Estimation of selected metals in the tissues of prostate carcinoma patients : A Research

ABSTRACT

It Indicated that the Prostate cancer is common it affects nearly one-third of male over the age of 45. For two fundamental reasons, prostate cancer (PCa) is a serious health issue and a good prospect for tissue-scale, individualized modeling of cancer progression. In vivo validation might be allowed due to its compact size and the ability to measure serum PSA, a for prostate cancer blood biomarker can be diagnosed with support if certain markers identified by immunohistochemistry on tissue sections can aid in the diagnosis of adenocarcinoma that is primary in the prostate gland or metastatic. The biology of prostate cancer can be deeply understood by the gene identification and gene patterns expression. Using the Affymetrix Uranium95a, U95b, and Uranium95c chip sets (37,777 genes and expression sequence tags), Comprehensive gene expression is performed study on 152 hompsapien samples, which were from men of all ages and included cancer tissues, prostate tissues next to tumors, and prostate tissue of donor. In the prostate tissues, the majority of metals show a random distribution; nevertheless, patients show comparatively more unpredictability than controls. However, our findings indicate that the pattern of gene expression in cancer-related tissues is altered to such an extent that it resembles the effects of a cancer field. In contrast to controls, PCA and CA demonstrated how hazardous metals interfered with the critical metals' normal physiological and metabolic roles in the prostate tissues of both patient groups. In comparison to hyperthyroid patients and controls, hypothyroid patients' prostate tissues had greater mean levels of Fe, Ni, Cr, and Hg. Additionally; we discovered that by employing a unique model, Prostate cancer aggressiveness can be predicted by gene expression patterns.

Keywords: Prostate cancer, tissue-scale, patients, gene expression**.**

1. Introduction

Metals are solid, shiny, conductive elements known for their malleability, ductility, and high reflectivity [1] .Most are found in ores, though some like copper and gold occur freely due to low reactivity [2]. Lithium, zinc, iron, and copper are essential metal traces that are necessary for the functioning of enzymes and proteins, which support a variety of metabolic processes [3]. Heavy metals like chromium, mercury, arsenic, and cadmium are toxic even at low concentrations, with industrial use raising health and environmental concerns [4]. Cadmium disrupts cellular respiration and DNA repair, contributing to oxidative stress and apoptosis [5]. Chromium affects immune functions, with high levels reducing alveolar macrophage activity [6]. Cobalt exposure can cause respiratory diseases and cancer [7]. Copper, while essential, can be toxic in excess, affecting antioxidant functions and DNA integrity Copper (Cu) an Essential Redox-Active Transition, Mercury, liquid at room temperature, is highly toxic and requires careful handling to prevent contamination [8]. Magnesium, crucial for industrial applications, can cause toxicity if not properly excreted [9]. Iron is key for oxygen transport and cellular respiration, with deficiencies leading to anemia and excess intake potentially increasing cancer risk [10]. Tin, mainly extracted from cassiterite, is generally non-toxic, though certain organotin compounds are highly toxic [11]. Cancer is a disease where cells grow uncontrollably and spread to other body parts. There are over 100 types, commonly categorized by origin and cell type. Benign Tumors are Non-cancerous growths that do not spread but may press on vital structures . Causes include environmental toxins, genetics, and stress with treatments varying from "watchful waiting" to surgery [12]. Malignant Tumors are Cancerous and can spread (metastasize) to other body parts, maintaining their original [13]. The diagnosis is established through biopsies and imaging testing.As the most common type of cancer, carcinomas begin in epithelial cells. Both soft tissues and bones can develop sarcoma. Leukemia is a form of cancer that affects the tissues that produce abnormal white blood cells and make blood. Lymphoma that begins in lymphocytes affects lymph nodes and arteries. Starting in plasma cells, multiple myeloma progresses to bone cancers. Usually developing on the skin, melanoma can also occur in other pigmented tissues and is caused by melanocytes [14]. Both the brain and spinal cord Based on the type of cell and where the tumor is located in the central nervous system, it can be classified as benign or malignant. The underlying cause of cancer is genetic changes that disrupt normal cell division and growth. These changes can be caused by inherited

genes, incorrect cell division, or environmental harm (such UV rays and tobacco smoke). Cancer risk increases as a result of the body's diminished ability to eliminate damaged cells with age. Diverse cells within the same tumor may have diverse genetic mutations, and each malignancy has its own individual collection of changes.The process of staging cancer entails assessing the disease's severity, which has traditionally been accomplished by clinical examination and minimal imaging. Advanced diagnostic techniques like as CT, MRI, ultrasound, and PET have largely supplanted invasive staging procedures [15].

