM might induce local microvascular dysfunction and prostate ischemia which present initiation and development of carcinoma prostate¹⁹. vitamin C has role in regeneration of tocopherol from phenoxy free radical derivative²⁰ vitamin E and Vitamin C levels are reduced in prostate cancer patients²¹. Insulin can mediate its mitogenic effect on prostate cells through signal transduction mechanism.²² Recent physiological and genetic studies have levels that the insulin signaling pathway plays a pivotal role in the regulation of variety of interrelated fundamental processes such as metabolism, growth, reproduction, and aging the mammalian target of rapamycin is a downstream molecule of the P13K / PTEN – AKT-mTOR pathway of insulin and IGF -1 receptor this signaling network lays a crucial role in the translational level by modifying phosphorylation of pivotal targets such as the translation initiation factor GE-binding proteins and S6KS. The mTOR pathway seems also to be involved in prostate cancer.²³ Specifically it mediates cell growth and proliferation as well as increase and angiogenesis induced by platelet derived growth factor – D (PDGF-D) in

PDGF-D over depressing prostate cancer cells²⁴. In the early stages of prostate cancer, every cancer cells are mainly androgen dependent and highly sensitive to anti androgens. Recent work has shown that Vitamin E suppresses the expression of androgen receptor in prostate cancer cells and helps to establish new therapeutic concepts for the prevention & treatment of prostate cancer²⁵.

MATERIALS AND METHODS

Patients of prostate cancer were recruited from the dept of urology, Narayana Medical College, Nellore 60-80 year old males with biopsy proven adenocarcinoma of prostate irrespective of the staging were taken as cases. 60-80 year old age matched disease free individuals, without any complications were taken as controls the study was conducted over a period of one year. Fifty prostate cancer cases and 50 controls age matched without any complications were tested. Sample collected 5 ml of fasting blood sample was collected by venipuncture and allowed to clot for serum separation serum was kept immediately in freezing temperatures, to preserve insulin and ascorbic acid as their half lives are 4 to 6 minutes. For accurate comparison to established normal values, a fasting morning serum sample should be obtained. The blood should be collected in a plain redtop venipuncture tube without additives of anti – coagulants. Allow the blood to clot. Centrifuge the specimen to separate the serum from the cells. Samples may be refrigerated at 2-80 C for a maximum period of five (5) days. If the specimen (s) cannot be assayed within this time, the sample(s) may be stored at temperatures of -20-0 C for up to 30 days. When assayed in duplicate 0.05 ml of the specimen is required. Total cholesterol, triglycerides, HDL-cholesterol and glucose are measured using enzymatic kits using autoanalyzer. VLDL-cholesterol is calculated by Friedwald's formulae. Serum insulin was estimated by immunoenzymatic assay using insulin calibrators and insulin enzyme reagent, in this procedure, immobilization takes place

during the assay at the surface of a microplate well through the interaction of streptavidin coated on the calculated as fasting glucose (mg/dl) x fasting insulin (mU/mL)/405.

RESULTS

The results of the present study are consistent with the findings showing an association between increased glucose, insulin resistance, lowered antioxidant vitamin status and the pathogenesis of prostate cancer. PSA levels for cases were found to be 21.48 ± 7.15 which is significantly higher when compared to controls levels of 4.76 ± 0.69 . The two tailed P-value less than 0.0001 by conventional criteria; this difference is considered to be extremely statistically significant. The mean PSA of cases minus mean PSA of controls equals 16, 72 and 95% confidence interval of this difference from 14.10 to 19.35. The 30 prostate cancer patients aged 60-80 were taken as cases. So normal age matched disease free without any complications were taken as controls. In both group insulin resistance and antioxidant vitamin status was studied. The fasting insulin values for cases are 19.26 ± 3.52 , which is significantly higher when compared to controls value of 15.13 ± 3.39 . The two tailed P value is less than 0.0001 by conventional criteria this difference is considered to be extremely statistically significant the mean fasting insulin of cases minus mean fasting insulin of controls equals 4.13. 95% confidence interval of difference from 2.34 to 5.92. The fasting blood glucose value for cases is found to be mean \pm standard deviation 63.76 ± 3.90 , which is higher significantly when compared to controls value of 62.93 ± 2.44 . HOMA –IR for cases is $3.07 \pm .75$, which is significantly higher compared to the mean value of controls 2.35 ± 0.58 . The two tailed P value equals 0.001 this difference is statistically extremely significant. The mean HOMA – IR of cases minus mean HOMA-IR of controls equals 0.71. Serum vitamin E values in the present study for cases found to be 0.33 ± 0.12 , which is significantly lower compared to controls value 0.58 ± 0.11 . The two tailed P value is less than 0.0001 which is statistically significant. The mean

