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Review

Metabolomic profiling of oesophago-gastric cancer: A systematic review

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Abstract ***Aims:*** This review aims to identify metabolomic biomarkers of oesophago-gastric (OG) cancer in human biological samples, and to discuss the dominant metabolic pathways associated with the observed changes.
Methods: A systematic review of the literature, up to and including 9th November 2012, was conducted for experimental studies investigating the metabolomic profile of human biological samples from patients with OG cancer compared to a control group. Inclusion criteria for analytical platforms were mass spectrometry or nuclear magnetic resonance spectroscopy. The QUADAS-2 tool was used to assess the quality of the included studies.
Results: Twenty studies met the inclusion criteria and samples utilised for metabolomic analysis included tissue ($n = 11$), serum ($n = 8$), urine ($n = 1$) and gastric content ($n = 1$). Several metabolites of glycolysis, the tricarboxylic acid cycle, anaerobic respiration and protein/lipid metabolism were found to be significantly different between cancer and control samples. Lactate and fumurate were the most commonly recognised biomarkers of OG cancer related to cellular respiration. Valine, glutamine and glutamate were the most commonly identified amino acid biomarkers. Products of lipid metabolism including saturated and un-saturated free fatty acids, ketones and aldehydes and triacylglycerides were also identified as biomarkers of OG cancer. Unclear risk of bias for patient selection was reported for the majority of studies due to the lack of clarity regarding patient recruitment.
Conclusion: The application of metabolomics for biomarker detection in OG cancer presents new opportunities for the purposes of screening and therapeutic monitoring. Future studies should provide clear details of patient selection and develop metabolite assays suitable for progress beyond phase 1 pre-clinical exploratory studies.

1. Introduction

Oesophago-gastric (OG) cancer affects approximately 1.5 million people a year worldwide and accounts for

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15% of cancer related deaths.[1] In Western countries, the incidence is increasing, in particular adenocarcinomas of the distal oesophagus and gastro-oesophageal junction.[2–4] Prognosis remains poor with 5-year survival rates of 34% for localised disease and 17% for all stages combined.[5]

Treatment options and overall survival depend on both the stage of the disease and a patient's general health. The early symptoms of OG cancer are usually insidious and the majority of patients present late to their doctor with incurable disease. Surgical resection of the tumour remains the mainstay of curative treatment. In the United Kingdom (UK), only 38% percent of newly diagnosed patients are suitable for treatment with curative intent.[6] Identification of these cancers at an earlier stage could potentially improve the survival outcomes of OG cancer. There are currently no screening tests in mainstream clinical practice, despite evidence that treatment of early OG cancer has more favourable outcomes.[7–9] Oesophago-gastroduodenoscopy (OGD) and biopsy remain the gold standard procedure for the diagnosis of OG cancer. However, this is an invasive procedure and is too costly to be employed in a screening capacity. Radiological tests such as barium oesophograms and serum biomarkers are available; however their use has been limited due to poor sensitivity and specificity.

Metabolomics is defined as a quantitative description of all endogenous low-molecular-weight components (<1 kDa) in a biological sample, such as tissue, urine or plasma.[10] It is an evolving field and it has the potential to be an effective tool for the early diagnosis of OG cancer, through identification of one or more diagnostic biomarkers. The composition of these endogenous compounds is affected by the upstream influence of the proteome and genome as well as environmental factors, lifestyle factors, medication and underlying disease. The exact number of different metabolites in humans is currently unknown. Recent estimates by the human metabolite database (HDMB) suggest up to 5000 compounds, with reference to bio-fluid or tissue concentration data existing in the current literature.[11]

The majority of analytical platforms for metabolomic profiling are based on spectroscopic techniques. Mass spectrometry (often combined with chromatographic separation) and nuclear magnetic resonance (NMR) spectroscopy are the two most commonly employed analytical platforms; both techniques allow extensive and rapid analysis of small molecule metabolites,[12] resulting in multi-parameter datasets containing quantitative information on a range of metabolites. Due to the complexity and volume of the resultant spectral data, computer-based pre-processing and multivariate modelling techniques have been developed to facilitate the analysis and interpretation of the data.

Metabolomics studies have primarily focussed on the identification of cancer-specific metabolites. Examples include analysis of serum for the diagnosis of colorectal cancer,[13] exhaled breath for lung cancer[14] and urine for prostate cancer.[15] The aim of these studies has been to identify a panel of metabolites that may provide a metabolic fingerprint of malignancy. In combination, their sensitivity and specificity of predicting cancer has greater statistical power than single metabolites.

This systematic review aims to identify metabolomic biomarkers of OG cancer, found in human biological samples, and to assess the quality of the published data. The dominant metabolic pathways of malignant transformation, associated with the observed changes, will also be discussed.

2. Methods

2.1. Search strategy

A literature search (title and abstract) of Ovid Medline(R) (1948–2012), Embase (1974–2012), Web of Science and PubMed electronic databases was conducted up to and including 9th November 2012 for studies of metabolomic profiling of oesophago-gastric cancer. The search was conducted using the MeSH terms: *mass spectrometry, nuclear magnetic resonance spectroscopy, metabolomic, metabonomic, metabolic profiling* in multiple combinations (AND) with *gastric cancer* and *oesophageal/esophageal cancer*.

Two reviewers (N.A. and S.K.) independently screened titles and abstracts of studies identified through the electronic search. Full texts of potentially relevant articles were retrieved. Further potentially relevant articles were identified through the searching of reference lists of relevant studies. Experimental studies investigating the metabolomic profile of human biological samples from patients with gastric or oesophageal cancers, compared to an appropriate control group were included in our analysis. Inclusion criteria for analytical platforms were mass spectrometry (MS) or NMR. Exclusion criteria were: studies analysing the proteome rather than the metabolome, *in vitro* cell line studies, animal studies and studies without a control group. Studies that reported the same patient population were also excluded, except for the most recent or complete publication.

Two reviewers (N.A. and S.K.) independently extracted data from selected studies including primary author; year of publication; number and types of specimen; analytical platform and significantly different metabolites in the cancer and control groups. Compounds presented with varying chemical nomenclature in different articles are described by their common name in this review. The primary outcome measure was the

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