AJAB

Asian J Agric & Biol. 2022(4).
DOI: 10.35495/ajab.2020.12.566

Review Article

Metabolomics approaches for early cancer diagnosis: a review

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Received:
December 27, 2020

Accepted:
March 22, 2022

Online First:
April 24, 2022

Published:
September 4, 2022

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Abstract

Cancer remains a major burden on global public health with high mortality rates worldwide. Current diagnosis can detect cancer in late stages when therapy options become limited. Early diagnosis is broadly recognized as the key to a better treatment to save lives. The metabolomics approach provides a better understanding of the different types of cancer. They offer promising and potential interventions in biomarkers discovery which eventually will be better suited for individualized medicine. It elucidates endpoint products for other omic processes while significantly improving the understanding of pathogenesis and mechanisms yet to be discovered. Metabolomics offers a less-invasive, cost-effective for predicting, screening, diagnosis, prognosis, and monitoring therapeutic responses of the disease. There are two methods to study the metabolism and metabolites: targeted and untargeted. The workflow of these approaches requires different analytical platforms, such as Nuclear Magnetic Resonance spectroscopy (NMR), Mass Spectrometry (MS), and different bioinformatic tools. This review provides a systematic summary of metabolomics methods in identifying metabolic biomarkers of cancers (colorectal, prostate, breast, bladder, pancreas, lung, and buccal cancers). In addition, the current review will try to shed light on DNA lesions as a potential metabolic biomarker for cancer.

Keywords: Cancer, Metabolomics, NMR, Early diagnosis, DNA lesions

How to cite this:

Boumehira AZ, Akchiche YF, Cherfi W, Talhi O, Djidjik R, Dailin DJ, Ho T and El Enshasy HA. Metabolomics approaches for early cancer diagnosis: a review. Asian J Agric & Biol. 2022(4): 202012566. DOI: https://doi.org/10.35495/ajab.2020.12.566

Introduction

The cancer incident rates, and mortality are steadily increasing, making cancer a leading death cause worldwide. Available data from Globocan, 2018 stated that 1 in 5 men and 1 in 6 women are likely to develop cancer, and 1 in 8 men and 1 in 10 women risks dying from it before the age of 75. These findings make this disease a major public health concern (Bray et al., 2018; Cai and Liu, 2019). In 2020, the number of new cancer cases was estimated to be 19 million, and the number of cancer deaths is 10 million. Such data represents an increase of 5% in cancer incidence and 5.2% in cancer mortality compared to 2018. Notably, the number of new cancer cases and deaths per year is expected to rise to 29 and 16 million, respectively, in the coming two decades (IARC, 2018).

While the cancer burden is noticeable worldwide, low, and middle-income countries have been experiencing increasing cancer-related mortality because of a weak health care system and infrastructure. In addition, large numbers of cancer patients in these countries do not have access to timely, high-quality diagnosis or treatment. Moreover, the number of deaths due to cancer in Low- and Middle-Income Countries (LMICs) surpasses those due to HIV/AIDS, malaria, and tuberculosis combined and account for two-thirds of global cancer deaths. These consequences are related to poor diagnosis and a lack of accessibility to proper cancer treatment. The likelihood of death and disability from cancer increase significantly as the disease progresses (WHO, 2017a; WHO, 2017b; Boumehira et al., 2016). That is why an early diagnosis and timely treatment can help in reducing mortality and improving the outcomes and quality of life of cancer patients. However, the radiographic techniques typically used in cancer detection do not allow an early diagnosis.

Conversely, cancer is frequently detected at an advanced stage where limited therapeutic options (Gowda et al., 2008). Therefore, alternative, novel and chemically based detection methods are more convenient options. In this regard, metabolomics offers a powerful technique to observe cancer-associated metabolism. Thus, fostering the understanding of the pathogenesis of the disease, the knowledge of the scale of metabolism deregulation of cancer, and finding promising early diagnostic biomarkers and therapeutic monitoring (Ellero-Simatos et al., 2019; Gowda et al., 2008).

Cancer: a metabolic or genetic disease?

Cancer is a general word applied to many heterogeneous diseases linked to hereditary, environmental, inflammatory, or other factors that can affect any part of the body. It is a non-communicable disease (NCD) characterized by the rapid proliferation of abnormal cells that can spread into other organs to form metastases. It is known for its heterogeneity, with several anatomical and molecular subtypes, each requiring a specific diagnosis (Cai and Liu, 2019; Bray et al., 2018; WHO, 2017a). This condition has been widely considered a proliferation disorder and a genetic disease linked to nuclear mutations in oncogenes and tumor suppressor genes (Coller, 2014). However, since Otto Warburg's original theory that respiratory failure is the cause of cancer, new proof proposes that cancer should be considered a mitochondrial metabolic disease (Zhang et al., 2019; Seyfried, 2015; Warburg, 1956). According to this concept, cancer cells form from normal cells, having adapted to a decrease in energy, resulting from an irreversible dysfunction of cellular respiration in the mitochondria and modifying their morphology to differentiate and grow anarchically (Razungles et al., 2013).

In cancer cells, the observed metabolic profile often includes an increased glutamine and glucose consumption, increased secretion of lactate, increased glycolysis, and changes in the use of metabolic enzyme isoforms (Coller, 2014). In his study "Cancer as a mitochondrial metabolic disease," Seyfried supported the theory of the Warburg effect and reported that "cancer originates from damage to mitochondria in the cytoplasm instead of damage to the genome in the nucleus. The genomic damage in tumor cells follows rather than precede the disturbances in cellular respiration." while stressing that real progress in cancer management and prevention will emerge once the field of cancer abandons the theory of somatic mutations and recognizes the role of mitochondria in the origin, management, and prevention of the disease (Seyfried, 2015).

In summary, although metabolic changes that happen in cancer cells have long been measured as a secondary phenomenon, lately, they are reconsidered as being more essential to the disease itself (Coller, 2014). Therefore, metabolomic studies in cancer can be interesting to understand better the mechanisms involved in cancer and its early diagnosis.

Early diagnosis, best hope for recovery

While cancer's global profile is narrowly associated with lifestyle and socioeconomic development factors, its mortality is more closely due to late diagnosis. Moreover, two-thirds of cancer deaths globally occur in less developed countries due to its diagnosis at advanced stages where the response to treatment is less efficient. As cancer progresses, patients' probability of mortality and disability keeps arising. However, most cancer types need several years to grow like a malignant disease, which offers the chance of early detection and better survival chances. In this context, an efficient early diagnosis enables identification and recovery at an early stage by detecting precancerous lesions or malignant tumors at the right time and intervening rapidly with less complex, less morbid, more efficient treatments which avoid unnecessary pain and premature death (Cai and Liu, 2019; WHO, 2017a; WHO, 2017b).

Notably, in a study by Mandel et al., 2000, an association between colorectal cancer screening and its incidence decrease has been demonstrated due to adenomatous polyps' detection and elimination within patients with such antecedent lesions (Curry et al., 2003). Likewise, one of the reasons for 25% global cancer mortality decrease (1990-2015), in the USA, with a more important mortality rates decrease of colorectal cancer (47 % for men and 44 % for women) and breast cancer (39% within woman), is certainly the implementation of screening and early detection of colorectal and breast cancers (Corinne, 2017; Smith et al., 2018). Furthermore, other studies reported the occurrence and death rates of cervix cancer decreased since the introduction of the Pap test (Papanicolaou test) in the middle of the twentieth century. Also, buccal cancer screening allowed a significant mortality reduction (Nagao and Warnakulasuriya, 2020; Smith et al., 2018; Chuang et al., 2017). In addition, early diagnosis noticeably reduces its financial consequences because, at early stages, treatments are less costly, allowing people to afford them and still be able to provide for their needs. In 2010, the annual cancer economic cost (healthcare expenditure and loss of productivity) in USA was estimated to be $1.16 billion (WHO, 2017b). However, what's more, interesting about early diagnosis, is the possibility to proceed with a liquid biopsy, which allows the detection of a large variety of circulating biomarkers in easily accessible and less invasive ways, in the contrast to conventional tissue biopsy (Bellassai et al., 2019).

Metabolomics: a promising member of the "Omic" family

The «omics» have developed the current mantra of molecular research as they detect metabolites (metabolomics), genes (genomics), proteins (proteomics), and mRNAs (transcriptomics) in a non-targeted and unbiased manner (Figure 1). The approach represents the second call of "high-dimensional biology" (Ellero-Simatos et al., 2019; Narad and Kirthanashri, 2018; Debnath et al., 2010). The analysis will holistically decipher the different cellular populations, tissues, and the body while promoting the understanding of their functions and the various mechanisms and interactions implemented during normal physiological processes or in case of pathology (Narad and Kirthanashri, 2018). Moreover, they have been explored in numerous branches of health and medical sciences to know the etiology of a disease. It is also used to monitor its condition through screening, diagnosis, and prognosis while focusing on new therapeutic targets, which has made them very useful for drug discovery and toxicity assessment. In addition, further studies, and the simultaneous analysis of several molecules, provided by omics approaches have opened new avenues to identify novel biomarkers and early diagnostics for cancer (Narad and Kirthanashri, 2018; Debnath et al., 2010). The use of experimental models to assess toxicity is very useful (Gouva et al., 2020; Rehma et al., 2020).

Metabolomics is an omic technology that has been developed since the late 1990s and is particularly used to study metabolomes biofluids in cells, tissues, or organisms at a given time and under given circumstances. It is formally defined as the high-throughput study of metabolites and represents a fundamental tool for their overall assessment within a biological system. The technique is the downstream endpoint of all biological processes, giving the closest measurement to the molecular phenotype (Figure 1) compared to transcriptomics and proteomics (Boumehira et al., 2019; Andrisic et al., 2018). In addition, since the metabolic alteration is the last step in cellular reaction to disease, metabolomics can be beneficial for identifying new biomarkers (Dufour-Rainfray et al., 2020). Nevertheless, it is not the only term used; we also find metabonomics.

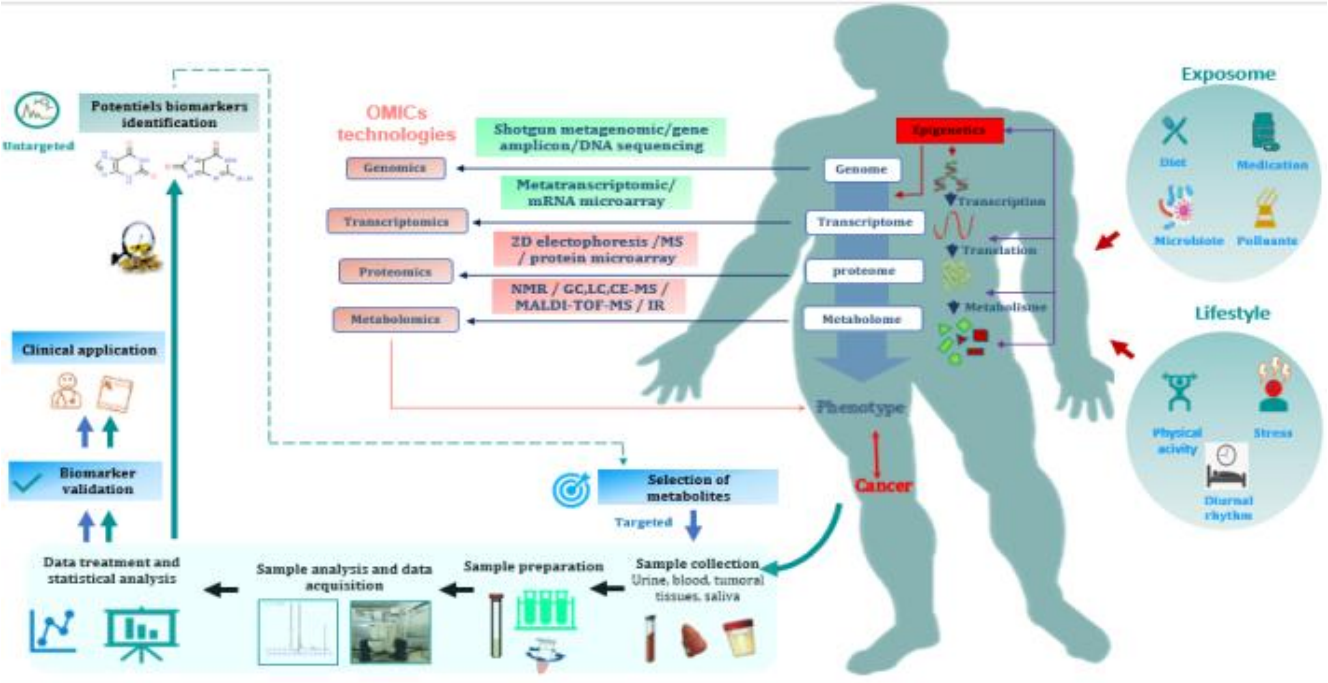

Figure-1. The metabolomic is omic that best modulates the molecular phenotype.