serum vitamin E of cases minus mean serum vitamin E of controls equals 0.2 and 95% confidence interval of this difference from - 0.30. A decreased prostate cancer risk was observed with increasing intakes of vitamin C risk vegetable (16) in this study serum calcium values for cases was 9.95 ± 0.36 which is significantly higher compare to controls value 9.45 ± 0.60 the two tailed P value 0.002 which is statistically significant. The mean serum calcium of cases minus mean serum calcium of

controls equals 0.50.95% confidence interval of this difference from 0.24 to 0.76. Serum phosphorus levels were found to be significantly increased ($p < 0.01$) as compared to Controls. Total cholesterol, LDL cholesterol and triacylglycerol are elevated significantly in Prostatic cancer . The Prostatic cancer cases are associated with significant rise in total cholesterol, LDL cholesterol, VLDL cholesterol, and triacylglycerol as compared to controls.

Figure 1
Normal Prostate tissue

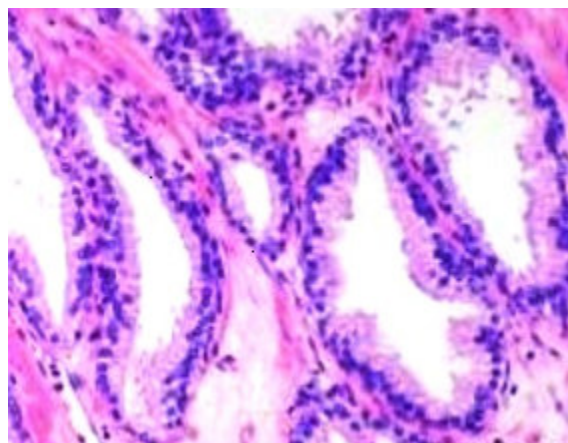


Figure 2
Prostate cancer with Gleason pattern

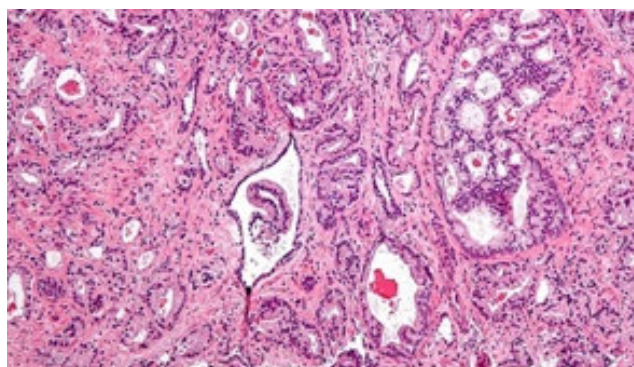