A collection of cells that share a common structure and function and are packed with intercellular matrix is called tissue. Nervous, muscular, connective, and epithelial are the four primary categories [16].Organs and blood arteries are lined with epithelial tissue, which offers protection, secretion, absorption, and feeling [17].It feeds itself by diffusion because it lacks blood arteries [13].Comprising fibers, ground substance, and cells such as macrophages and fibroblasts, connective tissue serves to support and link other tissues. It mediates the exchange of waste and nutrients and offers structural support [18].The three types of muscle tissue skeletal, cardiac, and smooth muscle all include actin and myosin and enable movement through contraction. The nervous system is made up of neurons and glial cells that transmit electrical signals for communication and information processing in the central nervous system (CNS) and periphery [19].Prostate Tissue develops from epithelial outgrowths in the urogenital sinus and mesonephric.It is a walnut-sized gland below the bladder, surrounding the urethra. The prostate produces fluids that enhance male fertility and is prone to cancer, with about 1 in 7 men diagnosed during their lifetime. Prostate cancer is a leading cancer among men, with increasing global prevalence. Modifications in lifestyle, like giving up smoking, exercising, and keeping a healthy weight, may lower the risk [20]. Screening and managing early prostate cancer are complex and controversial [21].

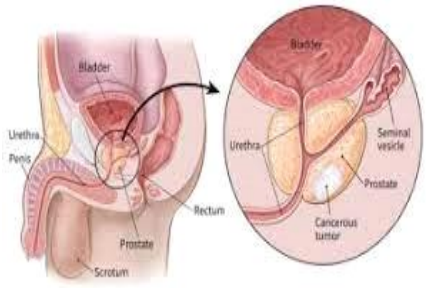

Figure 1: Developmentof Prostate Cancer

There were three categories of risk inducing factors: non-modifiable, which included genetic polymorphisms and situations in which no specific gene(s) has identified yet; blood-based markers; and external exposures, which included lifestyle where modification is possible. Age is the most important non-modifiable factor. Among all cancers, prostate carcinoma has the sharpest age-incidence arc in unscreened populations, rising at about the sixth age power. Of all malignancies, 25% are discovered prior the age of 65 [22]. Men are more likely to develop prostate cancer overall if they have a first-degree relative who has the disease (RR = 2.48; 95% CI 2.25–2.74) due to **genetic factors**. In comparison to older men, men under 65 had a higher risk (RR = 2.87; 95% CI 2.21–3.74), and if the affected person was a brother not a father (RR = 3.14; 95% CI 2.37–4.15), this risk is higher. 6. While family history is undoubtedly significant, known genes presently account for just 35% of the familial risk [22]Prostate cancer has been linked to both UV radiation from sun exposure (13), and ionizing radiation 12 in **external exposure,** however, more research and precise risk assessments are required [22].

Some studies suggest a potential link between urinary tract infections and increased prostate cancer risk due to chronic inflammation. However, more research is required to clarify this association [22].Photometers are used by spectrophotometry, called spectrophotometers, to extent a light beam's intensity at different wavelengths [23].Using methods such as GC and LC separations, AAS is a sensitive way to find metals in materials, frequently at picogram levels. When free gaseous atoms absorb electromagnetic radiation at a particular wavelength, a corresponding, measurable signal is created. This process is known as atomic absorption spectrometry, or AAS. The concentration of free atoms in the channel is correlated with the absorption signal. The quantity of analyte element present can be quantitatively determined by measuring the amount of light absorbed [24]. Atomic absorption spectrometry (AAS) can be very helpful for the examination of clinical samples, which typically involves identifying the presence of metals in fluids and tissues for toxicological investigation or therapeutic purposes [25].

Figure 2: Spectrophotometer

[26]. Compare the essential and harmful components in the tissues of the sick and control groups. Find reliable relationships between the element levels in the tissues of patients with prostate cancer and controls [27].Determine whether the element concentrations in the different types and stages of prostate cancer differ significantly. Examine how tissue analysis can be used as a diagnostic tool in clinical studies.[28].

2. Material and Method

Demographic and lifestyle data was collected, including age, sex, height, weight, financial status, and diet, from about 110 healthy individuals and prostate cancer patients [29] [30]. The participants, who were primarily neighbors, family members, and relatives, completed questionnaires to supply this data so that the two groups could be compared [31] [32].