Metabolomics or metabonomics?

In the literature, metabolomic and metabonomic are two terms used interchangeably to describe the holistic study and unbiased analysis of metabolites in a known biological sample using sophisticated analytical methods including nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry (MS) and data mining and modeling procedures (Ellero-Simatos et al., 2019; Gika et al., 2014). However, both terms slightly differ as they are not the same techniques. Metabolomics, described by *Fiehn* as "a complete and quantitative investigation of all metabolites," corresponds more precisely to the exhaustive and non-selective identification and quantification of all metabolites in a biological system for the detection, monitoring, characterization, and determination of a metabolic phenotype. On the other hand, metabonomics, described by Nicholson and Lindon (2018) as "the quantitative measurement of the dynamic multiparametric metabolic response of living systems to physiopathological stimuli or genetic modification", refers more specifically to the study of a global and dynamic metabolic response of an organism to biological stress (disease, exposure to a toxic agent, etc.) or genetic manipulation, in contrast to more targeted methods of metabolic profiling to comprehend the mechanism involved in response to the studied biological phenomenon and to understand systemic change (Athersuch, 2019; Jobard et al., 2010). In short, metabonomics considers the notion of a "dynamic" metabolic response and formally includes metabolomics (Ellero-Simatos et al., 2019).

From metabolites to metabolome

Metabolites are molecules of low molecular weight (less than 1500Da), covering an extensive array of chemical classes, such as oligopeptides, lipids, sugars, amino acids, organic acids, nucleotides, etc. They are classified according to their origin into two categories: endogenous and exogenous (Figure 1). The first is the intermediaries and the products of the metabolism, described as the whole of the biochemical reactions, involving either processes of degradation of the organic matter (catabolism) or processes of synthesis (anabolism). On the other hand, the latter comes from the interaction of the body with the external environment (xenobiotics, toxins, etc.) and temporarily constitutes part of the chemical medium (Athersuch, 2019; Andrisic et al., 2018; Jobard et al., 2010). These molecules of low molecular weight participate in regulating a good number of cellular processes and can act as indicators of homeostatic imbalance; these are the substrates, products, or cofactors of diverse biological reactions. Both endogenous and exogenous, they integrate into a plethora of cellular and systemic functions and

collectively contribute to the mechanistic link between exposures, responses, and related adverse reactions (Athersuch, 2019, Donovan et al., 2019). The whole and complete collection of these small molecules in a biological entity constitute the metabolome, the metabolic analogy of the genome or proteome. It is described as the metabolic structure of a cell, tissue, organ, or organism at a given time. It is dynamically modified according to lifestyle and exposure to external factors, which directly reflects alterations and connections among protein expression, gene expression, and the environment. In addition, since metabolites are the endpoints of the biomolecular cascade (genes-protein-metabolites), the metabolome is the last level of cell regulation and thus comes closest to the phenotype**,** which makes his study very interesting (Figure 1) (Ellero-Simatos et al., 2019; Sengupta and Narad, 2018).

Metabolomics approaches: targeted and non-targeted metabolomics

Metabolomic/metabonomic approaches have a wide potential, both in terms of object of study and the variety of fields of application (toxicology, physiology, medicine, cell biology, pharmacometabolomics, etc.). They are common tools in discovering biomarkers, generally suitable for the study of fluids (cerebrospinal liquid, bile, amniotic liquid, seminal liquid, cell culture supernatant, etc.), biological tissues, or intact model organisms (biopsies, cells, etc.). These methods seek to describe the metabolic outline of multifaceted structures over a mixture of high-throughput analytical techniques and multivariate data analysis (Figure 1) and thus allow the arrangement and/or classification of illness or treatment-associated molecular forms produced from metabolites and the identification of different metabotypes of disease brutality and make positive clinical and molecular phenotyping and patient stratification) (Chen et al., 2016; Johnson et al., 2016; Jobard et al., 2010).

Metabolomic studies can be carried out using two main approaches, a so-called targeted approach, and another so-called non-target (*metabolite fingerprinting or profiling*). The first is concerned only with studying a specific type of metabolites. It measures one or more well-defined metabolite(s) and therefore requires a pre-selection of the compound(s) to be detected. A complete or partial understanding of the molecule(s) to be targeted, hence the name of "targeted metabolomics". The choice of metabolites is usually depicted by pathophysiology and could be inadequate to exact metabolic pathways. Thus, prior knowledge of physiological disorders occurring during the disease is necessary. This quantitative and validated method offers higher sensitivity and selectivity than the non-target. However, the potential for missing information due to the inadequate quantity of metabolites in the analysis is an important matter and may constitute a false negative.

On the other hand, the second does not target specific metabolites; it measures the widest variety of metabolites present in a sample, in the absence of necessarily a prior knowledge of the metabolome. Its main concern is to obtain a maximum of information by comparing profiles between several groups of samples to detect or not the presence of a metabolic fingerprint characteristic of a given biological state, hence the second term "*metabolite fingerprinting"*. This unbiased study is then a strategy of choice for generating hypotheses and an effective first step for discovering biomarker metabolites. However, even though it allows the non-biased detection of metabolites, it is semi-quantitative (*profiling*) and little validated. Furthermore, due to the wide range of analytes detected, non-significant and disease-unrelated signals can be confused with directly related ones and thus constitute a false positive. Therefore, no approach is flawless, and there is value in combining both. The non-targeted one can then verify the results obtained through the targeted approach to ensure no missing information. At the same time, the assumptions/results of the not-targeted approach can be invested, tested, and confirmed by the targeted with the aim of their validation and development (Böhme et al., 2019; Ellero-Simatos et al., 2019; Cheung et al., 2019; Christians et al., 2017; Johnson et al., 2016).

Along with the targeted and non-target approach, there is a semi-targeted strategy, which consists of screening many specific key metabolites through several dosages. It is a more quantitative than non-targeted approach and can thus minimize interference and false positives (Christians et al., 2017).

Analytical approach in metabolomics (Workflow):

The metabolomic analysis strategy should be tailored to the addressed biological issue and the available resources. However, all metabolomic research adhere to a mutual procedural pipeline from sample gathering, preparation, and analysis to spectral data acquisition, processing, and translation (Figure 1) (Dufour-Rainfray et al., 2020; Andrisic et al., 2018;

Boudah et al., 2012).

The first step is the assembly and composition of samples, mostly blood, urine, and tissue. The choice of the biological matrix should be based on the assumption made since each kind of sample provides diverse and complementary data. To avoid degradation, the samples must be obtained and treated quickly. The collection of specimens requires special attention; it is necessary to guarantee that all samples are gained under similar environments in various pool or packing. Clinical details should also be gathered that could influence the previous metabolism of the patient. In addition, one of the key difficulties in interpreting the data is that various variables such as age, sex, diet, medication, and chronobiological variability affect metabolic trends.

On the other hand, the preparation of the sample is a critical step in determining the quality of the results obtained, especially in the context of targeted analyses where selective metabolite extraction is required to increase the sensitivity of detection. In contrast, in the global approach, the treatment of the sample must be reduced to a minimum to limit any source of external variability, especially the loss of information (Dufour-Rainfray et al., 2020; Boudah et al., 2012). The samples are then analysed using sophisticated analytical platforms, including NMR, which senses the particular resonance interest patterns of the metabolites in a magnetic field and the MS measuring the mass/load ratio of metabolites in their ionized form while separating them. The data obtained in spectra are then analysed (Cheung et al., 2019).

Spectral analysis allows the characterization of a specific metabolic signature (*metabolite fingerprinting*); however, the metabolites from the signals or peaks are still not recognized at this phase. It prevents the validation/qualification of the resulting molecular markers. The data is first processed automatically to design a matrix to produce the desired information. It is then subjected to statistical analyses to identify the differences between the sick and healthy samples. At this level, metabolites of interest can be identified through databases and/or analytical technologies that elucidate their three-dimensional structure, such as 2D-NMR or MS/MS (metabolic profiling**).** Once the molecular marker(s) of interest has been recognized, it is finally possible to proceed to the next step of establishing targeted and validated tests to quantify these exact compounds with a sum of acceptable sensitivity and imprecision, allowing subsequent clinical use (Figure 1). However, in addition to sample preparation, careful attention should be paid to the analytical and statistical methods used, since variances can hamper the comparability of outcomes among studies and consequently compromise the discovery of novel biomarkers) (Dufour-Rainfray et al., 2020; Cheung et al., 2019; Andrisic et al., 2018; Christians et al., 2017; Boudah et al., 2012).

The different steps are similar between the targeted and non-target approaches; the biggest difference is in the discovery of metabolites (Figure 1). Metabolites are selected and recognized from the outset in the targeted workflow; only these metabolites are studied, while metabolite detection is the last step in the non-targeted approach: only statistically relevant signals between different patient groups are detected (Dufour-Rainfray et al., 2020).

The metabolic phenotype of individuals results from the expression of genes and their interactions with the environment. Exposome: all exposures to environmental factors, as well as lifestyle (physical activity, emotional stress, etc.), are both environmental pressures that can alter it through epigenetics (red arrows), which may be the cause of a tumor phenotype. Metabolomics is downstream of genomics, transcriptomics, and proteomics (omics technologies). These four main levels of biological investigation are concerned with the study of the central dogma of molecular biology (DNA, RNA, proteins, and metabolites) using NGS –based analysis (green rectangle) in the case of genomics and transcriptomics or Analytical techniques–based analysis (salmon rectangle) in the case of proteomics and metabolomics. Of the four, metabolomics confers the measure that is the closest to the phenotype (arrow in salmon), it studies the metabolome: the last level of cell regulation, located after the genome, transcriptome, and proteome and the complete collection of metabolites from the organism (in green) or the environment (in red). These small molecules contribute to the regulation of several cellular processes, the allosteric regulation of proteins, post-transcriptional modification of RNA, and epigenetic modifications of DNA (purple arrows). Metabolomic studies follow a fairly similar methodological pipeline (black arrows). The difference between the targeted and non-targeted metabolomics workflow are highlighted through blue (targeted approach) and green (non-targeted approach) arrows. The green arrow in dashes shows the value of using the targeted approach in validating the results of the non-target approach.

Metabolomics is a novel source of biomarkers

Several metabolomic studies were conducted aiming at the discovery of novel prospective biomarkers permitting timely detection of different types of cancers, based on the analysis of biofluids (urine, serum, plasma, saliva, seminal fluid, and sweat) and tissues. These attempts were performed by the usage of robust, sophisticated analytical platforms, such as NMR and MS.

