ORİJİNAL MAKALE / ORIGINAL ARTICLE

Balıkesir Sağlık Bilimleri Dergisi / BAUN Sağ Bil Derg
Balıkesir Health Sciences Journal / BAUN Health Sci J
ISSN: 2146-9601- e ISSN: 2147-2238
Doi: https://doi.org/10.53424/balikesirsbd.963520

Is There a Prognostic Significance for Copper, Beryllium, Boron, Titanium and Vanadium Ions in Prostate Cancer?

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Geliş Tarihi / Received: *07.07.2021*, ***Kabul Tarihi / Accepted:*** *10.01.2022*

ABSTRACT

Objective: There are several epidemiological, clinical and experimental studies that relate heavy metal exposure to Prostatic adenocarcinoma (PCa). In this study, the relationship between benign/malign prostatic lesions and some metal/non-metal concentrations was investigated. **Materials and Methods:** Seventy-one patients were included in this study. The samples were analyzed via Inductively Coupled Plasma Mass Spectrometry (ICP-MS) to determine the level of tissue concentrations of platinum, thallium, lead, molybdenum, cadmium, selenium77, selenium82, iron, potassium, lithium, beryllium, boron, sodium, magnesium, phosphorus, calcium, titanium, vanadium, chromium, manganese, cobalt, nickel, copper, zinc, arsenic, strontium, tin, and antimony. **Results:** When metal/nonmetal levels in prostate tissue were examined in benign and malignant patient groups, a statistically significant difference was found in the levels of lithium, beryllium, boron, sodium, magnesium, phosphorus, calcium, titanium, vanadium, chromium, manganese, cobalt, nickel, copper, zinc, arsenic, strontium, tin and antimony ($p<0.05$). Beryllium, boron, titanium and vanadium concentrations were at least five times higher in benign tissues. When tissue metal/nonmetal levels were compared according to the new Gleason prognostic grade grouping, a significant positive correlation was found between tissue copper levels and grade ($p<0.05$). **Conclusion:** This study showed that beryllium, boron, titanium, and vanadium are five times or more in benign prostatic lesions when compared with PCa tissues. It also showed that the histological grade increased with increasing copper concentration. Metal concentrations should be considered for prognosis in PCa.

Keywords: Prostate Cancer, Metal, Non-metal, ICP-MS.

Prostat Kanserinde Bakır, Berilyum, Bor, Titanyum ve Vanadyum İyonlarının Prognostik Bir Önemi Var Mı?

ÖZ

Amaç: Metal maruziyetin ile Prostatik adenokarsinom (PCa) ilişkilendiren birçok epidemiyolojik, klinik ve deneysel çalışma vardır. Bu çalışmada, benign/malign prostat lezyonları ile bazı metal/non-metal konsantrasyonları arasındaki ilişki araştırıldı. **Materyal ve Metod:** Bu çalışmaya 71 hasta dahil edildi. Materyaller İndüktif eşleşmiş plazma kütle spektrometresi (ICP-MS) ile platin, talyum, kurşun, molibden, kadmiyum, selenyum77, selenyum82, demir, potasyum, lityum, berilyum, bor, sodyum, magnezyum, fosfor, kalsiyum, titanyum, vanadyum, krom, manganez, kobalt, nikel, bakır, çinko, arsenik, stronsiyum, kalay ve antimon seviyeleri analiz edildi. **Bulgular:** Benign ve malign hasta gruplarında prostat dokusundaki metal/ametal düzeyleri incelendiğinde istatiksel olarak lityum, berilyum, bor, sodium, magnezyum, fosfor, kalsiyum, titanium, vanadium, krom, manganez, kobalt, nikel, bakır, çinko, arsenic, stronsiyum, kalay ve antimon bulundu ($p<0.05$). Benign prostat dokularında berilyum, bor, titanyum ve vanadyum konsantrasyonları en az beş kat daha yüksekti. Gleason prognostik derece gruplamasına göre doku metal/ametal seviyeleri karşılaştırıldığında, doku bakır seviyeleri ile derece arasında anlamlı pozitif korelasyon bulundu ($p=0.02$). **Sonuç:** Bu çalışma berilyum, bor, titanyum ve vanadyumun benign prostat lezyonlarında PCa dokularına göre beş kat veya daha fazla olduğu gösterilmiştir. Ayrıca bakır konsantrasyonunun artmasıyla histolojik derecenin yükseldiğini göstermiştir. Metal konsantrasyonları PCa da prognoz açısından dikkate alınmalıdır.