Figure 3
Prostatic adenocarcinoma with perineural invasion

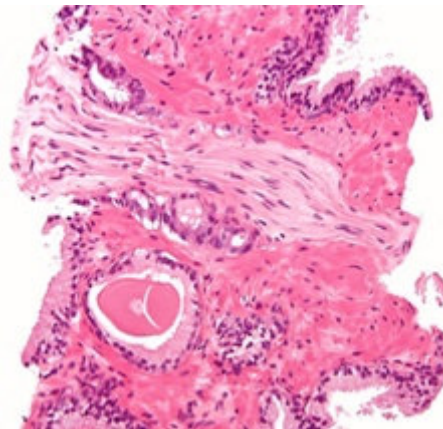


Table 1
shows Biochemical parameters in prostate cancer

PARAMETER	PATEINTS		CONTROLS		p' VALUE	t-VALUE
	mean	± S.D	mean	± S.D		
PSA(ng/ml)	21.48	7.15	4.76	0.69	<0.0001	12.739
Fasting insulin(mIU/L)	19.26	3.52	15.13	3.39	<0.0001	4.6301
Fasting glucose (mg/dl)	63.76	3.90	62.93	2.44	<0.0325	0.991
HOMA – IR (μU/ml)	3.07	0.75	2.35	0.58	<0.0001	4.1047
Vitamin E (μg/ml)	0.33	0.12	0.58	0.11	<0.0001	7.8627
Vitamin C (μg/ml)	30.44	10.72	51.69	14.49	<0.0001	6.4524
Calcium (mg/dl)	9.95	0.36	9.45	0.60	<0.0002	3.9425
Phosphate (mg/dl)	3.19	0.26	3.06	0.12	<0.0138	2.5389
Cholesterol (mg/dl)	210	46.3	168.6	18.4	<0.0001	4.5513
TG (mg/dl)	159.6	60.2	68.7	19.3	<0.0001	7.8756
HDL (mg/dl)	39.4	8.2	48.7	9.4	<0.0001	4.0836
LDL (mg/dl)	106.5	30.1	83.8	12.9	<0.0004	3.7967
VLDL (mg/dl)	33.2	14.1	13.8	4.7	<0.0001	7.1493

Figure1

Low level of antioxidant vitamin status and PSA pathogenesis of prostate cancer

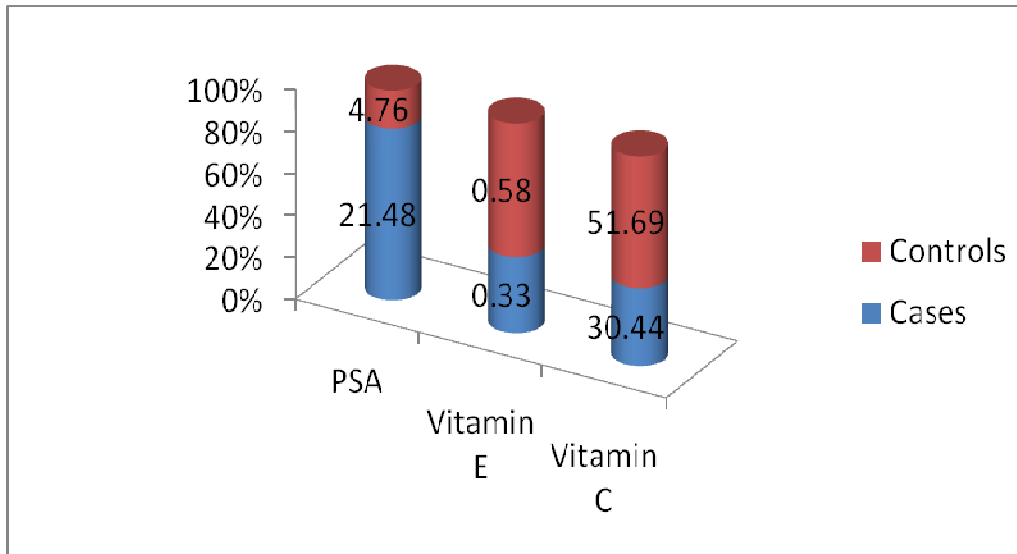


Figure2

Shows Increased levels insulin resistance in prostate cancer.