Table 1 outlines certain research based on cancer type while quoting different techniques used and highlighting metabolites with significantly modified expression in cancer samples. To begin with, in breast cancer, different biological matrices have been explored (blood, tissue, urine, saliva, exhaled breath) by resorting to diverse analytical techniques, mainly NMR and MS with their different variants, aiming to evaluate metabolites concentration levels that significantly changed in a cancer case. Thereby, an increase in certain metabolites rates such as creatine, glutamine, lysine, valine, glucose, and creatinine, accompanied by a decrease of rates of lipoproteins, glycoproteins, unsaturated lipids, lipids, acetone, and glycerol-derived compounds, have been observed in tumor tissues, by an NMR-based analysis. Another analysis based on the GC-MS technique emphasized a cytidine-5-monophosphate / pentadecanoic acid metabolic ratio as a significant discriminator between cancer and normal tissues (Cheung et al., 2019, Budczies et al., 2012). Elsewhere, 14 potentially interesting metabolites (proline, alanine, lactate, threonine, glutathione, glutamine, leucine, taurine, isoleucine, glutamate, valine, choline, Myo-inositol, and glucose) were distinguished and quantified in a record time (20 minutes) from cancer cell extracts analysis based on 2D NMR that be dependent on a spatial encoding procedure, qualified as a robust tool that allows quantitative analysis of complex matrices (Le Guennec et al., 2012).

Otherwise, for biofluids, blood samples became an attractive source of many breast cancer studies. Notably, Lécuyer et al., 2018; 2019, demonstrated respectively, using NMR-based and LC-MS-based analysis of blood samples from a cohort of women attenuated by breast cancer and healthy subjects, higher fasting plasma levels of creatine, lysine, valine, glutamine, arginine, glucose, creatinine, norvaline and lower fasting plasma levels of lipids, glycoproteins, lipoproteins, glycerol, acetone, unsaturated lipids, derived compounds, and o-succinyl-homoserine, constituted a plasma metabolic signature associated to a higher risk of developing breast cancer as well as, lower rates of o-succinyl-homoserine and higher rates of valine, glutamine, γ-glutamyl-threonine, norvaline, isoglutamine, 5-aminovaleric acid, phenylalanine, tryptophan, acetyl tributyl citrate, and pregnene-triol sulfate were also related by lasting breast cancer threat (Lécuyer et al., 2019; Lécuyer et al., 2018).

Additionally, analysis based on UPLC-MS-MS, LC-MS and NMR of blood (serum) also allowed, respectively, the highlighting of an increase of acetyl-L-alanine, indoxyl sulfate and kynurenine and a decrease of 5-oxo-L-proline post-chemotherapy in a cohort of women diagnosed with early-stage breast cancer, offering a better elucidation of biological mechanisms associated with the development of psychoneurological symptoms post-chemotherapy (Lyon et al., 2018) ; the identification of 9 metabolites (prostaglandin C1, ricinoleic acid, oleic acid amide, ethyl docosahexaenoic, hulupapeptide, lysophosphatidylethanolamine, cysteinyl-lysine, methacholine, and vitamin K2) that were used as a model allowing the prediction of chemotherapy response, with a specificity of 100% and sensitivity of 81.2% (Lin et al., 2019a) ; the discovery of a metabolic panel significantly correlating with breast cancer recurrence after surgery within early-stage patients, characterized by significantly lower levels of histidine and higher levels of glucose and lipids compared with patients with no relapse. Based on that, a predictive risk model that predicted relapse with 90% sensitivity, 67% specificity, and 73% predictive accuracy was proposed to evaluate relapse risk and avoid unnecessary adjuvant treatments and their associated toxicities within patients presenting low recurrence risk (Tenori et al., 2015).

Another study (Playdon et al. 2017) claimed to be the first to utilize metabolomics to agnostically assess prediagnostic circulating diet-related metabolites about breast cancer hazard, the analysis of blood samples by GC-MS and LC-MS-MS techniques demonstrated an association of 3 nutritional metabolites caprate (decanoic acid); γ –carboxyethyl hydrochroman (γ –CEHC); and 4-androstane-3b,17b-diol-monosulfate with overall breast cancer risk in a post-menopausal cohort, and a significant correlation between higher levels of metabolites related to alcohol, butter and fried food such as α-hydroxyisovalerate, caprate, some androgynes and 2-hydroxyoctanoate and estrogen receptor (ER)–positive (ER+) breast cancer (Playdon et al., 2017).

Furthermore, discriminatory metabolites between

different breast cancer subtypes have been identified through an NMR-based analysis of cancer patients' blood and tissues. Increased serum levels of valine, carnitine, proline, lysophosphatidylcholine, and 2-octenedioic acid characterized the HER2-positive subtype, whereas higher concentrations of glycochenodeoxycholic acid characterized the ER-positive sub-type (Chen et al., 2019). Otherwise, lower rates of glutamine and higher rates of glutamate, 2-hydroglutarate, xanthine, and particularly β-alanine have been observed in tissues of patients diagnosed with ER-negative sub-type when compared to ER-positive patients (Budczies et al., 2013).

Moreover, reported studies based on urine and saliva provided evidence of significant changes in metabolites rates that could represent potential biomarkers (Dinges et al., 2019; Tsutsui et al., 2013). Besides, exhaled breath from a cohort of healthy individuals and breast cancer patients' analysis using SESI-MS permitted the identification of 8 discriminatory features corresponding to m/z 106, 126, 147, 78, 148, 52, 128, 315, with a sensitivity and a specificity above 0.9. This pilot study assumed that the detection of cancer–related metabolic volatile profile is possible (Sinues et al., 2015). Ultimately, according to Yang et al, 2020, in their review, where they analyzed *High frequency clinical metabolic biomarkers related to BC diagnosis*, tyrosine was found to be the most frequent biomarker metabolite in multiple studies, followed by alanine, glutamic acid, valine, phenylalanine, glutamine, lysine, isoleucine, histidine, choline, glycine, and arginine respectively, thus composing the top ten most frequent clinical metabolic biomarkers (Yang et al., 2020).

In the colorectal cancer case, several studies were established on different biological samples, namely, tumoral tissues, fecal samples, blood, urine, as shown in Table 1. First, tumor tissues analysis engaged the use of robust analytical platforms for instant HR-MAS-NMR that was solicited by different studies, including Jiménez et al., 2013; Tessem et al., 2010 and Chan et al., 2009 where multiple potential biomarkers have been elucidated, such as choline, tyrosine, phenylalanine, and isoglutamine Jiménez et al., 2013); glycerophosphocholine (GPC) and Myo-inositol (Tessem et al., 2010); PEG (polyethyleneglycol), glucose and scylloinositol (Chan et al., 2009). More particularly, the noticed increase in taurine and lactate rates was common in all three studies; on top of that, high rates of glycine were also commonly demonstrated in the works of (Tessem et al., 2010) and Chan et al., 2009). More of that, decreased levels of lipids were observed in both (Jiménez et al., 2013) and (Chan et al., 2009) studies. Moreover, GC-MS-based tumor tissue analysis demonstrated higher levels of lactate and L-phenylalanine and lower glucose levels (Chan et al., 2009). Likewise, in a MALDI-TOF-MS and 2D-MS-MS-based analysis of tumor tissues, results obtained were characterized by higher fucosylation and sialylation and lower acetylation, sulfation, and reduced expression of globo-type glycans (Cheung et al., 2019, Holst et al., 2013).

Regarding the use of fecal samples, they presented a potential biomarker source, as many prior works that linked fecal metabolites from healthy and colorectal cancer (CRC) patients were able to discriminate them, for instant Phua et al., 2014, established proof-of-principle for GC-TOF-MS-based fecal metabonomic detection of CRC (Phua et al., 2014). However, the complete mechanistic association among colonic tissues and feces of CRC patients is still restricted (Lin et al., 2019b). Whereas, in a similar study of colonic tumor tissues and their normal adjacent tissues alongside patient-matched feces study, using 1H-NMR, a set of overlapping discriminatory metabolites were recognized, together with higher levels of alanine, succinate, glutamate, lactate, and decreased levels of butyrate in both tumoral tissues and fecal samples. Besides, fecal acetate levels are certainly linked to Myo-inositol and glucose alterations in tumoral tissues. Therefore, the fecal metabolic signature could reflect the microenvironment of the CRC tissue, highlighting the importance of the separate fecal metabolic profiles as potential novel and non-invasive relevant CRC detection indicators as the findings appeared to be promising (Lin et al., 2019b).

Many investigations were performed to improve lung cancer's usually late diagnosis, following the lack of initial signs and the absence of effective screening tools. Among them, the Miyamoto et al., 2015 study found through a GC-TOF-MS analysis significantly altered levels of certain metabolites in the blood of cancerous patients, reflecting alterations in lipid metabolism, fatty acid, amino acid, and energy (Miyamoto et al., 2015). On the other hand, the review study by Dinges et al., 2019, which was interested in metabolomic markers in urine, reported significantly altered urinary levels of creatinine, phenylalanine, and hippurate in patients with lung cancer, demonstrated in two studies (Dinges et al., 2019). In addition, the LC-Q-TOF-MS/MS sweat analysis highlighted the ability of some metabolites, mainly trisaccharide

phosphate, to differentiate among healthy controls and lung cancer patients, together with active smokers with high specificity and sensitivity (Calderón-Santiago et al., 2015). Biofluids are an interesting source of non-invasive or minimally invasive metabolic markers.

As far as prostate cancer (PCa) is concerned, metabolomic studies using NMR and MS have also been carried out on different matrices (tissue, blood, urine) to find novel biomarkers that are more specific and sensitive. Indeed, tissue studies have shown significant accumulation of certain metabolic intermediates in the tricarboxylic acid (TCA) cycle, indicating hyperactivation of the Tricarboxylic Acid (TCA) cycle in tumor tissues (prostate cancer). Besides that, amounts of malate and fumarate were greatly associated with the tumor phase) (Shao et al., 2018). Altered levels of metabolites primarily involved in fatty acids, energy metabolism, amino acids, choline, and uridine were observed at tissue levels, serum, and urinary tract of Pca patients and thus provided potential biomarkers diagnosis. Citrate and glutamine have been downregulated in all three samples (Zheng et al., 2020). Furthermore, NMR, GC-MS, and LC-MS analyses of biofluids have also identified many potential diagnostic biomarkers of PCa, including the syringe, tryptophan, tyrosine, citrulline, and leucine (Dinges et al., 2019), some TCA intermediates, fatty acids, and carnitines (Struck-Lewicka et al., 2015) and some volatile compounds at the urinary level (Khalid et al., 2015) as well as citrate, spermin, myoinositol at the level of prostatic and seminal fluids of cancerous patients (Lima et al., 2016).

As far as bladder cancer is concerned, studies on biofluids via NMR and MS have shown very encouraging results for its non-invasive diagnosis and early detection. Indeed, the analysis of blood samples by NMR has revealed distinct serum profiles between cancerous patients, individuals suffering from calculi, and healthy controls. Serum samples from bladder cancer patients have shown decreased levels of citrate, lactate, isoleucine/leucine, glycine, tyrosine, and higher levels of glucose and lipids compared to those of healthy individuals (Cao et al., 2012). In addition, in the urine analyses, the Cheng et al., 2018 study conducted via the LC-HRMS has revealed a panel of metabolites allowing the distinction between high-grade Non-Muscle-Invasive Bladder Cancer NMIBC patients and healthy controls, low-grade NMIBC patients and healthy controls, as well as high-grade NMIBC and low-grade NMIBC patients. Moreover, this study has reported high urinary stages of metabolites complicated in the metabolism of fatty acids and low levels of those involved in their oxidation in cancerous patients compared to healthy controls, which reinforces the Warburg theory (Cheng et al., 2018). At the same time, Dinges et al., 2019 have reported in their review significantly altered urinary levels of 18 metabolites, including main citrate, ribitol, and 2,5-furan dicarboxylic acid, which have been encountered in more than three studies and that 5 MS studies have been able to differentiate successfully, the different stages of tumors, their grades as well as recurrence in bladder cancer (Dinges et al., 2019).

