Cancer Metabolomics: A Tool of Clinical Utility for Early Diagnosis of Gynaecological Cancers

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Abstract

The primary reason for cancer-related fatalities among Indian women is gynecological malignancies. Early cancer diagnosis is challenging because of the poor prognosis and the absence of symptoms in the early stages. In a developing economy, the lack of mandated screening programmes and the lack of awareness present significant challenges. To improve cancer patient survival rates and minimize the social and financial burden, prompt intervention is necessary. Currently used cytological and conventional screening methods have significantly lowered the incidence of cancer. However, because these tests have limited sensitivity and specificity and are not frequently used for risk assessment, it is difficult to diagnose cancer in its early stages.

Keywords: Cancer • Human Genome Project • Biomarkers

Introduction

The success of the Human Genome Project (HGP) has made way for innovative "omics" systems. Insights into gene expression, protein function, and how specific mutations in specific genes correspond to certain phenotypes have been made possible thanks to promising research in genomics and proteomics, which has changed cancer detection and screening approaches. These, however, lack the ability to apply the knowledge in a therapeutic setting. The biggest obstacles include limited sensitivity, diurnal protein fluctuation, poor reproducibility, and analytical variability. As a result, attention is now being paid to metabolomics, a platform that is much more recent than genomes and proteomics. The focus of metabolomics is on endpoint metabolites, which are byproducts produced when a living system responds to genetic or environmental changes. As a result, the metabolome provides information about the functional state of the cell, which is directly related to its phenotypic [1]. The goal of metabolic profiling is to examine alterations in metabolic pathways. This chemical profile can distinguish between cancer patients and healthy people. Due to the fact that considerable metabolic problems are associated with the conversion of healthy cells to abnormal cells, the pathways that a cell follows to become malignant are remarkably varied. In this review, metabolomics will be discussed in relation to its potential use in the early detection of gynecological cancers, specifically breast, ovarian, and cervical cancer.

DNA dysregulation is a disease that affects cancer and is regulated by both internal and environmental factors. Infection, cigarette addiction, poor food, and physical inactivity are external causes of carcinogenesis. Endogenous causes include inherited genetic mutations, hormonal imbalances, and immunological conditions. Globally, according to a GLOBOCAN survey from 2018, there were 18.1 million new cases of cancer and 9.6 million cancer-related deaths, down from 14.1 million and 8.2 million, respectively, in 2012. Nearly 1.16 million new cases of cancer were detected in India in 2018, and 0.78 million people died from cancer there [2]. Cervical and ovarian cancers are currently the second and third largest causes of death among Indian women, respectively. If detected early, these tumours can be prevented. Poor prognosis and a lack of symptoms, along with a lack of knowledge and screening programmes, pose significant obstacles to early cancer diagnosis in developing nations like India. Not only do early interventions increase cancer patient survival rates, but they also lessen the social and economical burden. The Pap test for cervical cancer and the Cancer Antigen (CA-125) test for breast and ovarian cancer are only a few of the screening and cytological methods used. Women with early clinical signs or those with a significant family history of cancer are advised to undergo radiology-based screenings such sonography and mammography. These screening methods have significantly decreased the incidence of cancer. According to Ewandowska AM et al., executing a four-tiered cancer awareness and screening programme that included acetic acid-based low impact visual inspection, cytology, and Human Papilloma Virus (HPV) testing decreased cervical cancer mortality in the screening group by 31% [3].These tests don't get much usage for risk assessments because they have limited sensitivity and specificity. The application of several 'omics' platforms for early cancer diagnosis has been made easier thanks to the deciphering of the human genome. Thus, we examine metabolomics and its potential application in the early detection of breast, ovarian, and cervical malignancies in this study.

Gynecological cancer incidence has significantly decreased as a result of the use of conventional screening methods. These methods do, however, have some serious shortcomings. Papanicolaou (Pap) smears are frequently used for cervical cancer screening, and their accuracy depends on how well they are prepared and how accurately they are interpreted by a professional [4]. Due to interference from blood cells on glass slides, it cannot effectively detect squamous cell abnormalities and has a high probability of returning false-negative results. Comparably, CA-125, despite being commonly utilized for ovarian tumour screening, frequently yields false-negative results in the early stages. In many situations, the diagnosis is missed if the patients do not follow up despite experiencing repeated clinical symptoms. So far as screening and diagnosis go, histopathology is still regarded as the gold standard. Although histopathology is quite effective at detecting cancer, risk assessment does not use it. Histopathology has the drawbacks of being intrusive, uncomfortable, time-consuming, and expensive. It can't be used for universal screening [5].Furthermore, the interpretation of the results, which depend on the tissue biopsy sample, requires expertise. Histopathology is typically used in conjunction with conventional radiological techniques like X-rays, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) to diagnose and locate advanced stages of cancer. However, these methods are unable to detect tumours with no imaging abnormalities or early-stage lesions. Therefore, it is necessary to develop a general cancer screening test that is affordable, minimally invasive, highly sensitive, specific, and able to be used by India's rural population. These characteristics are absent or insufficiently present in the existing diagnostic techniques used to identify early-stage cancer.

Comprehensive analysis of the metabolites in cancer is what is done in the discipline of metabolomics known as cancer. The fundamental idea is to investigate changes in metabolic pathways, predicated on the idea that large metabolic disturbances are associated with the transformation of healthy cells into aberrant cells. The ways that dysplastic cells might become cancerous are incredibly varied. Because of this, a cell's metabolite profile is better able to reflect the condition of the cell at any given time and can be connected to its phenotypic. This metabolite profile can distinguish between healthy people and cancer patients. When using metabolomics to diagnose cancer, there are two main goals [4].

