# Assessment of Serum Tumor Markers in Regular Hemodialysis Patients

**Thesis**

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in Internal Medicine

## By

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***Ibrahim Shebl Abu Elnasr***

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# List of abbreviations

| | |
|---|---|
| AFP | Alpha fetoprotein |
| AUA | American Urological Association |
| BCC | Basal cell carcinoma |
| BCR-ABL | The breakpoint cluster region protein-Abelson (Philadelphia Chromosome) |
| BEN | Balkan endemic nephropathy |
| BFP | Basic fetoprotein |
| BPH | Benign prostatic hypertrophy |
| CA125 | Cancer antigen 125 |
| CA15-3 | Cancer antigen 15-3 |
| CA19-9 | Cancer antigen 19-9 |
| CA50 | Cancer antigen 50 |
| CA72-4 | Cancer antigen 72-4 |
| CEA | Carcinoembryonic antigen |
| CKD | Chronic kidney disease |
| CLIP | Cancer of the liver Italian program |
| CLM | Colorectal liver metastases |
| CRC | Colorectal cancers |
| CrCl | Creatinine clearance |
| DM | Diabetes mellitus |
| DNA | Deoxyribonucleic acid |
| DRE | Digital rectal examination |
| eGFR | Estimated glomerular filtration rate |
| ESRD | End stage renal disease |
| FIT | Fecal immunochemical test |
| FOBT | Fecal occult blood test |
| fPSA | Free prostate specific antigen |
| GISTs | Gastrointestinal stromal tumors |
| GNs | Glomerulonephritis |
| GPL | Glycosyl phosphatidylinositol |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| hCG | Human chorionic gonadotropin |
| HCV | Hepatitis C virus |
| HD | Hemodialysis |
| HE4 | Human epididymis protein 4 |
| HPAFP | Hereditary persistence of alpha fetoprotein |

| | |
|---|---|
| HPV | Human papilloma virus |
| IAP-1 | Inhibitor of apoptosis-1 |
| IgA | Immunoglobulin A |
| IRMA | Renal Insufficiency and Anticancer Medications |
| kDA | Kilo Dalton |
| KIT | Proto-oncogene receptor tyrosine kinase |
| LCA | Lens culinaris agglutinin |
| MDRD | Modification of Diet in Renal Disease |
| ml/min | Milliliter/minute |
| MRI | Magnetic resonance imaging |
| ng/ml | Nanogram/milliliter |
| NHANES | National Health and Nutrition Examination Survey |
| NSE | Neuron-specific enolase |
| PAI-1 | Plasminogen activator inhibitor type-1 |
| PAP | Papanicolaou |
| PDGFRA | Platelet-derived growth factor receptor alpha |
| PSA | Prostate specific antigen |
| PSAP | Prostatic acid phosphatase |
| RRT | Renal replacement therapy |
| SCC | Squamous cell carcinoma |
| SLX | Sialyl Lewis X-1 |
| t1/2 | Half life time |
| TCC | Transitional cell carcinoma |
| tPSA | Total prostate specific antigen |
| U/ml | Unit/milliliter |
| ug/L | Microgram/liter |
| uPA | Urokinase-type plasminogen activation |

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## Figures of the Study Results

# Introduction

Chronic kidney disease (CKD) constitutes a public health problem, worldwide. The number of end-stage renal disease (ESRD) patients receiving renal replacement therapy (RRT) is estimated at 41.4 million, with an annual growth rate of 8% ***(Radhakrishnan et al., 2014).***

Furthermore, CKD is considered as an important cause for global mortality. The number of deaths from CKD has risen by 82.3% in the last two decades, the third largest increase among the top 25 causes of death ***(Radhakrishnan et al., 2014).***

Although kidney transplantation is an effective treatment for ESRD, dialysis is still the commonest treatment for such patients. Patients maintained on dialysis are potentially at increased risk of cancer for several reasons, including: secondary immune deficiency, previous treatment with immunosuppressive or cytotoxic drugs, underlying kidney disease, uremic toxins, hyperparathyroidism, nutritional deficiencies, and altered DNA repair ***(Derakhshan et al., 2004).***

Tumor markers are a very heterogeneous group of molecules that are generally found in very small

concentrations in the plasma and serum of healthy individuals. In the process of neoplastic differentiation, the cell can synthesize, release, or induce synthesis of other cells, thus increasing their concentration in plasma and serum ***(Trapé et al., 2011).***Tumor marker can be used to monitor the course of a malignancy or to detect a relapse ***(Sharma et al., 2015).***

Tumor marker may also increase their plasma concentration in patients without cancer due to processes that increase the release or reduce catabolism, and so give rise to false positives results ***(Trapé et al., 2011).*** Elevated levels of several tumor markers can be frequently detected in patients with impaired kidney function because their renal elimination is retarded ***(Coppolino et al., 2014).***