Anahtar Kelimeler: Prostat Kanseri, Metal, Ametal, ICP-MS.

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Bu makaleye atıf yapmak için / Cite this article: Altun, E., Çalışır, Ü., & Çiçek, B. (2022). Is there a prognostic significance for copper, beryllium, boron, titanium and vanadium ıons in prostate cancer? *Balıkesir Sağlık Bilimleri Dergisi,* *11*(2):235-241. https://doi.org/10.53424/balikesirsbd.963520

INTRODUCTION

The prostate is a compound tubuloalveolar exocrine gland of the male reproductive system. Infectious, inflammatory, hyperplastic, and neoplastic diseases could be seen in this organ. Clinically, the most serious of these diseases is prostate cancer (Crawford, 2003). Benign prostatic hyperplasia (BPH) is a very common condition in males over years of age. BPH is characterized with hyperplasia of both stromal and glandular elements. This hyperplasia thought to be dependent on androgen, increases with age and may result in urinary obstruction (Rebbeck, 2006). Prostatic adenocarcinoma (PCa) is the most common malignancy seen in males and has a lower mortality rate than other types of cancers (Crawford et al., 2016). The natural course of PCa demonstrates considerable differences. Some cases may be very aggressive, resulting in death, while some others may have a clinically very insignificant, moderate course. In fact, prostate cancer is commonly encountered in autopsies of males that die from some other reason. Most men die with prostate cancer lesions in his prostate tissue, not cause from prostate cancer related conditions such as metastases or invasions (Vinay Kumar, Abul Abbas, 2014). Studies have shown that androgens, heredity, acquired somatic mutations and environmental factors play a role in the pathogenesis of PCa. There are several epidemiological, clinical and empirical studies linking heavy metal exposure with PCa (Sarafanov et al., 2011; Spitz et al., 2000). It is believed that the accumulation of some elements has an important role in the development of cancers such as PCa. Additionally, some habits, such as smoking, are thought to be associated with metal accumulation in prostate tissue and have a role in carcinogenesis (Neslund-dudas, 2015). However, there is a lack of knowledge about which mechanisms are affected by the accumulation of elements in the prostate tissue and how it causes development of neoplasia (Çelen, Müezzino, Ataman, & Bak, 2015; Sarafanov et al., 2011). There are commonly known difficulties for elemental analysis of formaldehyde-fixed and paraffin-embedded tissue specimens. Since formaldehyde fixation is a standard procedure in all tissue samples, the effect on the specimens will be equal. Therefore, the formaldehyde fixation will not affect the element rates of the analyzed tissue samples. The xylene used in the paraffin removal process does not involve any metal dissolution (Falkeholm, Grant, Magnusson, & Möller, 2001). In current work samples taken from the paraffin blocks of the patients were subjected to microwave digestion, and the samples were analyzed via ICP-MS to determine the concentration of the level of 27 different certain elements in the prostate tissue and show the relationship between histopathological diagnosis and metal/nonmetal concentrations.