One of these is biomarker discovery, also known as untargeted metabolomics, in which all metabolites present in the sample are detected globally and quantified. Additionally, these 1 metabolites are linked to metabolic networks and pathways to identify any notable deviations from controls. This method increases the likelihood of precision. In conclusion, both strategies are interdependent and result in high throughput and extensive metabolic marker coverage [1].

Cancer is associated with several disordered biomolecules, pathway products, and intermediates. In addition to having significantly higher levels of metabolites linked to oxidative DNA damage and the methylation process, breast cancer patients have been reported to have increased choline abnormalities in oestrogen metabolism. In addition to the metabolites that cause oxidative DNA damage. Saranath D discovered lower levels of amino acids and metabolites of the tricarboxylic acid cycle and elevated levels of carnitine and metabolites of fatty acid metabolism [6]. Patients with cervical intraepithelial neoplasia were found to have 3-hexanone, hexanal, dodecane, 4-methyl, and 3-ethylcyclopentanone. Another study identified eight metabolites as possible biomarkers for the detection of cervical cancer, including Cer (d18:1/16:0), PC (15:0/16:0), PC (16:0/16:0), PE (16:0/20:0), PC (14:0/20:0), PS [17:0/22:2(13Z,16Z)], PG [21:0/22:4(7Z,10Z,13Z,16Z), and SM (d18:1/20 Metabolomics was used to identify the presence of high risk HPV strains and was shown to be 94% sensitive and 83% specific. Studies were done on four cell lines, one of which was normal, three of which were malignant (SiHa HPV 16+, HeLa HPV 18+), and one of which was not (C33A). Warburg metabolism was present in the cell line that was HPV 16 and 18 positive, and this was consistent with the function of HPV protein E6. Additionally, in order to maintain angiogenesis, the SiHa and HeLa cell lines used the purine salvage route, while the C33A cell line underwent a novel process by producing cytidine [7]. Thus, urine metabolic profile can be used to distinguish between gynecological malignancies.12 biomarkers were found using an Ultra-High Performance Liquid Chromatography-Quadrupole Time-Of-Flight (UPLC/QTOF) MS-based metabolomics method and multivariate data analysis that may be connected to abnormal fatty acid oxidation, phospholipid metabolism, and bile acid metabolism in ovarian cancer. The validity of two of the found metabolites was assessed using a Multivariate Logistic Regression Model (2-piperidinone and 1-heptadecanoylglycerophosphoethanolamine) [8]. These discoveries advance knowledge of the pathogenesis of ovarian cancer and could aid in clinical detection and therapy.

Additionally, improvements in bioinformatics and computational biology have made it easier to combine metabolomics with fluxomics for the development of biomarkers. Comparing a specific illness state to a control group using metabolomics has resulted in the identification of a potential biomarker, and fluxomics has assisted in identifying the rate of metabolite (i.e., M per unit time) or metabolite turnover in a certain pathway. As a result, both metabolomics and fluxomics techniques work in concert to provide a complete picture of prospective biomarkers as well as their reflux. A specific marker's importance in highlighting a route disruption is amplified by two fold [6]. The study of biochemical refluxes resulting from responses to varied host circumstances and environmental stimuli is rapidly developing into a new field of study called metabolic profiling. This biochemical reflux is crucial for maintaining and enhancing the oncogenic state in cancer metabolomics. It also offers additional benefits than the traditional approach. By acquiring biological samples, such as blood, urine, and biopsy tissue, using non-invasive or minimally invasive techniques, metabolic analysis can be performed. Additionally, only a very tiny amount of sample is needed for the analysis, and it can be kept at -40°C or -80°C for a long time without changing the results of successive analyses. Even before clinical manifestation, early identification is still a possibility. Metabolomics, which has been linked to the development of biomarkers, also has traits like high sensitivity and the capacity to predict cancer.

When compared to other "omics" disciplines, eMetabolomics is superior and has significantly advanced the fields of metabolite identification, pattern recognition, and statistical analysis [9]. This can identify cancer earlier, when it is still treatable. Even though the results are encouraging, transferring this knowledge into clinical practice and cancer diagnosis continues to be difficult. Metabolite analysis is a significant barrier to procedure standardization and data analysis. It is challenging to get an accurate interpretation from complex data. The metabolite profile may also be impacted by confounding variables like food, age, gender, ethnicity, lifestyle, stress, drugs, and environment. Metabolomics holds considerable promise to serve as a good platform for early cancer diagnosis. Clinically useful biomarkers have been found as a result of metabolic profile using metabolite analysis. Depending on the clinical stage in which they appear, these biomarkers can also be divided into prognostic, diagnostic, and tumour categories. Some biomarkers are universal markers because they can be found in all cancer types. They are nevertheless byproducts of altered metabolism and a characteristic of cancer cells. A few biomarkers have been specifically linked to certain cancers [10]. Currently, in addition to gynecological cancers, the metabolomics technique has been investigated in renal cell carcinoma, human bladder cancer, gastric tumours, and prostate cancer. The result is encouraging because a certain tumour exhibits a distinctive metabolic profile. More biomarkers responsible for oncogenesis in particular malignancies will be confirmed through thorough research in this area, and it may soon be conceivable to envision a single test to screen numerous tumours depending on their metabolic profile.

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