Moreover, in pancreatic cancer studies, the Luo et al., 2020 study has found significant variations in plasma levels of different metabolites through LC-TQ-MS analysis in plasma and tissue specimens of cancerous and healthy control patients while highlighting the ten main discriminatory metabolites, including five validated: sphinganine, beta-sitosterolcreatine, inosine, and glycocholic acid, which when integrated into one pattern offer a much greater detailed and specificity to directly diagnose this cancer compared to common biomarkers. Gluconic acid and succinic acid have shown a huge ability to observe the development and metastasis of pancreatic cancer at dissimilar phases (Luo et al., 2020). At the same time, the metabolomic NMR of blood has revealed a significant difference in serum concentrations of certain metabolites, including lactate, creatinine, and 3-hydroxybutyrate between cancerous pancreatic patients and normal controls (Yang et al., 2011) and a variation in plasma levels of a group of potentially biomarker metabolites, distinguishing between PC patients, those with chronic pancreatitis and healthy individuals. Besides, CE-TOF-MS saliva analyses have revealed eight metabolites that distinguish between healthy individuals and pancreatic cancer patients. Thus, metabolomics approaches based on NMR and MS seem promising in the non-invasive diagnosis of pancreatic cancer and its early detection (Sturque et al., 2019, Zhang et al., 2012).

Metabolomics work is a relevant source of various potential and non-invasive biomarkers for oral cancer cases. Indeed, the Ishikawa et al., 2019 study was the first of its kind to identify salivary metabolites distinguishing between patients with oral squamous cell carcinoma/epithelial dysplasia (OSCC/OED) and those with suspected persistent oral mucosal lesions (PSOML), instead of differing only between patients

with oral cancer and healthy individuals (Ishikawa et al., 2019). In particular, the CE-TOF-MS analysis of saliva and tumor tissue has revealed significant alterations in the expression of several metabolites, including 17 metabolites whose increase was perceived at the tissue level as well as in saliva (Ishikawa et al., 2016). Finally, about stomach, liver, and esophageal cancers, metabolomics has been an effective means to discover various potential and non-invasive metabolic markers for early diagnosis (Table 1).

Table-1: Summary of metabolites related to cancer

Cancer type	Technique	Biological sample	Metabolite	References
*Colorectal cancer	HR-MAS NMR	Tumoral tissue	Increase: isoglutamine, choline, phosphocholine, taurine, lactate, tyrosine, and phenylalanine. Decrease: lipids and triglycerides	(Jiménez et al., 2013)
	HR-MAS NMR	Tumoral tissue	Increase: lactate, glycine, taurine. Decrease: Myo-inositol, glycerophosphocholine (GPC)	(Tessem et al., 2010)
	MALDI-TOF-MS 2D LC-MS/MS	Tumoral tissue	Increase: fucosylation and sialylation Decrease: acetylation, sulfation, glycans	(Holst et al., 2013)
	GC-MS	Tumoral tissue	Increase: lactate, phosphate, l-glycine, 2-Hydroxy-3-methyl valerate, L-proline, L-phenylalanine, palmitic acid, margaric acid, oleic acid, stearic acid, uridine, 11,14-eicosadienoic acid, 11-eicosenoic acid,1-monooleoyglycerol, 1-O-heptadecylglycerol, propyl octadecanoic, cholesterol Decrease: fumarate, malate, D-mannose, D-glucose, D-galactose, 1-hexadecanol, arachidonic acid.	(Chan et al., 2009)
	HR-MAS NMR	Tumoral tissue	Increase: ChoCC (choline-containing compounds), taurine, scyllo-inositol, glycine, PE (phosphoethanolamine), lactate, PC (phosphocholine) Decrease: lipids, PEG (polyethylene glycol), glucose	
	NMR	Tumoral tissue	Increase: lactate, glutamate, alanine, choline, succinate, taurine, glycine Decrease: butyrate, glutamine, myoinositol, creatine, glucose	(Lin et al., 2019b)
		Fecal sample	Increase: glutamate, lactate, alanine, succinate Decrease: butyrate, propionate, acetate	
	GC-TOF-MS	Fecal sample	Decrease: fructose, linoleic acid, nicotinic acid	(Phua et al., 2014)
	GC-MS	Blood	L-alanine, glucuronoic lactone, L-glutamine	(Ikeda et al., 2012)
	GC-TOF-MS UPLC-Q-TOF-MS	Blood	Increase: 2-aminobutyrate, 2-hydroxybutyrate, 2-oxobutyrate Decrease: indoxyl, indoxyl sulfate, N-acetyl-5-hydroxytryptamine	(Tan et al., 2013)
	NMR	Blood	Increase: 3-hydroxybutyrate, acetate, formate, glycerol, lipid (-CH_2-OCOR), N-acetyl signal of glycoproteins, phenylalanine, and proline Decrease: alanine, citrate, creatine, glutamine, peptide NHS, lactate, leucine, pyruvate, tyrosine, valine	(Bertini et al., 2012)
	GC-TOF-MS	Blood	Increase: pyruvate, lactate, 2-hydroxybutyric acid, 3-hydroxybutanoic acid, malic acid, oleic acid Decrease: urea, valine, leucine, proline, threonine, threonic acid, 4-hydroxyproline, citrulline, 2-Piperidinecarboxylic acid, ornithine, hippurate, lysine, tyrosine, tryptophan, oleamide, uridine	(Qiu et al., 2009)
	UPLC-Q-TOF-MS	Blood	Increase: glycerol phosphate, pyruvic acid, lactate, carnitine Decrease: tyrosine, uridine, phenylalanine,	

			tryptophan, mysti acid, palmitic acid, nervonic acid, arginine, glutamic acid, nicotinamide, dopamine	
	GC-TOF-MS	Urine	Increase: fumarate, putrescine, 4-hydroxybutyrate, two aminobutyrate Decrease: pyruvate, myristate citrate, homovanillate, phenol, p-cresol, hippurate, uracil, hydroxy acetate, xylose, arabitol, glucuronate, sorbose, threonine, alanine	(Cheng et al., 2012)
	UPLC-Q-TOF-MS	Urine	Increase: acetyl-creatinine, histidinol Decrease: urea, myristate, tryptophan, kynurenate, 5-hydroxy-tryptophan, indole-acetate, indole, tyrosine, 4-aminohippurate, trimethylamine N-oxide, uridine, pyridoxal (B6 vitamin), 2-hydroxyestradiol, N-acetyl-l-lysine, creatinine	
	GC-MS	Urine	Increase: 5-hydroxyindoleacetate, 5-hydroxytryptophane, tryptophan, 5-oxoproline, N-acétyl-aspartate, 2-hydroxyhippurate, phenylacetate, phenylacetylglutamine, hydroxyphenylacetate Decrease: succinate, isocitrate, citrate, 3-methyl-histidine, histidine	(Qiu et al., 2010)
	NMR/MS	Urine	Decrease: alanine, hippurate	(Dinges et al., 2019)
*Prostate cancer	GC-MS	Tumoral tissue Blood Urine	Increase: uridine, formate Decrease: citrate, creatinine, acetate, leucine, valine, glycine, lysine, histidine, glutamine, choline	(Zheng et al., 2020)
	GC-MS	Tumoral tissue	Increase: Glycerol-3-phosphate, proline, malate, fumarate, succinate, 2-Hydroxyglutaric acid (2-HG), fatty acids, glycerolipids, Myo-inositol, alanine, uracil	(Shao et al., 2018)
	GC-MS LC-MS	Blood	Increase: palmitic acid, myristic acid, linolenic acid, aspartic acid, choline, vitamin B2, alanine, isoleucine, lysine, cysteine, cholate, glycocholate, sarcosine, alanine, pyruvate Decrease: acid stearic, lysophosphatidic-choline, serotonin, methyl-malonic acid, glutamine, valine, tryptophan, carnitine, glycine.	(Lima et al., 2016)
	GC-MS LC-TOF-MS	Urine	Increase: sphingolipids hydroxysphinganine, C16 sphingosine. Decrease: glycine, serine, threonine, alanine indole, hippurate, hydroxyhippurate, tryptophan, kynurenate, tyrosine, indole acetate, indolelectate, quinate, phenylacetamide, isocitrate, aconitate, succinate, sucrose, sorbose, arabinose, arabitol, inositol, galactaric acid, dimethylheptanoyl carnitine, propanoylcarnitine, butyrylcarnitine, octanoyl carnitine	(Struck-Lewicka et al., 2015)
	GC-MS	Urine	Increase: pentanal Decrease: 2,6-dimethyl-7-octen-2-ol, 3-octanone, and 2-octanone	(Khalid et al., 2015)
	NMR MS	Urine	Decrease: serine, tryptophan, tyrosine, citrulline, leucine	(Dinges et al., 2019)
	NMR	Seminal liquid Prostatic liquid	Decrease: citrate, spermine, myoinositol	(Serkova et al., 2008)
*Breast cancer	NMR	Tumoral tissue	Increase: valine, lysine, arginine, glutamine, creatine, creatinine, glucose Decrease: lipoproteins, lipids, glycoproteins, acetone, glycerol derived compounds, unsaturated lipids	(Cheung et al., 2019)

	GC-MS	Tumoral tissue	Cytidine monophosphate Pentadecanoic acid	(Budczies et al., 2012)
	NMR	Cellular extract	Alanine, lactate, leucine, threonine, taurine, glutathione, glutamate, glutamine, choline, valine, isoleucine, Myo-inositol, proline, glucose	(Le Guennec et al., 2012)
	NMR	Sang	Increase: valine, lysine, arginine, glutamine, creatine, creatinine, glucose, norvaline Decrease: lipoproteins, lipids, glycoproteins, acetone, glycerol derived compounds, unsaturated lipids, o-succinyl-homoserine	(Lécuyer et al., 2019; Lécuyer et al., 2018)
	UPLC-MS-MS	Blood	Increase: acetyl-L-alanine, indoxyl sulfate, kynurenine Decrease: 5-oxo-L-proline	(Lyon et al., 2018)
	LC-MS	Blood	Prostaglandin C1, ricinoleic acid, oleic acid amide, ethyl docosahexaenoic, hulupapeptide, lysophosphatidylethanolamine, cysteinyl-lysine, methacholine, vitamin K2	(Lin et al., 2019a)
	NMR	Blood	Increase: glucose, lipids Decrease: histidine	(Tenori et al., 2015)
	GC-MS LC-MS-MS	Blood	Decanoic acid (caprate), γ-carboxyethyl hydrochromane (γ-CEHC; saturated fatty acid), -tocopherol (vitamin E derivative), 4-androsten-3β,17β-diol-monosulfate (androgen) Metabolites related to ER+: androgens, α-hydroxyisovalerate, caprate, 2-hydroxyoctanoate	(Playdon et al., 2017)
	NMR	Blood	1-HER2-positive: increase of carnitine, lysophosphatidylcholine, proline, valine, 2-octenedioic acid 2-ER-positive: increase of glycochenodeoxycholic acid	(Chen et al., 2019)
		Tumoral tissue	3-ER-negative: Increase: beta-alanine, glutamate, xanthine, 2-hydroyglutarate Decrease: glutamine	(Budczies et al., 2013)
	LC-MS-MS GC-TOF-MS	Tumoral tissue Blood	Phosphatidylcholines Cytidine-5 monophosphate, pentadecanoic acid	(Jacob et al., 2019)
	RMN MS	Urine	Increase: 5-hydroxymethyl-2-deoxyuridine, 8-hydroxy-2-deoxyguanosine, succinyladenosine Decrease: valine, leucine, succinate, hippurate, sucrose, uracile, alanine	(Dinges et al., 2019)
	UPLC-ESI-MS/MS	Urine	Increase: 8-oxo-dG	(Guo et al., 2017)
	ESI-MS-MS	Urine	Increase: hydroxymethyl-2′-deoxyuridine, 8-hydroxy-2′-deoxyguanosine, 1-methyladenosine, N ,N -dimethylguanosine	(Cho et al., 2009)
	UPLC-MS-MS	Saliva	Increase: Ac-SPM, DAC-SPD, DAC-SPM (polyamines)	(Tsutsui et al., 2013)
	CE-LC-MS	Saliva	Increase: Spermine	(Murata et al., 2019)
	SESI-MS	Exhaled breath	8 discriminatory features corresponding to to m/z 106, 126, 147, 78, 148, 52, 128, 315	(Sinues et al., 2015)
	MS NMR	Tumoral tissue, blood, urine, saliva	Tyrosine, alanine, glutamic acid, valine, phenylalanine, glutamine, lysine, isoleucine, histidine, choline, glycine, arginine	(Yang et al., 2020)
Liver cancer	NMR	Blood	Increase: very-low-density lipoprotein, ketone	