MATERIALS AND METHODS

Procedure

The study included 71 patients who underwent Transurethral Resection of the Prostate (TURP), Open Prostatectomy, and Radical Prostatectomy in the pathology laboratory archives of the Balikesir University faculty of medicine in Balikesir. Patients were divided into two groups: patients histopathologically diagnosed with prostate adenocarcinoma and who underwent radical prostatectomy between 2012 and 2016 year and patients diagnosed with BPH after transurethral resection or open prostatectomy with a diagnosis of lower urinary tract obstruction. Demographic data, pathologic diagnosis and Gleason scores for patients were obtained from archive files. Gleason prognostic group was calculated from patients Gleason scores. When the cancerous tissue was selected, the tumor area was firstly marked on the slide. The marked area was then cut out of the paraffin block. All tissue samples were already embedded in paraffin wax after the operation. To melt the paraffin, samples were placed in an oven set to 70°C. After the melting process, 10.0 ml of ultra-pure diethyl ether solution were added to the samples and mixed by vortex for 2 min, and then the diethyl ether solution was removed to evaporate the residual diethyl ether, samples were kept at room temperature for 5-10 min. After the drying process, the samples were weighed and their quantities were recorded. The weighed samples were taken directly into the microwave digestion tubes. A total of 8 ml concentrated HNO3 and H2O2 were added to the tubes in equal volumes. They were then taken to a microwave wet-burning unit. The temperature was determined to be the most suitable temperature from the program for the digestion of the samples. According to the optimized microwave digestion procedure, the microwave oven was set for 5 minutes to reach 100 ºC, 15 minutes to keep the temperature at 100 ºC, 5 minutes to reach 150 ºC and 15 minutes to maintain this temperature (40 minutes in total). After digestion, the PTFE digestion tubes were kept at room temperature. Digested sample solutions were filtered through a 0.45 µm filtration system. After purification, they were brought to the final volume of 25 ml with deionized distilled water.

All reagents used in this study were of analytical purity. Calibration standard solutions used during measurement from ICP-MS device (100 ppm Li, Be, Mg, P, Ca, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Sr, Mo, Cd, Sn, Sb, Tl, Pb, multi-element stock solution (CHEM-LAB) and mono 1000 ppm Pt, B, Na, and K solution (Sigma Aldrich) were prepared with pure water from a Thermo Scientific Smartpure 2 Ultrapure water apparatus. Standards were prepared in 1% Merck Suprapur nitric acid. The microwave digestion process directly used 65% nitric acid (Merck) and 30% hydrogen peroxide (Sigma Aldrich). The glassware used in the digestion process was cleaned with 5% nitric acid. The PTFE wet-burning tubes used for digestion were washed with nitric acid. All the glassware was cleaned with deionized pure water.

A closed-system microwave digestion device (Milestone Start SYNTH) containing a fiber optic temperature sensor and PTFE digestion tubes were used to digest prostate tissue samples. Samples were filled up to 25ml. All 27 elements were analyzed using a Thermo Scientific iCAP Q inductively-coupled plasma mass spectrometer.

Tissue samples were analyzed using a micro-concentric nebulizer (Micromist, Glass Expansion, Inc., Pocasset, MA) and a Thermo Scientific iCAP Q ICP-MS (Thermo Electron Corp., Bremen, Germany) containing a cyclonic spray chamber (Tracey, Glass Expansion, Inc, Pocasset, MA). For calibration, 10-25-50-100-250-500-1000-5000 µg/L mixed metal solutions were used. For analytical characterization in ICP-MS, the percent relative to standard deviation (% RSD), limit of detection (LOD), limit of quantification (LOQ), and correlation coefficient (R2) are given in Table 1.

Statistical analysis

Spearman correlation and student t test were used as the data were normally distributed. SPSS 21.0 software was used with a 95% confidence interval in all analyses.

Ethical considereation

In this study, the investigation protocol was in accordance with the Helsinki Committee requirement and was approved by the institutional ethical committee of Balıkesir University (Decision no: 2016/76, 2016/17/08).