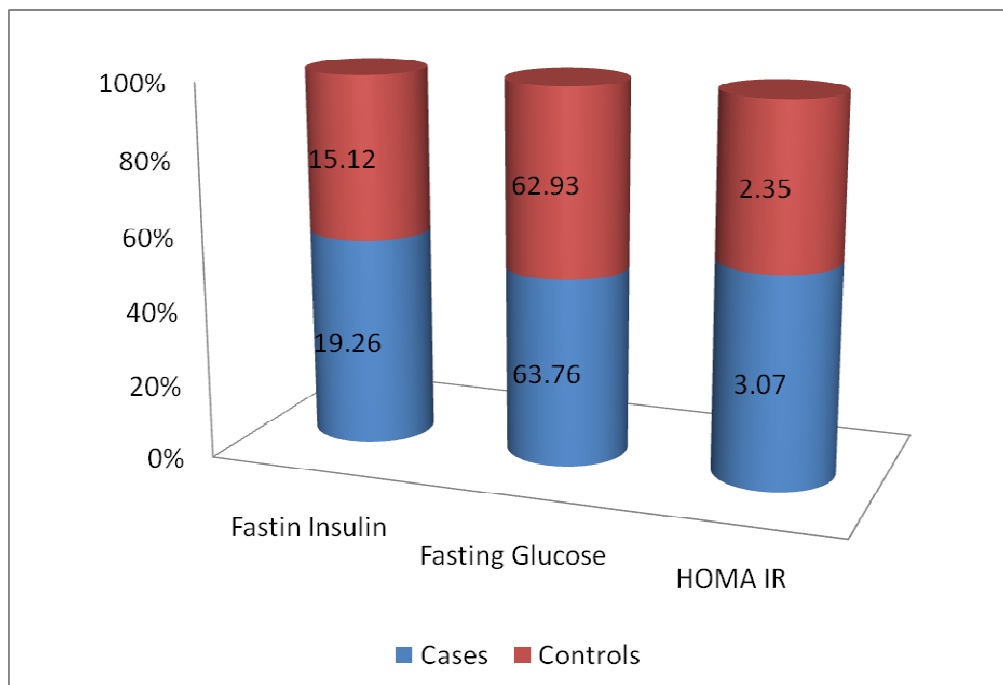


Figure 3
Increased levels of phosphate and calcium in prostate cancer.