	MS		bodies (such as acetone and beta-hydroxybutyrate), 2-oxoglutarate, bile acids (glycochenodeoxycholic acid, glycocholic acid, deoxycholic acid, cholic acid). Decrease: lysophosphatidylcholines (LPC)	(Kim et al., 2016)
		Urine	Increase: methylated purines (7-methylguanine, 1-methylguanine, N-dimethylamine, 1-methylhypoxanthine, adenine, nucleosides adenosine, cytidine, and inosine)	
	NMR MS	Urine	Increase: creatine, glycocholic acid, acetylcarnitine, carnitine, glycine, spermidine, spermine, hypoxanthine, oxoglutarate, threonine, α-N-Phenylacetyl-L-glutamine Decrease: phosphate, urea, hippurate, citrate, cysteic acid, xylonate, glycine, xylitol, trimethyl-amine-N-oxide, creatinine	(Dinges et al., 2019)
Esophagus cancer	GC-MS	Blood	Malonic acid, L-serine	(Ikeda et al., 2012)
	NMR	Blood	Increase: β-hydroxybutyrate, acetoacetate, creatine, creatinine, lactate, glutamate, glutamine, histidine Decrease: tyrosine, α-glucose, β-glucose, acetate, unsaturated lipids, LDL/VLDL	(Zhang et al., 2013)
Stomach cancer	GC/MS	Blood	3-hydroxy propionic acid Pyruvic acid	(Ikeda et al., 2012)
	NMR MS	Urine	Increase: lactate, alanine, phenyl acetyl glycine, arginine, taurine, tyrosine, leucine, valine, 3-indoxyl sulfate, formate Decrease: citrate, méthylnicotinamide, succinate	(Dinges et al., 2019)
Bladder cancer	RMN	Sang	Increase: lipids and glucose. Decrease: isoleucine/leucine, tyrosine, lactate, glycine, citrate	(Cao et al., 2012)
	RMN MS	Urine	Increase: acetylcarnitine, adipate, lactate, taurine, valine, 3-hydroxysebacic acid, erythritol Decrease: ribonic acid, 2,5-furan dicarboxylic acid, 7-methylxanthine, succinate, hippurate, citrate, phenylacetylglutamine, ribitol, gluconate, fructose, glycerol	(Dinges et al., 2019)
	LC-HRMS	Urine	High-grade **NMIBC** / healthy control: Dopamine 4-sulfate, aspartyl-histidine, tyrosyl-methionine Low-grade **NMIBC** / healthy control: 3-hydroxytetradecanoyl carnitine, 3-hydroxy-5, 8-tetradecadiencarnitine, 3-hydroxy-cis-5-tetradecenoylcarnitine, and O-decanoyl-L-carnitine High-grade **NMIBC**/ Low-grade **NMIBC**: 5-hydroxyindoleacetaldehyde L-3-hydroxykynurenin	(Cheng et al., 2018)
Pancreas cancer	NMR MS	Sang	Increase: isoleucine, triglyceride, leucine, creatinine Decrease: 3-hydroxybutyrate, 3-hydroxyisovalerate, lactate, trimethylamine-N-oxide	(Yang et al., 2011)
			Increase: N-acetyl glycoprotein (NAG), dimethylamine (DMA), very low-density lipoprotein (VLDL), acetone Decrease: 3-hydroxybutyrate, lactate, high-density lipoprotein (HDL), low-density lipoprotein (LDL), citrate, alanine, glutamate, glutamine, histidine, isoleucine, lysine, valine	(Zhang et al., 2012)
	CE-TOF-MS	Saliva	Leucine, isoleucine, tryptophan, valine, glutamic acid, phenylalanine, glutamine, aspartic acid	(Sturque et al., 2019)
	LC-TQ-MS	Tumoral tissue	Increase: taurocholic acid, taurochenodeoxycholic	

		Blood	acid, taurodeoxycholic acid, tauroursodeoxycholic acid, glycocholic acid, melatonin, taurohyodeoxycholic acid, malonic acid, sphinganine, beta-sitosterol, glycochenodeoxycholic acid, uridine 5'-monophosphate, caproic acid, gluconic acid, succinic acid, dehydrocholic acid, methylmalonic acid, agmatine Decrease: spermidine, inosine, hippuric acid, D-fructose, glucose, hypoxanthine, creatine, L-aspartic acid	(Luo et al., 2020)
*Lung cancer	RMN MS	Urine	Increase: creatinine, phenylalanine Decrease: hippurate	(Dinges et al., 2019)
	LC-Q-TOF-MS-MS	Sueur	Trisaccharide phosphate, trihexose, nonanedioic acid, and a tetrahexose, suberic acid, monoglyceride MG	(Calderón-Santiago et al., 2015)
	GC-TOF-MS	Blood	Increase: maltose, palmitic acid, glycerol, ethanolamine, glutamic acid, lactic acid Decrease: tryptophan, lysine, histidine	(Jacob et al., 2019; Miyamoto et al., 2015)
Oral/buccal cancer	CE-TOF-MS	Saliva	Decrease: ornithine, carnitine, arginine, o-hydroxybenzoate, N-acétylglucosamine-1-phosphate et ribose 5-phosphate (R5P)	(Ishikawa et al., 2019)
	CE-TOF-MS	Tumoral tissue	Increase: lactate, arginine, ornithine, S-Adenosylmethionine Decrease: glyceraldehyde 3-phosphate (3PG) and phosphoenolpyruvate (PEP), homocysteine	(Ishikawa et al., 2016)
		Saliva	Increase: 43 saliva metabolites (such as S-adenosylmethionine (SAM) and pipecolate)	

Notes:
HR-MAS-NMR : high resolution magic-angle spinning nuclear magnetic resonance spectroscopy / MALDI-TOF-MS : Matrix-assisted laser desorption ionization-time of flight mass spectrometry / 2D LC-MS/MS : 2 Dimentional Liquid Chromatography Tandem Mass Spectrometry / GC-MS : Gas chromatography-mass spectrometry / RMN : Nuclear Magnetic Resonance / GC-TOF-MS : Gas chromatography- Time-of-Flight-mass spectrometry / UPLC-Q-TOF-MS : ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry / LC-MS : liquid chromatography-mass spectrometry / LC-TOF-MS : liquid chromatography time of flight mass spectroscopy / UPLC-MS-MS : ultra-performance liquid chromatography tandem mass spectrometry / UPLC-ESI-MS/MS : ultra-performance liquid chromatography -Electrospray Ionization- tandem mass spectrometry / ESI-MS-MS : Electrospray Ionization-tandem mass spectrometry / CE-LC-MS : Capillary electrophoresis–liquid chromatography-mass spectrometry / SESI-MS : Secondary electro-spray ionization-mass spectrometry / LC-HRMS : liquid chromatography–hight resolution mass spectrometry / CE-TOF-MS : Capillary electrophoresis–time of flight-mass spectrometry / LC-TQ-MS : liquid chromatography coupled with a triple quadrupole electrospray tandem mass spectrometry / LC-Q-TOF-MS-MS : liquid chromatography quadrupole time of flight tandem mass spectrometry / NMIBC : Non-muscle invasive bladder cancer. / * this indicates the top 4 most widespread cancers in the world in the respective incidence order: lung 11.6%, breast 11.6%, colorectal 10.2%, prostate 7.1%. Globocan, 2018.

DNA lesions, a potential biomarker for different cancer types

Humans are frequently exposed to numerous exogenous or endogenous agents that simultaneously damage DNA (ultraviolet UV radiation, chemical carcinogens, free radicals, cellular metabolites, etc.). This exposure generates a complex set of DNA lesions, affecting a huge cell number in the body and occurring at a rate of 10000 to 1000000 molecular lesions per cell per day (Alhmoud et al., 2020; Figueroa‐González and Pérez‐Plasencia, 2017). As a result of this damage, cellular responses allowing the cell to eliminate the various lesions formed through a variety of repair processes are induced to maintain the integrity of the genome. In certain cases, however, these genetic modifications cause changes in the physiology of cells (Interruption of replication, mutations, etc.) and disrupt the function of vital enzymes (decrease in DNA repair capacity) and the stability of the genome. This, in turn, promotes the accumulation of non-voluminous lesions and initiates the tumor (Figueroa‐González and Pérez‐Plasencia, 2017; Ignatov et al., 2017; Mouw et al., 2017; You and Wang, 2016). In addition, it has been identified that DNA oxidative damage is involved in cancer. Highly reactive • OH able to react straight with DNA and cause the development of a range of lesions such as sole nucleoside lesions. These include 8-oxo-7,8-

dihydro-2'-deoxyguanosine (8-oxo-dG), 2,6-diamino-4- hydroxy-5-formamidopyrimidine-2'-deoxynucleeoside (Fapy-dG), 8-oxo-7,8-dihydro-2'-deoxyadenosine (8-oxo-dA), 4,6-diamino-5-formamidopyrimidine 2'-deoxynucleeoside (Fapy-dA), guanidinohydantoïne 2'-désoxynucléoside (dGh), spiroiminodihydantoïne 2'-désoxynucléoside (dSp) et 5,6-dihydroxy-5,6-dihydrothymidine (thymidine glycol) (Yu et al., 2018; Guo et al., 2017; Figueroa‐González and Pérez‐Plasencia, 2017; Krokidis et al., 2017).

Other studies also indicate that reactive oxygen species (ROS) and reactive nitrogen species (RNS), produced by inflammatory cells, cause the formation of oxidative DNA lesions and mutagenic nitratives, such as 8-oxo-7,8-dihydro-2 '- deoxyguanosine (8-oxodG) and 8-nitroguanine, which are commonly involved in molecular mechanisms that induce cancer. These studies also state that infection and inflammation account for about 25% of cancer-causing factors and suggest that DNA damage associated with inflammation in cancer stem cells leads to the development of cancer (Murata, 2018; Kawanishi et al., 2017). In addition, because of their elevated metabolism, cancer cells have been documented to be at a level of high oxidative stress. Most accumulate hundreds to thousands of genomic aberrations that differentiate them from normal non-cancerous cells. Although the appearance of a tumor phenotype may be responsible for only a fraction of these genetic alterations, the study of DNA damage is important for the diagnosis and prognosis of many cancers (Alhmoud et al., 2020; Murata, 2018; Mouw et al., 2017). To recognize the presence or absence of possible biomarkers that allow for early cancer detection, several studies have been carried out to demonstrate the association between the levels of DNA lesions developed and the development of certain forms of cancer.