RESULTS

This study included 71 patients who underwent TURP or radical prostatectomy in the pathology laboratory archives of the Balikesir University faculty of medicine. The mean age of the patients was 68 (range: 55-88). Patients were divided into two groups according to their histopathologic diagnoses of BPH and PCa. The BPH group included 34 patients. The mean age of these patients was 68 (range: 55-88). Seven patients underwent open prostatectomy, and 27 underwent TURP. The PCa group included 37 patients. The mean age of these patients was 67 (range: 55-81).

Table 1. Analytical values of the elements.

Elements	% RSD	LOD (µg/L)	LOQ (µg/L)	R2
Li	0.3	0.0000	0.000	0.9998
Be	1.3	0.2337	0.045	0.9993
B	1.3	3.6089	4.939	0.9993
Na	0.3	0.8349	1.761	0.9999
Mg	0.4	0.2489	0.048	0.9996
P	2.4	9.2745	7.139	0.9996
K	2.2	4.2690	11.037	0.9999
Ca	1.2	0.3609	0.278	0.9995
Ti	0.5	0.0245	0.005	1.0000
V	3.4	0.0000	0.000	0.9994
Cr	0.3	0.0025	0.004	0.9998
Mn	0.5	0.0081	0.016	0.9997
Fe	0.7	0.0000	0.075	0.9999
Co	0.5	0.0089	0.007	0.9999
Ni	1.1	0.0062	0.004	1.0000
Cu	0.5	0.0063	0.009	0.9996
Zn	0.5	2.1074	9.700	0.9985
As	0.2	0.0000	0.000	1.0000
Se	2.8	1.8110	0.349	0.9996
Sr	1.5	0.0000	0.000	0.9993
Mo	1.1	0.0077	0.010	0.9988
Cd	1.3	0.0136	0.007	0.9999
Sn	0.7	0.0072	0.012	0.9989
Sb	0.3	0.0000	0.000	0.9988
Pt	1.3	0.0005	0.001	0.9993
Tl	0.8	0.0004	0.000	0.9999
Pb	1.2	0.0055	0.021	0.9997

Table 2. Comparison of levels of elements between BPH and prostate cancer PCa. Statistically different results are bold.

Atomic Number, Abbreviation	Element	BPH		PCa		
		Mean (mg/g)	Standard Deviation	Mean (mg/g)	Standard Deviation	P-value
$_{3}$**Li**	Lithium	0.198	0.112	0.109	0.148	**0.006**
$_{4}$**Be**	Beryllium	0.004	0.009	0.0006	0.002	**0.020**
$_{5}$**B**	Boron	19.980	21.460	2.560	5.440	**0.001**
$_{11}$**Na**	Sodium	1,689.250	2,619.190	521.790	283.900	**0.009**
$_{12}$**Mg**	Magnesium	351.590	128.310	177.060	63.500	**0.001**
$_{15}$**P**	Phosphorus	1,292.410	400.390	858.630	323.780	**0.001**
$_{19}$K	Potassium	89.040	94.250	127.500	143.590	0.191
$_{20}$**Ca**	Calcium	218.070	73.720	134.710	84.180	**0.001**
$_{22}$**Ti**	Titanium	43.050	73.170	6.480	18.280	**0.004**
$_{23}$**V**	Vanadium	62.550	67.340	16.500	14.250	**0.001**
$_{24}$**Cr**	Chromium	10.050	18.020	3.690	5.000	**0.040**
$_{25}$**Mn**	Manganese	1.670	1.380	1.040	0.815	**0.020**
$_{26}$Fe	Iron	112.710	81.640	80.020	70.330	0.070
$_{27}$**Co**	Cobalt	0.169	0.205	0.060	0.050	**0.003**
$_{28}$**Ni**	Nickel	1.670	1.370	0.870	0.900	**0.005**
$_{29}$**Cu**	Copper	8.350	11.650	3.620	2.740	**0.019**
$_{30}$**Zn**	Zinc	117.510	39.440	58.760	24.240	**0.001**
$_{33}$**As**	Arsenic	0.030	0.020	0.010	0.010	**0.002**
$_{34}$Se	Selenium77	0.220	0.110	0.190	0.070	0.220
$_{34}$Se	Selenium82	0.190	0.170	0.260	0.500	0.490
$_{38}$**Sr**	Strontium	7.510	3.050	3.800	2.330	**0.001**
$_{42}$Mo	Molybdenum	0.280	0.640	0.120	0.210	0.160
$_{48}$Cd	Cadmium	0.200	0.139	0.160	0.140	0.220
$_{50}$**Sn**	Tin	2.260	2.940	0.670	0.830	**0.002**
$_{51}$**Sb**	Antimony	0.130	0.160	0.010	0.030	**0.001**
$_{78}$Pt	Platinum	0.000003	0.00001	0.0004	0.002	0.340
$_{81}$Tl	Thallium	0.002	0.007	0.000	0.000	0.120
$_{82}$Pb	Lead	3.350	1.450	2.640	3.280	0.250