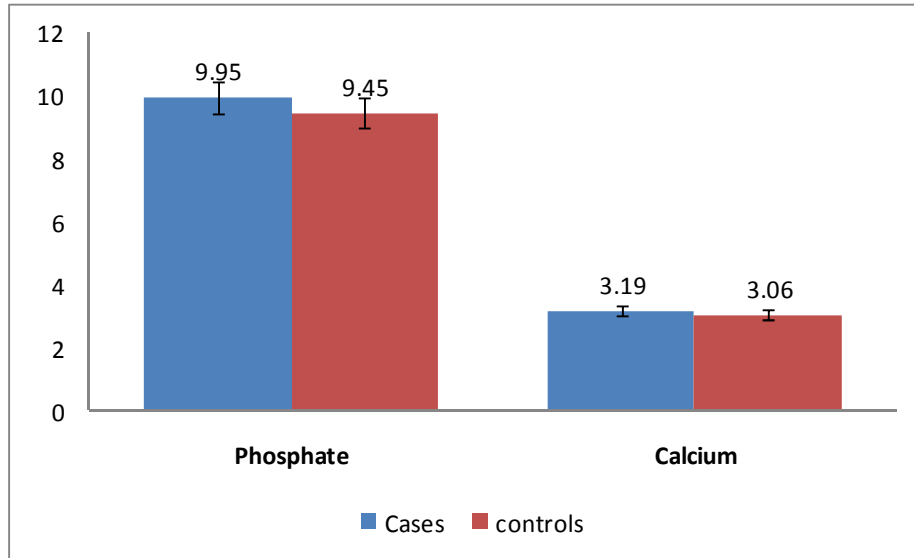
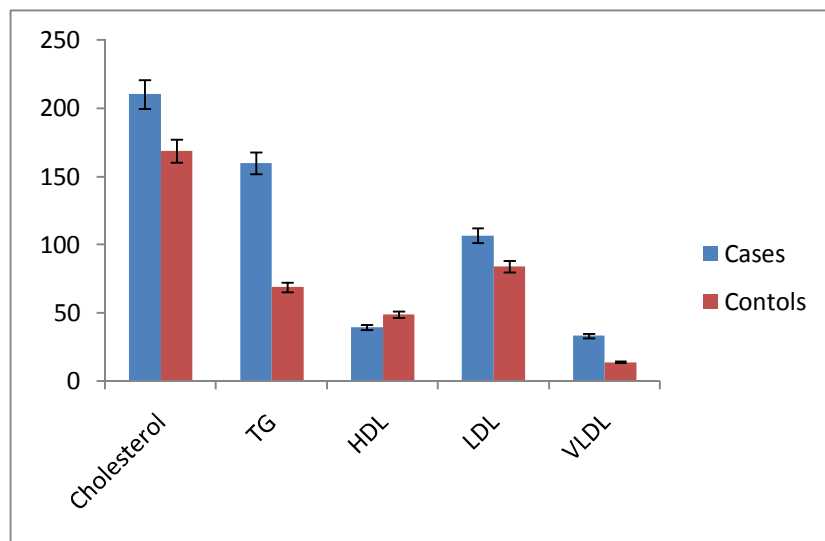


Figure 4
Serum Lipid profile in cases and controls



CONCLUSION

The last decades of medical research examining the pathogenesis of common tumors have provided compelling evidence for the involvement of insulin resistance in cancer. Development of prostate cancer is a several metabolism hypermethylation of glutathione transference Pi (GSTPi) gene promoter leading to a loss of function of a gene that detoxifies carcinogen is one early change. Several

molecular etiological pathways have been suggested for prostate cancer. Androgen transactivation pathways clearly have received the greatest attention. Among the most prominent of these additional pathways is vitamin D metabolism, insulin like growth factor signaling pathways and chemical carcinogenic pathways. The many studies have shown that low testosterone concentrations are related with the lower levels of HDL cholesterol and high levels of triglyceride, total cholesterol and LDL concentrations.²⁶ The results the present

studies are consistent with these findings showing an association between increased insulin resistance lowered antioxidant vitamin status and the pathogenesis of prostate cancer.²⁷ The development of prostate cancer is a many mechanisms.²⁸ Hyperinsulinemia associated with insulin resistance may play a role in the pathogenesis of prostate cancer through its sympathoexcitatory effect, by altering sex hormone metabolism, activating the IGF pathway, through signal transduction mechanisms and via dyslipidemia and inflammation.²⁹ Whether increased insulin resistance, either through lifestyle changes or genetic susceptibility, increases the risk of prostate cancer warrants further investigation, especially in prospective studies.³⁰ Elevated fasting plasma insulin and other components of the metabolic syndrome were associated with greater prostate cancer mortality. Prostate

cancer cells generate high levels a ROS and the generation of ROS increases with aggressiveness of the cells. Recent work has shown that vitamin E and selenium suppresses the expression of androgen receptor in prostate cancer cells and helps to establish new therapeutic concepts for the prevention and treatment of prostate cancer. In men with prostate cancer there is dyslipidemia and decreased antioxidant vitamins activity. Vitamin C has role in regeneration of tocopherol from phenoxy free radical derivative. A decreased prostate cancer risk was observed with increasing intakes of vitamin C-rich vegetables. Prostatic cancer can be decreased by decreasing insulin resistance. Insulin resistance can be decreased by life style modification like yoga, meditation, exercise and balanced diet.