Among them were those interested in the link among the levels of 8-oxodG in urine, serum or cancer tissue, and breast cancer. It was then found that the rise in 8-oxodG in serum and urine can help as a possible biomarker for screening and prompt discovery of breast cancer while allowing the distinction between early-stage and benign lesions. Whereas its low immunohistochemical expression was linked with an aggressive cancer phenotype, its negative immunolabeling was a strong prognostic factor for cancer-related deaths in breast cancer patients (Nour Eldin et al., 2019; Guo et al., 2017; Sova et al., 2010).

Other studies of the same type of cancer brought to high light levels of succinyl adenosine, 5-hydroxymethyl-2-deoxyuridine, N-dimethyl-guanosine, and 1-methyladenosine (methylated purines) in addition to 8-oxodG in urine samples of cancer patients. Moreover, a targeted metabolic analysis of 14 urinary nucleosides including 8-oxodG revealed lower levels of 8-oxodG and the last three lesions previously cited, in post-operative patients (tumor removal) and normal controls than the preoperative patients. This demonstrates that operation decreases oxidative stress and proves profiling of targeted metabolites is useful to better understand the pathogenesis of breast cancer and facilitate monitoring and evaluation of its medical treatment (Dinges et al., 2019; Cho et al., 2009).

The involvement of 8-oxodG and 8-nitroguanidine in the triggering of cholangiocarcinoma associated with inflammation has also been reported after observing their production, which is much more important in cancerous tissues than in non-cancerous, via the multi-tagging immunofluorescence technique (Double-immunofluorescence staining). A decrease in the urinary rate of 8-OHdG in the progressive phases of lung cancer associated with the preliminary phases was reported in the study by Yano et al. (Yano et al., 2009; Kawanishi et al., 2017). In addition, an association between low tissue levels of 5-Hydroxymethylcytosine (5-hmC) and various human cancers, including pancreatic, lung, liver, breast, and prostate cancers, has been demonstrated and suggests 5-hmC is a potential molecular biomarker useful for cancer recognition and diagnosis (Yu et al., 2018). Furthermore, low levels of hypoxanthine were found in the plasma of individuals with pancreatic cancer. Meanwhile, upper levels of the same metabolite have been observed in the urine of those with liver cancer (Luo et al., 2020; Dinges et al., 2019) and higher stages of the methylated purines (1-methylhypoxanthine, 7-methylguanine, N-dimethylguanine, 1-methylguanine) and adenine in the urine of patients with Hepatocellular Carcinoma (HCC), was also observed (Table 1) (Kim et al., 2016).

It can then be concluded that DNA lesions are potential biomarkers for prompt diagnosis and continuation of cancer treatment, with 8-oxodG as the most common lesion in various types of cancer. Besides, it has been reported that residues of 8-oxodG may be the main contributor to carcinogenesis due to their ability to associate with adenine and cytosine during DNA replication, which cause transverse mutations (GC in TA), the second most common

somatic mutation found in human cancers. Therefore, the presence of 8-oxodG in cells can lead to mutagenesis and cause cancer, so its detection in urine could be the first choice for estimating cancer risk, its early detection, treatment, and prognosis in a non-invasive manner (Guo et al., 2017). Moreover, many methods are available to analyze and quantify DNA lesions, such as Mass spectrometry coupled to liquid chromatography HPLC-MS, which provide information about the location and quantity of DNA damage. UPLC-MS, which is a strong method in the alkylated DNA lesions quantification and NMR spectroscopy, can monitor the base pair at the molecular level and has already allowed the description of the structure of many duplexes with mismatches, which favors lesion detection (Yu et al., 2018; Figueroa‐González and Pérez‐Plasencia, 2017; Lukin and de Los Santos, 2006).

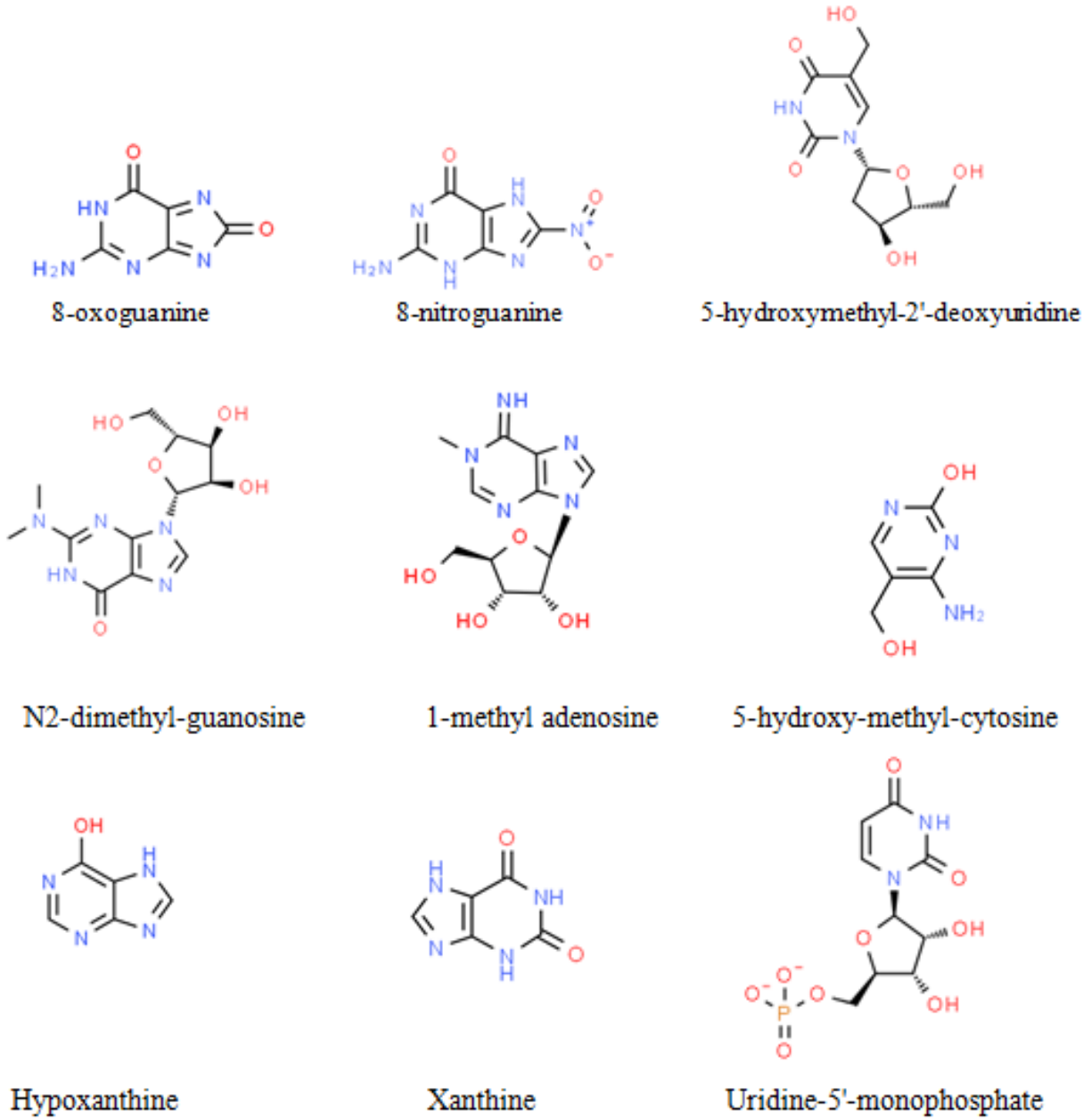

Figure-2: DNA lesions structures from Chemspider (Pence and Williams, 2010).

Conclusion

Even though metabolomics is a relatively emerging field compared to genomics, transcriptomics, and proteomics, it has a significant impact in finding biomarkers linked with several diseases, including cancer. It provides crucial information about different metabolic changes (alterations) occurring throughout cancer and thus reveals certain pathways involved in its manifestation. In addition, it pinpoints various onco-metabolites of which numerous new potential biomarkers can be used to make an early diagnosis and therapeutic monitoring, including DNA lesions 8-oxoguanine, which has manifested in diverse cancers besides breast cancer.

Acknowledgement

This work was supported by University of Algiers 1 (Algeria) and Centre de Recherche Scientifique et Technique en Analyse Physico-chimique – CRAPC (Algeria). The authors would also like to thank the Institute of Bioproduct Development (IBD) and Research Management Center at UTM, Malaysia, and Global Agro Innovation (HK) Limited for partial support through grant No. R.J130000.7609.4C273 and R.J130000.7609.4C336.

Disclaimer: None.
Conflict of Interest: None.
Source of Funding: University of Algiers 1 (Algeria) and Centre de Recherche Scientifique et Technique en Analyse Physico-chimique – CRAPC (Algeria). Global Agro Innovation (HK) Limited through grant No. R.J130000.7609.4C273 and R.J130000.7609.4C336 (partial support).

References

Alhmoud JF, Woolley JF, Moustafa AEA and Malki MI, 2020. DNA damage/repair management in cancers. Cancers, 12: 1050.

Andrisic L, Dudzik D, Barbas C, Milkovic L, Grune T and Zarkovic N, 2018. Short overview on metabolomics approach to study pathophysiology of oxidative stress in cancer. Redox. Biol. 14: 47-58.

Athersuch T, 2019. Metabonomics. Unraveling the exposome. Springer. Cham, Switzerland.

Bellassai N, D'agata R, Jungbluth V and Spoto G, 2019. Surface plasmon resonance for biomarker detection: advances in non-invasive cancer diagnosis. Front. Chem. 7:570.

Bertini I, Cacciatore S, Jensen BV, Schou JV, Johansen JS, Kruhøffer M, Luchinat C, Nielsen DL and Turano P, 2012. Metabolomic NMR fingerprinting to identify and predict survival of patients with metastatic colorectal cancer. Cancer Res. 72: 356-364.

Böhme K, Calo-Mata P, Barros-Velázquez J and Ortea I, 2019. Recent applications of omics-based technologies to main topics in food authentication. Trends Anal. Chem. 110: 221-232.

Boudah S, Roux A and Junot C, 2012. Mise à jour des connaissances-analyse métabolomique par chromatographie liquide couplée à la spectrométrie de masse à haute résolution: état des lieux et perspectives. Spectra Biologie. 31: 22-22.

Boumehira AZ, Arous O, Elsayed E, Hacene H, Yezli N, Sukmawati D and El-Enshasy H, 2019. Application of attenuated total reflection/fourier transform infrared spectroscopy in screening strains producing bioactive molecules: a metabolomics approach. J. Sci. Ind. Res. India. 78: 301-306.

Boumehira AZ, El-Enshasy HA, Hacène H, Elsayed EA, Aziz R and Park EY, 2016. Recent progress on the development of antibiotics from the genus *Micromonospora*. Biotechnol. Bioprocess Eng. 21: 199-223.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A, 2018. Global cancer statistics 2018: GLOBOCAN estimates incidence and mortality worldwide for 36 cancers in 185 countries. CA: Cancer J. Clin. 68, 394-424.

Budczies J, Brockmöller SF, Müller BM, Barupal DK, Richter-Ehrenstein C, Kleine-Tebbe A, Griffin JL, Orešič M, Dietel M and Denkert C, 2013. Comparative metabolomics of estrogen receptor positive and estrogen receptor negative breast cancer: alterations in glutamine and beta-alanine metabolism. J. Proteom. 94: 279-288.