Thirty of these patients underwent radical prostatectomy and 7 underwent TURP. When metal/nonmetal levels in prostate tissue were investigated in BPH and malignant patient groups, a statistically significant difference was found between the levels of lithium (p=0.006), beryllium (p=0.02), boron (p=0.001), sodium (p=0.009), magnesium (p=0.001), phosphorus (p=0.001), calcium (p=0.001), titanium (p=0.004), vanadium (p=0.001), chromium (p=0.04), manganese (p=0.02), cobalt (p=0.003), nickel (p=0.005), copper (p=0.019), zinc (p=0.001), arsenic (p=0.002), strontium (p=0.001), tin (p=0.002) and antimony (p=0.001). In addition, these metal/nonmetal concentrations were found to be higher in BPH tissues (Table 2). Of the other metals/nonmetals evaluated at the tissue level, platinum (p=0.34), thallium (p=0.12), lead (p=0.25), molybdenum (p=0.16), cadmium (p=0.22), selenium77 (p=0.22), selenium82 (p=0.49), iron (p=0.07) and potassium (p=0.191) values were observed to be similar in both groups (Table 2). Among these elements, the concentrations of beryllium, boron, titanium, and vanadium were found in concentrations five times higher or more in BPH tissues, which was particularly noteworthy. When tissue metal/nonmetal levels were compared according to the Gleason prognostic grade grouping, a significant positive correlation was observed between tissue copper levels and grade (p=0.02).

DISCUSSION

Concentration ranges obtained for the various elements in this study were similar to the concentration ranges reported in the literature for BPH and malignant prostate tissues. Prostate zinc concentrations were found to be low in PCa patients and higher zinc in BPH which similar to literatures (Figure 1). In addition to zinc, other elements, lithium, beryllium, boron, sodium, magnesium, phosphorus, calcium, titanium, vanadium, chromium, manganese, cobalt, nickel, and arsenic concentrations were lower in malignant tissues compared to BPH tissue samples. Although the copper tissue concentration was lower in malignant tissues, the correlation between copper concentration and the

Gleason prognostic grade was remarkable. The tumor grade rose with increasing copper concentrations. Increased copper concentration is thought to convert benign tumors into more aggressive tumors (Figure 2).

