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Review Article

ANALYSIS OF URINE FOR EARLY DETECTION OF VARIOUS CANCERS

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ABSTRACT

From the ancient time, urine is been used as an important fluid for determination of various disorders. Recently, it was found that presence of certain metabolites in the urine can help in prediction of fatal disease like cancer. These molecules can be determined by noninvasive and cost-effective methods. Current modern analytical development has enabled us to effectively measure such metabolites for earlier and deeper understanding of various cancers. In the year 2006, the very first study using NMR and mass spectrometry (MS) was done for this and since then various analytical techniques have been used for determination of various cancers biomarkers in early stage present in the urine. Till date various tumor markers associated with breast, ovary, liver, gastrointestinal tract, lung, pancreas, bone and blood were successfully identified by using these methods. Here, a review is done for the major biomarkers associated with predominant cancers like breast, lung and prostate cancer.

Keywords: Urine Biomarker, Cancer, Early Detection, Analytical Techniques

1. INTRODUCTION

Urine is a liquid excretory product of animals including human beings. It contains molecules which are products of various metabolic pathways. During the ancient era, presence of these metabolites in the urine was used to determine various diseases. The most common example is to determine the presence of sugar in the urine which is an indication of diabetes mellitus.[1-3] Another popular example was to determine the presence of various solids in the urine through microscope, which provides the information about various minerals degradation in the body [4, 5]. However, at that time no advance methods were available for determination of such compound. Recent development in the analytical techniques has enabled to identify various metabolites present in the urine and also helped in determining their relation with various diseases [6,7]. Advance techniques like gas chromatography, liquid chromatography, mass spectrophotometry, nuclear magnetic resonance, infrared spectrophotometry, capillary electrophoresis has widely used for detection of various compounds. Methods have been developed for correlating the increase or decrease values of metabolites with various diseases [8-11].

2. CANCER AND BIOMARKERS

Cancer is considered as one of the most fatal disease of the world. Most of the reasons associated for causing cancer are associated with defective metabolic pathways [12,13]. Unfortunately, it is very difficult to identify such abnormalities in the earlier stages. If these compounds are detected in early stage then it is possible to identify the cancer in its early stage and could be treated well. This will also decrease the mortality rate. In this review, three most common and most fatal cancer and their biomarkers were focused. Among these, breast cancer is the predominant cancer in female. It is observed that around 6,11,625 patients were died because of breast cancer in the world out of which 80,224 were died in India only. Several millions are affected every year with this disease [14]. In India main reason for such prevalence of disease is unawareness of the disease and higher rate of illiteracy. Most of the patients only came to know about the cancer when it reaches in the either stage 3 or stage 4 and at this stage the chances of survival is very less as compare to stage 1 and stage 2. Currently, x-ray and mammography is used for determination of breast cancer [15-17]. In addition to this certain biomolecules more commonly known as biomarkers like carcinoembryonic antigen (CEA), cancer antigen 15.3 (CA 15-3), estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) are analyzed [6,12]. Till date most of these biomarkers are detected from the serum and they will give positive report if they are present in minimum detectable concentration. In case

of male, prostate cancer is the most predominant cancer. Worldwide around 1,07,114 were died due to prostate cancer. In India the count has reached at 30,386. Most of the patients were found elders. Till date the exact reason for prostate cancer in not known. It is thought to be associated with age. Prostate cancer can be detected by physical observation by a medical person. Concentration of prostate specific antigen (PSA) in serum is also widely used and reliable method for determination of cancer. Lung cancer is another common cancer found in both gender. Around 1,88,000 people die because of lung cancer. In India around 7,184 male and 5,633 females were died because of lung cancer [14]. The higher carcinogenicity is because of higher consumption of tobacco and tobacco products. X-ray and study of sputum is one of the most common and primitive method for determination of lung cancer [11]. Similar to breast cancer, this method will also give significant result when the cancer has reached to its advance stage. In addition to this carcinoembryonic antigen (CEA), carbohydrate antigen 19.9 (CA 19.9), cytokeratin 19 (CYFRA 21-1), alpha-fetoprotein and ferritin are also determined from serum [18,19]. Most of the biomarkers mentioned earlier are detected based in immunological assays. Most of these markers are prognostic only a few markers can be considered as diagnostic markers [20-23].

In comparison with normal cells, cancer cells utilize more glucose and other nutrient molecules. It may also follow different pathway for utilization of these molecules and produces different amount of energy and metabolites [24]. It was observed that concentrations of certain molecules are either decreased or increased in case of cancer due to abnormal metabolism of cell. Reason for higher concentration is higher rate of metabolic activity due to higher activity of certain enzymes and pathways [25-27]. For example, higher degradation of amino acid metabolism leads to higher production of creatinine in lung cancer. Similarly, higher metabolism of purine and pyrimidine in breast cancer leads to higher production of 5'-hydroxymethyl-2'dedeoxyuridine, 8-hydroxy-2-deoxyguanosine and succinyladenosine [28]. In contrast to this, certain metabolites are found in lower concentration than the normal concentration in cancerous cell suggesting the alternate pathway of metabolism by cell. For example, concentration of hippurate and succinate go down as the cancer cell will not follow the normal TCA cycle [6, 29]. In prostate cancer, production of tryptophine, tyrosine and citrulline will be reduced as the urea cycle is affected [27]. Since all these molecules are associated with metabolism, most of them found present in the cancerous cell and in body fluids even though there is no visible symptoms of disease. Most of these metabolites are not reabsorbed by the kidney and thrown out of the body in from of urine. Hence analysis of urine for such metabolites should be done for early detection of cancers [19, 30, 31]. However, it is not applicable to all the types of cancers as many metabolites may not throw out in form of urine. But major cancers like lung, breast, prostate, liver, colorectal, bladder and gastric produces such metabolites which can be found in urine [11, 19, 32].