REFERENCES

- Walz, Jochen, Markus Graefen, and Hartwig Huland. "Basic principles of anatomy for optimal surgical treatment of prostate cancer." *World J. Urol.* 25, (1): 31-38, (2007)
- Thompson, Ian M., Phyllis J. Goodman, Catherine M. Tangen, M. Scott Lucia, Gary J. Miller, Leslie G. Ford, Michael M. Lieber et al. "The influence of finasteride on the development of prostate cancer." *N. Engl. J. Med.* 349, (3): 215-224, (2003)
- Taichman, Russell S., Carlton Cooper, Evan T. Keller, Kenneth J. Pienta, Norton S. Taichman, and Laurie K. McCauley. "Use of the stromal cell-derived factor-1/CXCR4 pathway in prostate cancer metastasis to bone." *Cancer Res.* 62, (6): 1832-1837, (2002)
- Ross, RONALD K., NICK M. Makridakis, and J. K. Reichardt. "Prostate cancer: Epidemiology and molecular endocrinology." *Hormones, genes, and cancer* 273, (2003)
- Paolo Boffetta, Paul Brennan and Rodolfo Saracci. Oxford text book of public health 4TH Ed, 9.2 Neoplasms, United States, 1155 – 1192, (2002).
- Caire, Arthur A., Leon Sun, Thomas J. Polascik, David M. Albala, and Judd W. Moul. "Obese African-Americans with prostate cancer (T1c and a prostate-specific antigen, PSA, level of < 10 ng/mL) have higher-risk pathological features and a greater risk of PSA recurrence than non-African-Americans." *BJU international* 106, (8): 1157-1160, (2010)
- Lorincz, A. M., and S. Sukumar. "Molecular links between obesity and breast cancer." *Endocr-Relat Cancer* 13, (2): 279-292, (2006)
- Van Gaal, Luc F., Ilse L. Mertens, and E. Christophe. "Mechanisms linking obesity with cardiovascular disease." *Nature* 444, (7121): 875-880, (2006)
- Baxter, Robert C. "Insulin-like growth factor (IGF)-binding proteins: interactions with IGFs and intrinsic bioactivities." *Am J Physiol-Endoc M* 278, (6): 967-976, (2000)
- Baserga, Renato. "The insulin-like growth factor-I receptor as a target for cancer