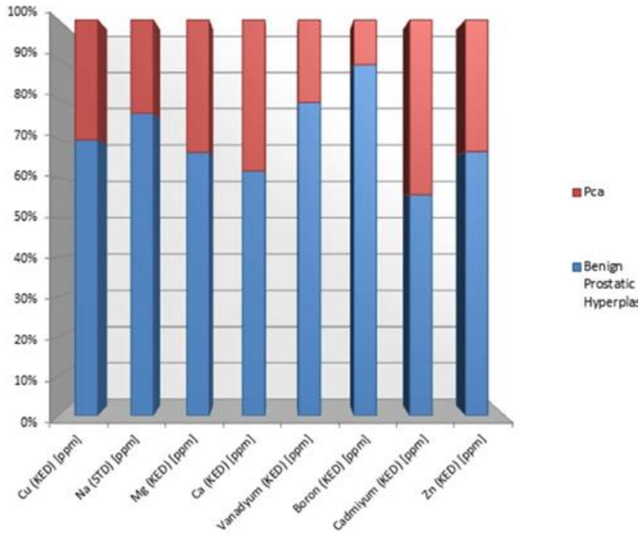

Figure 1. Prostate zinc and other elements concentrations in PCa and BPH patients.

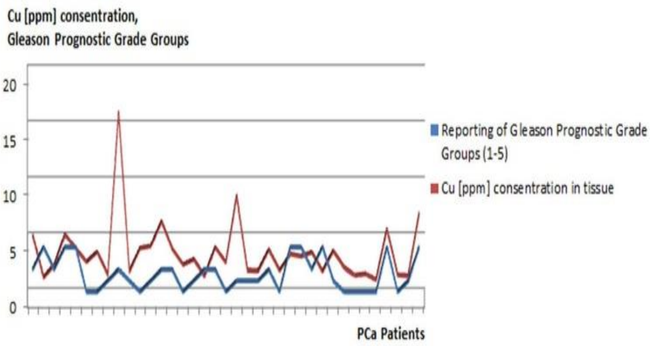

Figure 2. The correlation between copper concentration and the Gleason prognostic grade groups.

