



Invited critical review

# Metabolomics in noninvasive breast cancer<sup>☆</sup>

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## ARTICLE INFO

### Article history:

Received 6 April 2013

Received in revised form 3 May 2013

Accepted 5 May 2013

Available online 10 May 2013

### Keywords:

Metabolomics  
Breast cancer  
Biomarkers  
Metabolites  
Early diagnosis

## ABSTRACT

Breast cancer remains the most leading cause of death among women worldwide. Common methods for diagnosis and surveillance include mammography, histopathology and blood tests. The major drawback of mammography is the high rate of false reports, aside from the risk from repeated exposure to harmful ionizing radiations; histopathology is time consuming and often prone to subjective interpretations; blood-based tests are attractive, but lack the sensitivity and specificity. Obviously, more sensitive biomarkers for early detection and molecular targets for better treating breast cancer are urgently needed. Fortunately, molecular level 'omics' diagnosis is becoming increasingly popular; metabolomics, diagnosis based on 'metabolic fingerprinting' may provide clinically useful biomarkers applied toward identifying metabolic alterations and has introduced new insights into the pathology of breast cancer. By applying advanced analytical and statistical tools, metabolomics involves the comprehensive profiling of the full complement of low molecular weight compounds in a biological system and could classify the basis of tumor biology of breast cancer, to identify new prognostic and predictive markers and discover new targets for future therapeutic interventions. This advanced bioanalytic methods may now open new avenues for diagnostics in cancer via discovery of biomarkers. In this review we take a closer look at the metabolomics used within the field of breast cancer diagnosis. Further, we highlight the most interesting metabolomics publications and discuss these in detail; additional studies are mentioned as a reference for the interested reader. A general trend is an increased focus on biological interpretation rather than merely the ability to classify samples.

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## 1. Introduction

Breast cancer belongs to the most frequent and severe cancer types in women worldwide and its recurrence rates are very high [1]. The burden of breast cancer is growing worldwide and with it a more desperate need for better tools to detect, diagnose and monitor the disease is required. The gold standard method for identifying patients with breast cancer is the mammography, histopathology and blood tests [2–4]. However, these tests are not widely used as a risk assessment tool

because they are inconvenient, time-consuming, costly and have a poor specificity. Metabolomics, a dynamic portrait of the metabolic status of living systems, offers potential advantages that classically diagnose approaches that did not based on the discovery of a suite clinically relevant biomarker [5,6]. Because small changes in living systems can lead to large changes in metabolite levels, the metabolome can be regarded as the amplified output of a biological system. Monitoring fluctuations of certain metabolites in body fluids, has become an important way to detect early stages in breast cancer [7]. Moreover, metabolomics approaches are likely to be used to screen for potential diagnostic and prognostic biomarkers of breast cancer [8].

Recent metabolomics studies have improved the understanding of the basic mechanisms underlying cancer pathogenesis, which will help to improve treatment strategies [9]. It aimed at characterizing the metabolism of breast cancer to identify new biomarkers and new targets for therapeutic interventions. A comprehensive coverage of metabolism can be achieved by a combination of analytical approaches. The most popular approaches for metabolomics involve mass spectrometry (MS), and nuclear magnetic resonance (NMR) spectroscopy [10]. Over the past 10 years, continuous progress in the application of NMR spectroscopy and MS to the detection, diagnosis and characterization of human breast cancer has turned what began as scientific curiosity into a useful clinical option. This technology permits simultaneous monitoring of many hundreds, or thousands, as well as functional monitoring of multiple pivotal cellular pathways. Development of metabolomics platform has made it possible to acquire high-throughput profiles of potential biomarkers [11,12].

Emerging metabolomics is increasingly being used for breast cancer research and personalized medicine; it has provided new opportunities in the molecular analysis of human breast cancer with unprecedented speed and detail [13]. This approach has the potential to provide more information about the pathophysiological status of an organism and distinguish breast cancer stages [14,15]. Metabolomics biomarkers can potentially lead to breast cancer screening and diagnosis and may provide useful information on the cancer type and the disease's stage of progression. It has just begun to enter the mainstream of cancer diagnostics and therapeutics. In this review we intend to explore the potential role of metabolomics in understanding breast cancer process, refining its characterization and searching for predictive biomarkers, highlighting the potential value of metabolomics for the noninvasive analysis of breast cancer.