Budczies J, Denkert C, Müller BM, Brockmöller SF, Klauschen F, Györffy B, Dietel M, Richter-Ehrenstein C, Marten U and Salek RM, 2012. Remodeling of central metabolism in invasive breast cancer compared to normal breast tissue–a GC-TOFMS based metabolomics study. BMC genomics. 13: 1-11.

Cai Z and Liu Q, 2019. Understanding the global cancer statistics 2018: implications for cancer control. Sci. China Life Sci. 62: 1-4.

Calderón-Santiago M, Priego-Capote F, Turck N, Robin X, Jurado-Gámez B, Sanchez JC and De Castro MDL, 2015. Human sweat metabolomics for lung cancer screening. Anal. Bioanal. Chem. 407: 5381-5392.

Cao M, Zhao L, Chen H, Xue W and Lin D, 2012. NMR-based metabolomic analysis of human bladder cancer. Anal. Sci. 28: 451-456.

Chan ECY, Koh PK, Mal M, Cheah PY, Eu KW, Backshall A, Cavill R, Nicholson JK and Keun HC, 2009. Metabolic profiling of human colorectal cancer using high-resolution magic angle spinning nuclear magnetic resonance (HR-MAS NMR) spectroscopy and gas chromatography mass spectrometry (GC/MS). J. Proteome Res. 8: 352-361.

Chen Y, Xu J, Zhang R and Abliz Z, 2016. Methods used to increase the comprehensive coverage of urinary and plasma metabolomes by MS. Bioanalysis. 8: 981-997.

Chen Z, Li Z, Li H and Jiang Y, 2019. Metabolomics: a promising diagnostic and therapeutic implement for breast cancer. Onco. Targets Ther. 12: 6797-6811.

Cheng X, Liu X, Liu X, Guo Z, Sun H, Zhang M, Ji Z and Sun W, 2018. Metabolomics of non-muscle invasive bladder cancer: biomarkers for early detection of bladder cancer. Front. Oncol. 8: 494.

Cheng Y, Xie G, Chen T, Qiu Y, Zou X, Zheng M, Tan B, Feng B, Dong T and He P, 2012. Distinct urinary metabolic profile of human colorectal cancer. J. Proteome Res. 11: 1354-1363.

Cheung PK, Ma MH, Tse HF, Yeung KF, Tsang HF, Chu MKM, Kan CM, Cho WCS, Ng LBW and Chan LWC, 2019. The applications of metabolomics in the molecular diagnostics of cancer. Expert Rev. Mol. Diagn. 19: 785-793.

Cho SH, Choi MH, Lee WY and Chung BC, 2009. Evaluation of urinary nucleosides in breast cancer patients before and after tumor removal. Clin. Biochem. 42: 540-543.

Christians U, Klawitter J and Klepacki J, 2017. The role of metabolomics in studying kidney diseases and the development of diagnostic tools, pp. 33-118. In C.L. Edelstein (ed.), Biomarkers of kidney disease. Academic Press. Aurora, CO, United States.

Chuang SL, Su WWY, Chen SLS, Yen AMF, Wang CP, Fann JCY, Chiu SYH, Lee YC, Chiu HM and Chang DC, 2017. Population- based screening program reduces oral cancer mortality in 2,334,299 Taiwanese cigarette smokers and/or betel quid chewers. Cancer. 123: 1597-1609.

Coller HA, 2014. Is cancer a metabolic disease?. Am. J. Pathol. 184: 4-17.

Corinne T, 2017. Dépistage et détection précoce du cancer. Bulletin Infirmier du Cancer. 17: 118-120.

Curry SJ, Byers T and Hewitt M, 2003. Potential of screening to reduce the burden of cancer. In Fulfilling the potential of cancer prevention and early detection. National Academies Press. Washington.

Debnath M, Prasad G and Bisen P, 2010. Omics Technology, pp. 11-31. In Molecular Diagnostics: Promises and Possibilities. Springer. Dordrecht.

Dinges SS, Hohm A, Vandergrift LA, Nowak J, Habbel P, Kaltashov IA and Cheng LL, 2019. Cancer metabolomic markers in urine: evidence, techniques and recommendations. Nat. Rev. Urol. 16: 339-362.

Donovan BM, Bastarache L, Turi KN, Zutter MM and Hartert TV, 2019. The current state of omics technologies in the clinical management of asthma and allergic diseases. Ann. Allergy Asthma Immunol. 123: 550-557.

Dufour-Rainfray D, Lambérioux M, Boulard P, Guidotti M, Delaye JB, Ribeiro MJ, Gauchez AS, Balageas AC, Emond P and Agin A, 2020. Metabolomics–an overview. From basic principles to potential biomarkers (part 2), 158-163. In O. Couturier (ed.), Médecine Nucléaire 44, no. 3. Elsevier Masson. Paris.

Ellero-Simatos S, Claus S and Guillou H, 2019. La métabolomique : applications médicales. Med. des Mal. Metab. 13: 263-267.

Figueroa‐González G and Pérez‐Plasencia C, 2017. Strategies for the evaluation of DNA damage and repair mechanisms in cancer (Review). Oncol. Lett. 13: 3982-3988.

Gika HG, Theodoridis GA, Plumb RS and Wilson ID, 2014. Current practice of liquid chromatography–mass spectrometry in metabolomics and metabonomics. J. Pharm. Biomed. Anal. 87: 12-25.

Globocan, 2018. Cancer observatory, 2018 Retrieved, 20 July 2020 from https://gco.iarc.fr

Gouva E, Nathanailides C, Paschos I, Athanassopoulou F and Pappas I, 2020. Reduced metabolic rate and increased heart beat as early signs of sub lethal copper toxicity in developing Zebrafish. Asian J. Agric. Biol. 8: 119-128.

Gowda GAN, Zhang S, Gu H, Asiago V, Shanaiah N

and Raftery D, 2008. Metabolomics-based methods for early disease diagnostics. Expert Rev. Mol. Diagn. 8: 617-633.

Guo C, Li X, Ye M, Xu F, Yu J, Xie C, Cao X, Guo M, Yuan Y and Zheng S, 2017. Discriminate patients with early-stage breast cancer from benign lesions by detecting oxidative DNA damage biomarker in urine. Oncotarget. 8: 53100-53109.

Holst S, Stavenhagen K, Balog CI, Koeleman CA, Mcdonnell LM, Mayboroda OA, Verhoeven A, Mesker WE, Tollenaar RA and Deelder AM, 2013. Investigations on aberrant glycosylation of glycosphingolipids in colorectal cancer tissues using liquid chromatography and matrix-assisted laser desorption time-of-flight mass spectrometry (MALDI-TOF-MS). Mol. Cell. Proteomics. 12: 3081-3093.

IARC (International Agency for Research on Cancer), 2018. Cancer tomorrow. Global Cancer Observatory GLOBOCAN, Retrieved July 2020 https://gco.iarc.fr/ [Online]. [Accessed].

Ignatov AV, Bondarenko KA and Makarova AV, 2017. Non-bulky lesions in human DNA: the ways of formation, repair, and replication. Acta naturae. 9: 12-26.

Ikeda A, Nishiumi S, Shinohara M, Yoshie T, Hatano N, Okuno T, Bamba T, Fukusaki E, Takenawa T and Azuma T, 2012. Serum metabolomics as a novel diagnostic approach for gastrointestinal cancer, Biomed. Chromatogr. 26: 548-558.

Ishikawa S, Sugimoto M, Kitabatake K, Sugano A, Nakamura M, Kaneko M, Ota S, Hiwatari K, Enomoto A, Soga T, Tomita M and Iino M, 2016. Identification of salivary metabolomic biomarkers for oral cancer screening. Sci. Rep. 6: 2-8.

Ishikawa S, Wong DT, Sugimoto M, Gleber-Netto FO, Li F, Tu M, Zhang Y, Akin D and Iino M, 2019. Identification of salivary metabolites for oral squamous cell carcinoma and oral epithelial dysplasia screening from persistent suspicious oral mucosal lesions. Clin. Oral Investig. 23: 3557-3563.

Jacob M, Lopata AL, Dasouki M and Abdel Rahman AM, 2019. Metabolomics toward personalized medicine. Mass Spectrom. Rev. 38: 221-238.

Jiménez B, Mirnezami R, Kinross J, Cloarec O, Keun HC, Holmes E, Goldin RD, Ziprin P, Darzi A and Nicholson JK, 2013. 1H HR-MAS NMR spectroscopy of tumor-induced local metabolic "field-effects" enables colorectal cancer staging and prognostication. J. Proteome Res. 12: 959-968.

Jobard E, Trédan O, Elena B, Blaise BJ and Bachelot T, 2010. La métabolomique: un nouvel outil pour la recherche translationnelle en cancérologie. Bio. Trib. Mag. 36: 24-29.

Johnson CH, Ivanisevic J and Siuzdak G, 2016. Metabolomics: beyond biomarkers and towards mechanisms. Nat. Rev. Mol. Cell Biol. 17: 451-459.

Kawanishi S, Ohnishi S, Ma N, Hiraku Y, Oikawa S and Murata M, 2017. Nitrative and oxidative DNA damage in infection-related carcinogenesis in relation to cancer stem cells. Genes Environ. 38: 26.

Khalid T, Aggio R, White P, De Lacy Costello B, Persad R, Al-Kateb H, Jones P, Probert CS and Ratcliffe N, 2015. Urinary volatile organic compounds for the detection of prostate cancer. PloS one. 10: e0143283.

Kim JU, Shariff MI, Crossey MM, Gomez-Romero M, Holmes E, Cox IJ, Fye HK, Njie R and Taylor-Robinson SD, 2016. Hepatocellular carcinoma: Review of disease and tumor biomarkers. World J. Hepatol. 8: 471.

Krokidis MG, Terzidis MA, Efthimiadou E, Zervou SK, Kordas G, Papadopoulos K, Hiskia A, Kletsas D and Chatgilialoglu C, 2017. Purine 5′, 8-cyclo-2′-deoxynucleoside lesions: Formation by radical stress and repair in human breast epithelial cancer cells. Free Radic. Res. 51: 470-482.

Le Guennec A, Tea I, Antheaume I, Martineau E, Charrier B, Pathan M, Akoka S and Giraudeau P, 2012. Fast determination of absolute metabolite concentrations by spatially encoded 2D NMR: application to breast cancer cell extracts. Anal. Chem. 84: 10831-10837.

Lécuyer L, Dalle C, Lyan B, Demidem A, Rossary A, Vasson MP, Petera M, Lagree M, Ferreira T, Centeno D, Galan P, Hercberg S, Deschasaux M, Partula V, Srour B, Latino-Martel P, Kesse-Guyot E, Druesne-Pecollo N, Durand S, Pujos-Guillot E and Touvier M, 2019. Plasma metabolomic signatures associated with long-term breast cancer risk in the SU.VI.MAX Prospective Cohort. Cancer Epidemiol. Biomarkers Prev. 28: 1300-1307.

Lécuyer L, Victor Bala A, Deschasaux M, Bouchemal N, Nawfal Triba M, Vasson MP, Rossary A, Demidem A, Galan P, Hercberg S, Partula V, Le Moyec L, Srour B, Fiolet T, Latino-Martel P,

Kesse-Guyot E, Savarin P and Touvier M, 2018. NMR metabolomic signatures reveal predictive plasma metabolites associated with long-term risk of developing breast cancer. Int. J. Epidemiol. 47: 484-494.

Lima AR, De Lourdes Bastos M, Carvalho M and De Pinho PG, 2016. Biomarker discovery in human prostate cancer: an update in metabolomics studies. Transl. Oncol. 9: 357-370.