In this study, it was also noted that beryllium, boron, titanium, and vanadium concentrations were five times higher or more in BPH tissues than in malignant tissues (Table 2). This finding could be related to the development of BPH rather than cancer. Because of the significance for PCa diagnoses, these data are worth investigating in larger patient groups. Gumulec et al. found a decrease in serum zinc levels in lung, head and neck, breast, liver, stomach, and prostate cancers(Gumulec et al., 2014). The zinc concentration in the prostate gland is much higher than in other human tissues (Ck, Sviridova, & Zaichick, 1997; Zaichick, Nosenko, & Moskvina, 2012). Many studies have reported that PCa containing prostate tissues have several times less zinc than non-PCA tissues (Çelen et al., 2015; Leitzmann et al., 2003; Li et al., 2005; Singh et al., 2016; Yaman, Atici, Bakirdere, & Akdeniz, 2005). Low serum zinc levels in prostate cancer have been suggested as an aid to serum PSA for prostate cancer diagnoses (Li et al., 2005). Sarafanov et al. showed that low iron and zinc levels increase PSA recurrence Those results may indicate that low iron, zinc, and possibly high cadmium concentrations may have the ability to convert benign tumors to more aggressive ones(Sarafanov et al., 2011). In addition, the findings of this study suggest that increased copper concentrations may increase tumor grades. Çelen et al. investigated selenium, nickel, and calcium concentrations. They found no significant difference for selenium. However, nickel and calcium levels were observed at low concentrations in malignant tissues (Çelen et al., 2015). Singh et al., on the other hand, found higher selenium and zinc levels in BPH tissues (Singh et al., 2016). Neslund-Dudas et al. noted increased cadmium and reduced zinc levels in PCa tissues of smokers (Neslund-dudas, 2015). Yaman et al. found high nickel, iron, magnesium, and calcium levels in BPH tissues. However, they also found high zinc and calcium levels in malign tissues, which contradicts other results found in the literature (Yaman et al., 2005). High intake of inorganic arsenic with drinking water and chronic exposure of this element is associated with a variety of toxicities, including increased risk of prostate, skin, bladder, and lung cancers (Bulka, Jones, Turyk, Stayner, & Argos, 2016; Genchi, Sinicropi, Lauria, Carocci, & Catalano, 2020; Navarro Silvera & Rohan, 2007; Rock et al., 2020). There is no evidence linking organic arsenic found in food with any side effects, including cancer (Rock et al., 2020). Boyacioglu et al. showed that boron uptake at the optimum dose of 6.98 ± 3.39mg/day did not change expression levels of transcription factors and did not cause toxicity at the molecular level(Orenay Boyacioglu et al., 2017). They demonstrated that boron uptake at this level increase RNA synthesis (Orenay Boyacioglu et al., 2017). Studies have suggested that dietary boron intake affects steroid hormone levels and decreases PCa risk by affecting testosterone and estradiol levels (Cui et al., 2004; Rock et al., 2020). In one study, it was found that independent prostatic cancer cell proliferation at androgen receptors was inhibited with the administration of boric acid at increasing doses (Navarro Silvera & Rohan, 2007). While in epidemiological studies exposure to beryllium or beryllium compounds is generally not casually linked to the risk of lung cancer, there might be an increased risk of lung cancer (Boffetta, Fryzek, & Mandel, 2012; Sanderson, Ward, Steenland, & Petersen, 2001). Rooney et al. conducted a case-control study with a worker's group at the United Kingdom Atomic Energy Institution. They found no significant correlation between prostate cancer and plutonium, uranium, cadmium, boron or beryllium exposure (Rooney, Beral, Maconochie, Fraser, & Davies, 1993). There is no mention of any oncogenic risk increase in patients with chromium, titanium, and cobalt-based total knee and hip prosthesis. However, studies in these patients showed a decrease in lung and laryngeal carcinomas and an increase in endometrial and prostate cancers (Visuri, Pukkala, Pulkkinen, & Paavolainen, 2003; Visuri, Pulkkinen, Paavolainen, & Pukkala, 2010). In their study, Lim et al examined the relationships between serum concentrations of 10 heavy metals, including manganese, cobalt, nickel, copper, zinc, arsenic, selenium, cadmium, antimony, and lead, and Interactive and non-linear relationships have been observed for serum metal levels at risk for prostate cancer. A potential synergistic interaction between multiple metals on prostate cancer risk has been suggested (Lim et al., 2019). Investigations have been conducted in both normal cells and cancer cells to decipher the precise role of the zinc ion (To, Do, Cho, & Jung, 2020). Zinc loss has been documented in patients diagnosed with various types of cancer, including prostate cancer, hepatocellular cancer, pancreatic cancer, lung cancer, ovarian cancer, esophageal squamous cell carcinoma, and breast cancer (Jin et al., 2015; Takatani-Nakase, 1517; To et al., 2020). Much experimental evidence supports the idea that zinc derivatives and zinc supplements can suppress the proliferation, migration and invasion of prostate cancer cells (To et al., 2020).

CONCLUSION

This study found that, along with zinc, lithium, beryllium, boron, sodium, magnesium, phosphorus, calcium, titanium, vanadium, chromium, manganese, cobalt, nickel, and arsenic levels were lower in malignant prostate tissues than in healthy prostate tissues. The Gleason prognostic grade rises with increasing copper concentrations. It is also remarkable that beryllium, boron, titanium, and vanadium concentrations were five or more times higher in BPH tissues. Understanding the different elemental changes and their interdependence might be useful in identifying the complex metabolic changes in prostate carcinogenesis.

Abbreviations

PCa; Prostatic Carcinoma TURP; Transurethral resection of prostate ICP-MS; Inductively coupled plasma mass spectrometry BPH; Benign prostatic hyperplasia RSD; Relative to standard deviation LOD; Limit of detection LOQ; Limit of quantification R2; Correlation coefficient Total PSA; Total prostate-specific antigen AST; Aspartate Aminotransferase

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

Author Contributions

Plan, design: EA, BÇ**; Material and methods;** EA, ÜÇ; **Data analysis and comments;** EA, ÜÇ; **Writing and corrections:** EA, BÇ.

Funding

This study was supported by the Scientific Investigate Projects of Balikesir University (BAP 2017/205).

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