3. Sample Collection

- The Trial to Prevent Prostate Cancer, conducted from 1993-1997, enrolled 18,882 men to evaluate if finasteride could prevent prostate cancer. Eligible participants were at least 55 years old with specific health criteria. Cancer specimens, containing at least 80% cancer, were analyzed, excluding those with transition zone cancer. Participants provided demographic, lifestyle, and medical information, and their BMI was calculated. Tissue samples, including transition zone (TZ), peripheral zone normal (PZ-N), and peripheral zone cancerous (PZ-C), were randomly selected from patients with varying prostate gland masses and were stored at -270°C until analysis.
- The study involved 741 men who, between 1982 and 1989, experienced radical prostatectomy at J.H Hospital. Tissue specimens, including transition zone (TZ), peripheral zone normal (PZ-N), and peripheral zone cancerous (PZ-C) samples were taken from the tissue for the prostate

cancer and serum, research excellence in the Baylor Specialized program. Cancer specimens contained at least 80% cancerous tissue, and transition zone cancer was excluded. Controls were the patients' spouses or female companions, selected for their awareness of prostate cancer and similar lifestyle factors. All samples were frozen at -270°C for storage and analysis.

- This prospective single-institution trial, approved by the local IRB, enrolled 26 prostate cancer patients between July 2011 and April 2012. The prostate cancer tissue and serum research excellence in the Baylor Specialized program. Patients with intermediate- or high-risk prostate cancer as determined by biopsy were included, and those with transition zone cancer or significant imaging artifacts were excluded. Six patients were removed from the study due to imaging artifacts or lack of significant peripheral zone cancer, leaving a final group of 20 patients.

- Fresh prostate tissues were collected immediately after surgery and dissected to ensure purity, with samples matched for transition zone (TZ), peripheral zone normal (PZ-N), and peripheral zone cancerous (PZ-C) specimens. Only tumor less than 30% stromal component samples and normal tissues with at least 60% glandular components were selected. Transition zone cancer was excluded. Within 30 minutes of removal, tissues were processed, frozen, and kept at -270°C. The institutional review board gave its approval to these methods.
- In stage 1 of the study, prostate cancer cases from the UKGPCS were analyzed. The prostate cancer tissue and serum research excellence in the Baylor Specialized program. The tissue samples were donated by the Baylor Program of Research Excellence in Prostate Carcinoma Tissue and Serum Bank, with matched transition zone (TZ), peripheral zone normal , and peripheral zone cancerous specimens. Transition zone cancer, non-white participants, and those diagnosed through asymptomatic PSA screening were excluded. Samples were frozen at -270°C for storage and analysis.
- With approval from the University of Illinois Institutional Review Board, this study analyzed 114 prostate cancer tissue samples from the prostate cancer tissue and serum research excellence in the Baylor Specialized program. The samples, including transition zone, peripheral zone normal, and peripheral zone cancerous specimens, were nominated from patients with varying prostatectomy specimens and contained at least 80% cancerous tissue.

Transition zone cancer was excluded. Hematoxylin and eosin (H&E) staining, FT-IR imaging, and freezing at -270°C were the steps taken to prepare the tissues for analysis.

3.1 Methodology

- Only benign areas of biopsy cores were analyzed for inflammatory response, with samples processed similarly to HIC-HPLC for high-quality evaluation [33].Acute and chronic inflammatory cell types and their percentage in benign tissues were noted [34] [35].
- Scores for inflammation were assigned to several tissue compartments (stromal, intraepithelial, and luminal) according to its degree (mild, moderate, and severe) and extent (focal, multifocal, and diffuse). To determine intensity scores, extent was multiplied by grade, added up for each compartment, and then totaled for every patient [36].To maintain uniformity, a single pathologist examined every image while being blind to the presence of malignancy [37]
- Proteins in paraffin-enclosed, formalin-fixed human prostate tissues were examined using HIC-HPLC [38][18].The separation process used a 4.6 × 250 mm polypropylaspartamide column with 1000 Aangstrom pore size. Samples were collected in 1.5 M (NH4)2SO4 and eluted using buffers A and B. Anti-pi (GSTpi) and anti-methylacyl-CoA racemase (AMACR) antibodies were used for immunostaining. The Varian 9070 fluorescence sensor, which excites at 232 nm and emits at 334 nm, was used to identify proteins.
- A 4.6 × 250 mm polypropylaspartamide column with a 1000 Angstrom pore size was utilized for HIC-HPLC. Using buffers A (1.2 M Na_2SO_4, 25 mM Na_3PO_4 and B (50 mM Na_3PO_4, 5.0% 2-propanol), samples were added to 1.5 M $(NH_4)_2SO_4$ and then eluted. Using a Varian 9070 fluorescence sensor with emission at 334 nm excitation at 232 nm, proteins were found. Using a 5º-nuclease assay (Taqman) on an ABI Prism 7900HT system, genotyping was carried out accurately by including duplicates and negative controls [39].
- 4. A 4.6 × 250 mm polypropylaspartamide column with a 1000 Angstom pore size was utilized in HIC-HPLC. Using buffers A (1.2 M Na_2SO_4, , 25 mM Na_3PO_4) and B (50 mM sodium phosphate, 5% 2-propanol), samples were added to 1.5 M $(NH_4)_2SO_4$ and then eluted. Varian 9070 fluorescence detector was used to detect proteins at excitation