- therapy." *Expert Opin Ther Pat* 753-768: (2005)
11. Kaplan, George W., and Irene M. McAleer. "Avery's Neonatology 6th Edition." 11. internal medicine hyperplastic and malignant diseases of the prostate, Lippincott Williams & Wilkins 81: 543 -553, (2005)
 12. Hsing, Ann W., Yu-Tang Gao, Streamson Chua, Jie Deng, and Frank Z. Stanczyk. "Insulin resistance and prostate cancer risk." *J. Natl. Cancer Inst.* 95, (1): 67-71. (2003)
 13. Kumar, Binod, Sweaty Koul, Lakshmipathi Khandrika, Randall B. Meacham, and Hari K. Koul. "Oxidative stress is inherent in prostate cancer cells and is required for aggressive phenotype." *Cancer Res.* 68, (6): 1777-1785, (2008)
 14. Burtis CA, Ashwood ER, Bruns DE, Mineral and bone metabolism. In, Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 4th edn. Chapter 49, St. Louis Missouri, USA: Elsevier Saunders, 1891 – 1965. (2006)
 15. Cox, Michael E., Martin E. Gleave, Mahvash Zakikhani, Robert H. Bell, Esther Piura, Elaine Vickers, Matthew Cunningham, Ola Larsson, Ladan Fazli, and Michael Pollak. "Insulin receptor expression by human prostate cancers." *The Prostate* 69, no. 1 (2009): 33-40.
 16. Nandeesh, Hanumanthappa. "Insulin: a novel agent in the pathogenesis of prostate cancer." *Int Urol Nephrol*, 41, (2): 267-272, (2009)
 17. Burton, Anya J., Kate M. Tilling, Jeff M. Holly, Freddie C. Hamdy, Mari-Anne E. Rowlands, Jenny L. Donovan, and Richard M. Martin. "Metabolic imbalance and prostate cancer progression." *Int J Mol Epidemiol Genet.* 1, (4): 248, (2010)
 18. Zhang, Weiwei, and Renming Hu. "Why does diabetes offer protective effects against prostate cancer? The possible role of its microvascular complications." *Med. Hypotheses* 74, (2): 242-243, (2010)
 19. Traber, Maret G., and Ishwarlal Jialal. "Measurement of lipid-soluble vitamins- further adjustment needed?." *Lancet* 355: 9220, (2000)
 20. Sandhya, B., S. Manoharan, G. Sirisha Lavanya, and Ch Ratna Manmohan. "Lipid peroxidation and antioxidant status in prostate cancer patients." *Indian J Sci Technol.* 3, (1): 83-86, (2010)
 21. Ambrosini, G. L., N. H. De Klerk, L. Fritschi, D. Mackerras, and B. Musk. "Fruit, vegetable, vitamin A intakes, and prostate cancer risk." *Prostate Cancer P D* 11, (1): 61-66, (2007)
 22. Craft, Noah, Yuriy Shostak, Michael Carey, and Charles L. Sawyers. "A mechanism for hormone-independent prostate cancer through modulation of androgen receptor signaling by the HER-2/neu tyrosine kinase." *Nature Med.* 5, (3): 280-285, (1999)
 23. Manna, Pulak R., and Douglas M. Stocco. "The role of specific mitogen-activated protein kinase signaling cascades in the regulation of steroidogenesis." *J Signal Transduct* 1—13, (2011).
 24. Dwivedi, V. K., A. Soni, M. Chaudhary, R. Sehgal, and S. M. Shrivastava. "Fixed dose combination of ceftazidime plus tobramycin acts as free radical scavenger in liver of mus musculus mice." *Cur Enzyme Inhibition* 5,(3): 171-175, (2009)
 25. Zagouri, Flora, Christos A. Papadimitriou, Meletios-Athanassios Dimopoulos, and Dimitrios Pectasides. "Molecularly targeted therapies in unresectable-metastatic gastric cancer. A systematic review." *Cancer Treat Rev* 37, (8): 599-610, (2011)
 26. Talbott, Evelyn, David Guzik, Annette Clerici, Sarah Berga, Katherine Detre, Karl Weimer, and Lewis Kuller. "Coronary heart disease risk factors in women with polycystic ovary syndrome." *Arterioscler Thromb Vasc Biol*, 15,(7): 821-826, (1995)
 27. Mirabello, Lisa, Wen-Yi Huang, Jason YY Wong, Nilanjan Chatterjee, Douglas Reding, E. David Crawford, Immaculata De Vivo, Richard B. Hayes, and Sharon A. Savage. "The association between leukocyte telomere length and cigarette smoking, dietary and physical variables,

- and risk of prostate cancer." *Aging cell* 8, (4): 405-413, (2009)
28. Pienta, Kenneth J., and Deborah Bradley. "Mechanisms underlying the development of androgen-independent prostate cancer." *Clin Cancer Res* 12, (6):1665-167, (2006)
29. Nandeesh, H., B. C. Koner, L. N. Dorairajan, and S. K. Sen. "Hyperinsulinemia and dyslipidemia in non-diabetic benign prostatic hyperplasia." *Clin Chim Acta* 370, (1): 89-93, (2006)
30. Lightfoot, Nancy, Michael Conlon, Nancy Kreiger, Andrea Sass-Kortsak, James Purdham, and Gerarda Darlington. "Medical history, sexual, and maturational factors and prostate cancer risk." *Ann Epidemiol* 14,(9): 655-662, (2004)