Alpha fetoprotein (AFP) as an oncogenic glycoprotein is normally expressed during gestation. AFP can be synthesized by yolk sac, fetal liver, and some gastrointestinal cells. A rise of serum AFP level is routinely taken into account for abnormality in adults and frequently utilized as a suitable biomarker for yolk sac tumor, tumors of gonadal origin, hepatocellular carcinoma (HCC), and certain gastric carcinomas ***(Sun et al., 2015).***

Prostate specific antigen (PSA) is a serine protease glycoprotein produced by normal as well as malignant prostatic epithelium. It occurs in different structural and functional forms in seminal plasma and serum, where the levels can be determined by immunoassays ***(Murthy et al., 2015).*** Although new biomarkers are emerging, PSA and its derivatives remain the most widely used and practical test to detect prostate cancer. Percent free PSA (%fPSA) has been demonstrated to improve positive test results during prostate biopsy and to reduce the number of unnecessary biopsies in men with a moderately elevated serum PSA level ***(Chen et al., 2015).***

Carcinoembryonic antigen (CEA) is excreted by certain embryonic and adult tissues in addition to adenocarcinoma of the digestive organs. Extensive studies of patients bearing primary and metastatic colorectal neoplasms have determined that its primary use is in the detection of local and metastatic cancer recurrence after initial resection of the primary tumor, Clinical relevance of the CEA assay also has been used in the follow-up management of patients with, breast, lung, prostatic, pancreatic and ovarian carcinoma ***(Malati, 2007).***

There are controversial data about tumor markers in CKD and dialysis population, as some studies reported increased AFP, and CEA levels in hemodialysis (HD) patients while other studies observed normal levels of these markers in HD and kidney transplantation patients ***(Derakhshan et al., 2004).***

Regarding PSA levels some authors observed normal levels of PSA in their patients, while others observed high level of this marker in HD patients ***(Derakhshan et al., 2004).***

# Aim of the work

To evaluate the diagnostic value of AFP, total PSA (tPSA) and CEA in HD patient in comparison to normal population.

# Chronic Kidney Disease and Cancer

CKD and cancer are connected in a number of ways in both directions: cancer can cause CKD either directly or indirectly through the adverse effects of therapies, CKD may conversely be a risk factor for cancer, and both may be associated because they share common risk factors ***(Stengel, 2010).***

Observational studies have suggested an increased cancer risk in people with early-stage CKD, before requiring dialysis or transplantation. An excess risk of 1.2 times for all cancers was reported during the 5 years before RRT ***(Wong et al., 2009).***

The dialysis population exhibited a risk of cancers of the kidney and urinary tract over and above the heightened risk for cancer seen at many other sites. The excess risk was attributed to factors that differed for renal parenchyma and urothelium. Non specific change within the kidney resulting from loss of renal function suggested to be acquired renal cystic disease is the putative risk factor for the excess of renal parenchymal cancers that was seen independently of primary renal disease and increased in frequency with advancing duration of dialysis ***(Stewart et al., 2003).***

Patients maintained on dialysis are potentially at increased risk of cancer for several reasons, including: the presence of chronic infection, especially in the urinary tract; a weakened immune system; previous treatment with immunosuppressive or cytotoxic drugs; nutritional deficiencies; and altered DNA repair. In addition, the underlying disease leading to renal failure, the persistent metabolic changes associated with it, and the development of certain complications, such as acquired renal cystic disease, may predispose to cancer ***(Maisonneuve et al., 1999).***

In addition, Cancer represents one of the most important causes of long-term mortality after kidney transplantation; the development of malignancies is a well-known complication after organ transplantation. Reports from large kidney transplant registries demonstrate a rise in the incidence of cancer in this population. The overall incidence has been reported to be 2 to 10 fold, and in some cases it can even be 100 fold when compared to the general population ***(Navarro et al., 2008).***

Moreover the etiology of post-transplantation malignancy seems to be multi-factorial and probably involves a combination of the following events: impaired

immune activity against viruses, impaired immunosurveillance of neoplastic cells, DNA damage and disruption of DNA repair mechanisms, and the up regulation of cytokines that can promote tumor progression, all of these events certainly occur during long-term immunosuppressive therapy after renal transplantation ***(Rama & Grinyó, 2010).***

Also there is increase risk of malignancy with Cyclophosphamide therapy which is a common drug among glomerulonephritis (GNs) patients; as in idiopathic membranous GNs gives a threefold increase in cancer risk. For the average patient, this finding translates into an increase in annual risk from approximately 0.3% to 1.0%. The increased risk of malignancy must be balanced against the improved renal survival ***(Van den Brand et al., 2014).***

In Japan, the most common cancer in ESRD patients is renal cell carcinoma, and the second is multiple myeloma, followed by liver and colon cancer in males and uterine cancer in females. While the most common cancer in ESRD patients in the USA is renal cell carcinoma as is in Japan, the second is prostate cancer in males and breast cancer in females ***(Kitai et al., 2016).***