3. DETECTION OF METABOLITES

Recent development for detection of cancer is based on this aspect, where various advanced analytical methods are applied to identify and determine various metabolites present in the urine associated with cancers. Among various sophisticated analytical methods, chromatography is one of widely used and accepted method. Both gas chromatography and liquid chromatography coupled with mass spectrophotometry are used for determination of various metabolites [8, 9, 33, 34]. In a study carried out by Lee *et al*, they successfully used GC-MS and LC-MS to analyze the biomarkers like β-cortol and 5-methyl-2-deoxycystidine [28]. In another study carried out by Park *et al*, they have observed higher concentrations of N-(2-furoyl) glycine, D-tagarose, and histidine and lower concentration of trigonellinamide, creatinine, L-galacto-2-heptulose and xanthine in the patients with breast cancer in the HPLC analysis than the controls [12]. Gerace *et al* has developed a rapid method for identification of anti-estrogen present in urine using GC-MS [8]. Guo *et al* have worked on oxidative DNA damage markers like 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG). They have found that, early stage of breast cancer (I and II) shows higher concentration of this molecule in the urine as compare to normal. They have detected this compound by using ultra performance liquid chromatography-electrospray ionization-tandem mass spectrophotometry (UPLC-ESI-MS/MS) [31]. In the study of Beretov *et al*, they have shown the association of various biomarkers with various types and stage of breast cancer. They have shown urinary biomarker pattern of benign and cancer cell. They have used a label free approach of LC-MS/MS. Zhang *et al* [35] has developed as robust method for screening of prostate cancer metabolites in urine by orthogonal LC in

conjugation with HRMS. They have focused on four major metabolites including ureidoiso butyric acid (UIBA), which is a well established inborn error metabolic marker [34]. Chan *et al* has given a step by step method for generation of global metabolic profile for metabolites. They have advised all the precautionary steps to be considered while collecting, storage and preparation of sample. They have also provided detailed method determination of metabolites using GC/TOFMS [36]. In a study carried out by Aggio *et al*, they have used sensor based system for diagnosis of urological malignancies. They have identified various volatile organic compounds (VOCs) associated cancer. Not only this, they have created profile for localized as well as metastasis of breast cancer [33]. Mazzone *et al* has used colorimetric sensor array for determination of volatile organic compound in urine headspace and proved that it is capable of distinguish between lung cancer patient and healthy control [10]. In a case study done by Porto-Figueira *et al*, a complete profile of volatile organic metabolites (VOM) was developed from lung cancer patients using solid phase extraction method coupled with GC-MS [1]. Fan *et al* has used ion chromatography to generate urine amino acid profile associated with diagnosis of gastric cancer. They have suggested that urine free amino acid profiling has potential value in screening and diagnosis of various cancers.[9] Zhou *et al* has developed as pseudotargeted GC-MS method for determination of markers like 5-hydroxyvelric acid and glycolic acid. They have also shown the variation in metabolite profile caused cancerous cell due to altered pathway [37].

Nuclear magnetic resonance is another such technique which is used for other metabolites. This method is based on the signal is produced by excitation of the nuclei with radio waves. Each molecule gives characteristic pattern in NMR. Various type of NMR provides the information about structural arrangement of molecule [7, 13, 38]. Li and Deng has provided list of metabolites which can be detected using NMR in various cancers. According to that creatine and creatinine increases in urine in liver cancer; N-acetylglutamine, citrate, 3-hydroxyisobutyrate, 3-hydroisovalerate increases in lung cancer whereas hippurate, trigonellinamide, trigonelline decreases [39]. Mackinnon *et al* has used NMR for creating metabolite profile for prostate cancer. They have prepared a master list of metabolites produced in prostate cancer. During their study, they have observed that principal component assay (PCA) is not able to separate biopsy positive and biopsy negative samples. However urine sample was found dominant over PCA and hence suggested to use urine sample for prostate cancer [7]. Kim *et al* determine pattern of various metabolites in early stage and advance colorectal cancer. They also proved that metabolic profile significantly and accurately discriminate between cancer patients and health control. They have also shown variation of metabolite pattern with difference stage of cancer [6]. Loras *et al* have used NMR for profiling of metabolites to detect recurrence in non-muscle invasive bladder cancer. They have shown that these markers are very important to determine the recurrence when there is no visible lesion [40]. Wang *et al* and Ahmed *et al* have prepared metabonomic profile of serum and urine by NMR which clearly differentiate between obstructive pulmonary diseases and health individual. Several other studies have shown many advantages of using NMR for determination of various cancer metabolites. According to them, early diagnosis of these metabolites will be highly used in decease in the mortality rate. Metabolite profile can provide important information about asymptomatic stages of cancers [11].

4. CONCLUSION

From all the previously carries out studies and data available, it is very clear that certain metabolites play a vital role in differentiation between cancerous person and health person. These metabolites are the outcome of the abnormal metabolic pathway. These metabolites are found in tissue and body fluids like blood and urine. Analysis of urine for such metabolite can provide important information about the disease in the early stage of disease. Current analytical technique can be widely used for identification of such compound. Metabonomic profiles created by these techniques have played a significant role in clinical science.

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