## 2. Metabolomics technologies

With technological advances in analytical techniques, the ability to measure low-molecular-weight metabolites in a biofluid provides a powerful platform for identifying metabolites that are uniquely correlated with a specific human disease [16]. Technological developments are the driving force for advances in metabolomics, and identifying novel changes in specific metabolites. A key task in cancer medicine is to detect the disease as early as possible. In order to achieve this, many new technologies have been developed for cancer biomarker discovery [17]. Nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) are the main analytical spectroscopic approaches in metabolic profiling, usually offering complementary information, but with different performance characteristics. Their complementary nature makes the combination particularly attractive and can provide complementary snapshots of the metabolome of body fluids such as plasma, urine or cerebrospinal fluid [18]. High-definition MS has been carried out to obtain comprehensive metabolite profiling and pathways of large biological data sets. MS tends to have much higher analytical sensitivity, and enables broader surveys of the metabolome either in a targeted or nontargeted manner. Because no single analytical method can accommodate the chemical diversity of the entire metabolome; thus, a multiplatform approach may provide a more comprehensive

understanding of metabolic alterations [19]. A combined analytical approach can improve the potential for providing reliable methods to detect metabolic profile alterations in a biological specimen. In the study by Asiago et al., using a combination of NMR and GC × GC–MS methods, the metabolite profiles of 257 serum samples from 56 breast cancer patients were analyzed and eleven metabolite markers provided a sensitivity of 86% and a specificity of 84% [20]. The combination of two advanced analytical methods, NMR and MS, provides a powerful approach for the early detection of recurrent breast cancer. Additionally, an improved metabolic profile obtained by combining MS and NMR approach may be useful to achieve more accurate disease detection and gain more insight regarding breast cancer mechanisms and biology [21].

## 3. Potential role of metabolites

Metabolomics capitalizes on the unique presence and concentration of small molecules in body fluids to construct a 'fingerprint' that can be unique to the individuals, including health and disease states. It has been increasingly applied to discover biomarkers, identify perturbed pathways, diagnose diseases, and measure the response to treatment [22]. In the area of breast cancer, the integrated analysis of metabolites may provide a powerful platform for detecting changes related to cancer diagnosis and discovering novel biomarkers [23]. Biomarkers are biological characteristics that are objectively measured and evaluated as indicators of pathological processes [24]. It is a biological molecule found in body fluids that can be a sign of a disease, and has been widely used in clinical practice for the diagnosis, assessment of severity and response to therapy in a number of clinical disease states.

Analyzing metabolic differences between unperturbed and perturbed systems, such as healthy volunteers and patients with a disease, can lead to insights into the underlying pathology [25]. Assessment of a biological system by means of global and non-targeted metabolomics provides the investigator with molecular information that is close to the phenotype. Biomarker discovery is one of the newly emerging innovations in the diagnosis and treatment of cancer and many other diseases. With advances in methods and technology, together with the considerable efforts to find early and novel diagnostic breast cancer biomarkers, many candidates will be discovered; leading to early diagnosis, detection, monitoring and efficient treatment of breast cancers [26]. More specifically, metabolomics has a global and non-invasive analysis of biomarkers that are indicators of pathogenic process, thereby helping to monitor treatment response [27]. Recently, a variety of multiple biomarkers reflecting breast cancer pathologies have been developed and have the potential to serve an important role in diagnosis and management of human conditions.

## 4. Metabolomics features of breast cancer

Understanding the metabolome will not only provide insights into the critical sites of regulation in health promotion, but will also assist in identifying intermediate or surrogate cancer biomarkers for establishing preventative or therapeutic approaches for health. Metabolomics increased our knowledge of the dysregulated metabolic pathways associated with progression of diseases and provided potentially new therapeutic strategies targeting these pathways, through our understanding about the distinct and complete metabolic footprints of breast cancer [28]. Over the last few years, there has been a rapidly growing number of metabolomics applications aimed at finding biomarkers which could assist diagnosis, provide therapy guidance, and evaluate response to therapy for particular breast cancer. Metabolite changes that were observed in diseased individuals as a primary indicator have been an important part of clinical practice [29]. This dynamic, simultaneous assessment of thousands of metabolites allows identification of the presence, concentration and fluxes of specific metabolites, and recognition of the critical metabolic pathways recruited in carcinogenesis.

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