wavelengths of 232 nm and release wavelengths of 334 nm. To describe the tissue architectural characteristics, nine criteria were developed: gland roundness, nuclear grade, clefts, lumen/gland ratio, stromal reaction, cell gland continuity, separation, and Gleason score.

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3.2 Statistical analysis

We applied generalized linear models to assess tissue and health characteristics, accounting for baseline age, family background of prostate cancer, and race [40] We assessed tissue inflammation by evaluating prevalence (e.g., any core with inflammation), extent (e.g., percentage of tissue area with inflammatory response), and intensity scores for chronic inflammation. Logistic reversion was applied to evaluate OR and 95% CI for the interaction between inflammatory signs and prostate cancer, with adjustments made for BMI, smoking, and diabetes [41] [42]. To account for potential detection bias, we analyzed PSA levels at biopsy and conducted repeated analyses with lower PSA concentrations and under specific biopsy conditions [43] [31].

4. Results and discussions

Prostate tissue measurements of a few metals (Fe, Sn, Co, Cu, Mg, Cr, Ni, and Cd) in cancer patients were contrasted with those in healthy donors and controls. Their multivariate apportionment, relationships, and distribution were the main topics of the

analysis. Metal concentrations were expressed as µg/g, wet weight. The selected metal is evaluated for variations based on tobacco use, food choices, and gender in addition to the general distribution..Current study involved males as the substantial donors; male subjects patients and controls were 73%. Out of the 48 male subjects included in this study, 7% were the smokers. The odds ratios for reporting the majority of classical symptoms were significantly higher in patients with more severe hyperthyroidism. Weight increase, palpitations, and neck enlargement were more common in men than in women, whereas other symptoms showed similar patterns in both sexes.On the average basis, the prostate tissue of arthritis patients unveiled the following decreasing trend of metal levels: Fe > Calcium> Magnesium > Hg > Zinc> Co > Chromium > Cu > Mg > Cadmium.

The concentration spread in the cases of Calcium, Mg, Iron, and Hg was observed to be relatively large. A more typical distribution pattern was seen for several metals (Cobalt, Cr, Copper, Mg, and Zinc), which were bolstered by relatively low SE and SD standards. In the prostate tissue of normal presenters, following decreasing order was seen in the selected metals average concentrations : Ca, Fe, Mg, Hg, Cr, Co, Cu, Mg, and Cd.The prostate tissues of patients showed significantly different fluctuations in specific metal proportions compared to controls, suggesting that the distribution of certain metals depends on the health status of the subjects. Most metals exhibited similar distributions, except for Cd, Mg, and Cr, which showed slight variations. Notable positive connections were observed between Cr-Magnesium (r= .547), Calcium-Mg (r= .516), Copper-Mg (r= .426), Cu-Magnesium (r= .412), Copper-Cr (r= .351), Cd-Magnesium (r= .349), and Mg-Mg (r= .341). In contrast, Cd-Zn (r= - .380) demonstrated a significant negative connections.

An accumulation of the chosen metals in the patients prostate tissue was shown by an apparent positive connection between the selected metals and macronutrients.Strong correlations were noted between following metal pairs; Calcium-Mg (r= .753), Calcium-Mg (r= .677), Mg-Magnesium (r= .620), Cr-Calcium (r= .600), Mg-Cr (r= .580), and Cr-Magnesium (r= .579). Some other significant correlations were recorded for Cr-Cd (r= .468), Cd-Magnesiun (r= .481), Iron-Cd (r= .355), Co-Iron (r= .328), Cobalt-Mg (r= .315)

and Fe-Magnesium (r= .308). The remaining metal pairs showed very little evidence of a positive or negative association.