Lin X, Xu R, Mao S, Zhang Y, Dai Y, Guo Q, Song X, Zhang Q, Li L and Chen Q, 2019a. Metabolic biomarker signature for predicting the effect of neoadjuvant chemotherapy of breast cancer. Ann. Transl. Med. 7: 670-670.

Lin Y, Ma C, Bezabeh T, Wang Z, Liang J, Huang Y, Zhao J, Liu X, Ye W, Tang W, Ouyang T and Wu R, 2019b. 1H NMR-based metabolomics reveal overlapping discriminatory metabolites and metabolic pathway disturbances between colorectal tumor tissues and fecal samples. Int. J. Cancer. 145: 1679-1689.

Lukin M and De Los Santos C, 2006. NMR structures of damaged DNA. Chem. Rev. 106: 607-686.

Luo X, Liu J, Wang H and Lu H, 2020. Metabolomics identified new biomarkers for the precise diagnosis of pancreatic cancer and associated tissue metastasis. Pharmacol. Res. 104805.

Lyon, DE, Starkweather A, Yao Y, Garrett T, Kelly DL, Menzies V, Dereziński P, Datta S, Kumar S and Jackson-Cook C, 2018. Pilot study of metabolomics and psychoneurological symptoms in women with early stage breast cancer. Biol. Res. Nurs. 20: 227-236.

Mandel JS, Church TR, Bond JH, Ederer F, Geisser MS, Mongin SJ and Schuman LM, 2000 The effect of fecal occult-blood screening on the incidence of colorectal cancer. N. Engl. J. Med. 343(22): 1603-1607.

Miyamoto S, Taylor SL, Barupal DK, Taguchi A, Wohlgemuth G, Wikoff WR, Yoneda KY, Gandara DR, Hanash SM, Kim K and Fiehn O, 2015. Systemic metabolomic changes in blood samples of lung cancer patients identified by gas chromatography Time-Of-Flight mass spectrometry. Metabolites. 5: 192-210.

Mouw KW, Goldberg MS, Konstantinopoulos PA and D'andrea AD, 2017. DNA damage and repair biomarkers of immunotherapy response. Cancer Discov. 7: 675-693.

Murata M, 2018. Inflammation and cancer. Environ. Health Prev. Med. 23: 1-8.

Murata T, Yanagisawa T, Kurihara T, Kaneko M, Ota S, Enomoto A, Tomita M, Sugimoto M, Sunamura M, Hayashida T, Kitagawa Y and Jinno H, 2019. Salivary metabolomics with alternative decision tree-based machine learning methods for breast cancer discrimination. Breast Cancer Res. Treat. 177: 591-601.

Nagao T and Warnakulasuriya S, 2020. Screening for oral cancer: Future prospects, research and policy development for Asia. Oral Oncol. 105: 104632.

Narad P and Kirthanashri SV, 2018. Introduction to Omics, pp. 1-10 . In P. Arivaradarajan · and G. Misra (eds.), Omics Approaches, Technologies And Applications. Springer, Singapore.

Nicholson JK and Lindon JC. 2008. Metabolomics. Nature. 455(7216): 1054-1056.

Nour Eldin EEM, El-Readi MZ, Nour Eldein MM, Alfalki AA, Althubiti MA, Mohamed Kamel HF, Eid SY, Al-Amodi HS and Mirza AA, 2019. 8-Hydroxy-2'-deoxyguanosine as a discriminatory biomarker for early detection of breast cancer. Clin. Breast Cancer. 19: e385-e393.

Pence HE and Williams A, 2010. ChemSpider: an online chemical information resource. J. Chem. Educ. 87: 1123-1124.

Phua LC, Chue XP, Koh PK, Cheah PY, Ho HK and Chan ECY, 2014. Non-invasive fecal metabonomic detection of colorectal cancer. Cancer Biol. Ther. 15: 389-397.

Playdon MC, Ziegler RG, Sampson JN, Stolzenberg-Solomon R, Thompson HJ, Irwin ML, Mayne ST, Hoover RN and Moore SC, 2017. Nutritional metabolomics and breast cancer risk in a prospective study. Am. J. Clin. Nutr. 106: 637-649.

Qiu Y, Cai G, Su M, Chen T, Liu Y, Xu Y, Ni Y, Zhao A, Cai S and Xu LX, 2010. Urinary metabonomic study on colorectal cancer. J. Proteome Res. 9: 1627-1634.

Qiu Y, Cai G, Su M, Chen T, Zheng X, Xu Y, Ni Y, Zhao A, Xu LX and Cai S, 2009. Serum metabolite profiling of human colorectal cancer using GC− TOFMS and UPLC− QTOFMS. J. Proteome Res. 8: 4844-4850.

Razungles J, Cavaillès V, Jalaguier S and Teyssier C, 2013. L'effet Warburg-De la théorie du cancer aux applications thérapeutiques en cancérologie. Médecine/Sciences. 29: 1026-1033.

Rehma T, Naz S, Hussain R, Chatha AMM, Ahmad F, Yamin A, Akram R, Naz H and Shaheen A, 2020. Exposure to heavy metals causes

histopathological changes and alters antioxidant enzymes in fresh water fish (Oreochromis niloticus). Asian J. Agric. Biol. x(x): x-x.

Sengupta A and Narad P, 2018. Metabolomics. In P. Arivaradarajan · and G. Misra (eds.), Omics Approaches, Technologies And Applications. Springer, Singapore

Serkova NJ, Gamito EJ, Jones RH, O'donnell C, Brown JL, Green S, Sullivan H, Hedlund T and Crawford ED, 2008. The metabolites citrate, myo- inositol, and spermine are potential age-independent markers of prostate cancer in human expressed prostatic secretions. The Prostate. 68: 620-628.

Seyfried TN, 2015. Cancer as a mitochondrial metabolic disease. Front. Cell Dev. Biol. 3: 43-43.

Shao Y, Ye G, Ren S, Piao HL, Zhao X, Lu X, Wang F, Ma W, Li J and Yin P, 2018. Metabolomics and transcriptomics profiles reveal the dysregulation of the tricarboxylic acid cycle and related mechanisms in prostate cancer. Int. J. Cancer. 143: 396-407.

Sinues PML, Landoni E, Miceli R, Dibari VF, Dugo M, Agresti R, Tagliabue E, Cristoni S and Orlandi R, 2015. Secondary electrospray ionization-mass spectrometry and a novel statistical bioinformatic approach identifies a cancer-related profile in exhaled breath of breast cancer patients: a pilot study. J. Breath Res. 9: 031001.

Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram- Baptiste D, Saslow D, Brawley OW and Wender RC, 2018. Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening. CA: Cancer J. Clin. 68: 297-316.

Sova H, Jukkola-Vuorinen A, Puistola U, Kauppila S and Karihtala P, 2010. 8-Hydroxydeoxyguanosine: a new potential independent prognostic factor in breast cancer. Br. J. Cancer, 102: 1018-1023.

Struck-Lewicka W, Kordalewska M, Bujak R, Mpanga AY, Markuszewski M, Jacyna J, Matuszewski M, Kaliszan R and Markuszewski MJ, 2015. Urine metabolic fingerprinting using LC–MS and GC–MS reveals metabolite changes in prostate cancer: A pilot study. J. Pharm. Biomed. 111: 351-361.

Sturque J, Berquet A, Loison-Robert LS, Ahossi V and Zwetyenga, N, 2019. Interest of studying the saliva metabolome, transcriptome and microbiome in screening for pancreatic cancer. J. Stomatol. Oral Maxillofac. Surg. 120: 554-558.

Tan B, Qiu Y, Zou X, Chen T, Xie G, Cheng Y, Dong T, Zhao L, Feng B and Hu X, 2013. Metabonomics identifies serum metabolite markers of colorectal cancer. J. Proteome Res. 12: 3000-3009.

Tenori L, Oakman C, Morris PG, Gralka E, Turner N, Cappadona S, Fornier M, Hudis C, Norton L, Luchinat C and Di Leo A, 2015. Serum metabolomic profiles evaluated after surgery may identify patients with oestrogen receptor negative early breast cancer at increased risk of disease recurrence. Results from a retrospective study. Mol. Oncol. 9: 128-139.

Tessem MB, Selnæs KM, Sjursen W, Tranø G, Giskeødegård GF, Bathen TF, Gribbestad IS and Hofsli E, 2010. Discrimination of patients with microsatellite instability colon cancer using 1H HR MAS MR spectroscopy and chemometric analysis. J. Proteome Res. 9: 3664-3670.

Tsutsui H, Mochizuki T, Inoue K, Toyama T, Yoshimoto N, Endo Y, Todoroki K, Min JZ and Toyo'oka T, 2013. High-throughput LC–MS/MS based simultaneous determination of polyamines including N-acetylated forms in human saliva and the diagnostic approach to breast cancer patients. Anal. Chem. 85: 11835-11842.

Warburg O, 1956. On the origin of cancer cells. Science. 123: 309-314.

WHO (World Health Organization), 2017a. Guide to cancer early diagnosis from https://apps.who.int/iris/handle/10665/254500

WHO (World Health Organization), 2017b. Le diagnostic précoce du cancer permet de sauver des vies et d'abaisser le coût du traitement from https://www.who.int/fr/news-room/detail/03-02-2017-early-cancer-diagnosis-saves-lives-cuts-treatment-costs

Yang DO, Xu J, Huang H and Chen Z, 2011. Metabolomic profiling of serum from human pancreatic cancer patients Using 1H NMR spectroscopy and principal component analysis. Appl. Biochem. Biotechnol. 165: 148-154.

Yang L, Wang Y, Cai H, Wang S, Shen Y and Ke C, 2020. Application of metabolomics in the diagnosis of breast cancer: a systematic review. J. Cancer. 11: 2540-2551.

Yano T, Shoji F, Baba H, Koga T, Shiraishi T, Orita H and Kohno H, 2009. Significance of the urinary 8-OHdG level as an oxidative stress marker in

lung cancer patients. Lung Cancer. 63: 111-114.

You C and Wang Y, 2016. Mass spectrometry-based quantitative strategies for assessing the biological consequences and repair of DNA adducts. Acc. Chem. Res. 49: 205-213.

Yu Y, Wang P, Cui Y and Wang Y, 2018. Chemical analysis of DNA damage. Anal. Chem. 90: 556-576.

Zhang L, Jin H, Guo X, Yang Z, Zhao L, Tang S, Mo P, Wu K, Nie Y, Pan Y and Fan D, 2012. Distinguishing pancreatic cancer from chronic pancreatitis and healthy individuals by 1H nuclear magnetic resonance-based metabonomic profiles. Clin. Biochem. 45: 1064-1069.

Zhang PX, Xing YQ and Niu YD, 2019. Fundamentals of the warburg effect in cancer. J. Nutr. Oncol. 4: 108-114.

Zhang X, Xu L, Shen J, Cao B, Cheng T, Zhao T, Liu X and Zhang H, 2013. Metabolic signatures of esophageal cancer: NMR-based metabolomics and UHPLC-based focused metabolomics of blood serum. Biochim. Biophys. Acta. 1832: 1207-1216.

Zheng H, Dong B, Ning J, Shao X, Zhao L, Jiang Q, Ji H, Cai A, Xue W and Gao H, 2020. NMR-based metabolomics analysis identifies discriminatory metabolic disturbances in tissue and biofluid samples for progressive prostate cancer. Clinica. Chimica. Acta. 501: 241-251.

Contribution of Authors

Boumehira AZ & Akchiche YF: Conceived idea, prepared outlines and wrote the manuscript
Talhi O, Djidjik R & Dailin DJ: Contributed in manuscript writing and data analysis
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