The average intensities of Ni, Iron, Hg, Zn, and Cr were significantly raised in prostate tissues. However, the levels of Co, Magnesium, and Cd were particularly raised in the prostate tissues of patients compared to other donor groups. When comparing the prostate tissues of both patient groups to controls, PCA and CA indicated that toxic metals interfere with the normal physiological and metabolic functions of essential metals.In the selected metals, Nickel, Iron, Cobalt, and Hg were relatively raised in the prostate tissues of vegetarian patients, though the average intensities of the other metals (Copper, Zn, Mg, Cd, and Cr) were nearly the same in both vegetarian and non-vegetarian patients. In the prostate tissues of non-vegetarian patients, Mg and Cd levels were nearly identical, while Zn and Cu levels were slightly higher.

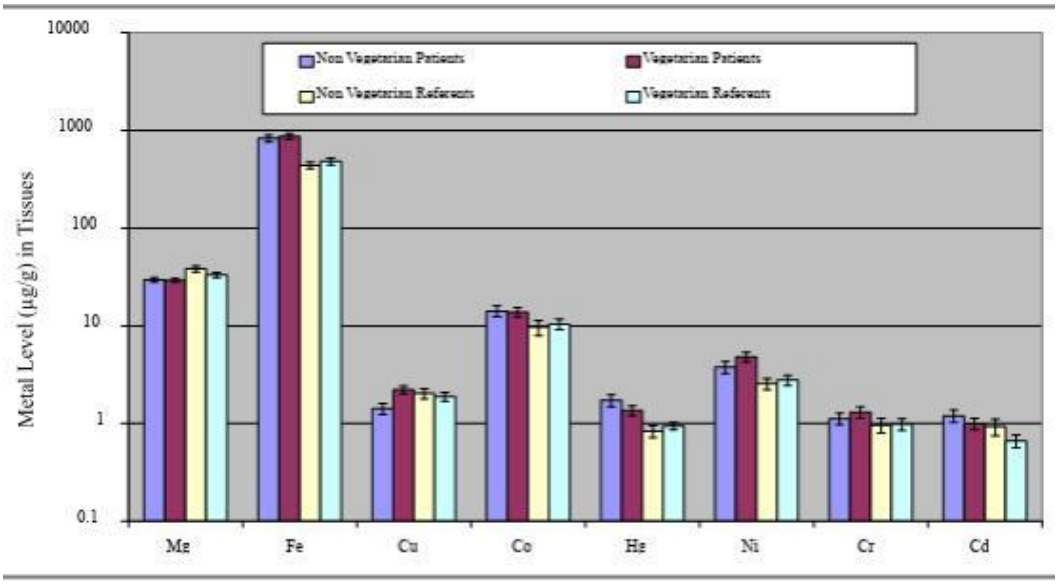

Figure 3: Comparative average concentrations of selected metals in the tissue of vegetarian and non vegetarian patients and healthy subject.

The prostate tissues of vegetarian controls had significantly greater average concentrations of Zn, Hg, and X, whereas the prostate tissues of non-vegetarian controls had significantly higher average concentrations of Fe, Ni, and Co. Patients who did not smoke had considerably higher amounts of Fe, Ni, Cr, and Hg in their prostate tissues, whereas patients who smoked had higher levels of Fe. Almost comparable levels in the prostate tissues of smokers and non-smokers of the patients were noted for Cu, Co, Mg and Cd . Prostate tissues from smokers had greater levels of Co, Fe, Cr, Ni, Hg, and Cd, but there were negligible variations in Cu, Mg, and Zn.

5. Conclusion

In patients, a notable accumulation of particular metals in the prostate tissue such as Mercury (Hg), Iron (Fe), and Nickel (Ni) indicates elevated levels of certain macronutrients. A comparison of hypothyroid patients with hyperthyroid patients showed lower levels of harmful metals in the latter. Intricate interactions between different metals, e.g., calcium-chromium, Magnesium-calcium may impact cancer stringency. This study highlights a relatively higher concentration of toxic metals in vegetarian patients than in non-vegetarians, illustrating the dietary influence. Depending on the impact of metal exposure on gene expression, a predictive model is developed to observe the cancer stringency.

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