Biomarkers in premalignant conditions of the gastrointestinal tract: Studies on Barrett’s esophagus and primary sclerosing cholangitis

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CHAPTER 1

General introduction and outline of this thesis
GENERAL INTRODUCTION

Over the last decades, many advances in cancer research have led to an ever-increasing knowledge about cancer biology and its treatment. Nevertheless, every year there are still approximately fourteen million people diagnosed with cancer and half of them will eventually die from it. This is mostly due to the complex and heterogeneous nature of the disease, which hampers curative treatment. Due to the increase in knowledge of possible etiological factors, it has become a well-accepted concept that cancer is mostly a preventable disease and prevention has become one of the keystones in reducing the global burden of cancer.

The identification of conditions with malignant potential offers the opportunity to intervene and prevent further development into invasive cancer. In addition, early recognition of precancerous lesions and early cancers greatly increases the chances of curative treatment. Precursor lesions have now been identified for many types of human cancers. The opportunities for early detection and prevention depend on several aspects including the accessibility of an organ, the treatment options, and the costs involved and the potential benefits must always be considered against the risks of interventions and invasive diagnostic procedures.

Premalignant lesions represent the earliest stages of carcinogenesis. They may seem morphologically similar but their molecular characteristics are often highly variable which may account for the differences in biological behavior. The molecular properties of premalignant lesions could provide us with important information and potentially serve as “biomarkers” with many clinical applications including screening, risk assessment, differential diagnosis, prognosis, predicting response to therapy and monitoring for disease progression or recurrence.

A biological marker of cancer can be any measurable biological parameter that is indicative of (future) disease or treatment response. The ideal biomarker should be non-invasive and cost-effective and strongly correlated with a particular outcome. The classical approach for cancer biomarker discovery is based on insights into the mechanisms of cancer biology and its environment and, traditionally, biomarkers have been single events that were discovered one at a time. Several molecular abnormalities involved in the process of malignant transformation now serve as biomarkers with clinical utility including alterations in tumor suppressor genes (e.g. BRCA1, BRCA2, P16, P53), oncogenes (e.g. Her-2/neu, EGFR, KRAS), proliferation makers (Ki-67), and markers of chromosomal instability (DNA ploidy status).

The introduction of high-throughput technologies such as genome-wide screening, gene-expression profiling and proteomic approaches has lead to a more unbiased and untargeted approach of biomarker discovery in which very large amounts of data can be rapidly analysed. Also it has become clear that often a single biomarker does not have sufficient accuracy and this can be improved by combining multiple markers. Another method that can be used to gain more insight into cancer evolution is the assessment of dynamics of somatic evolution. Quantification of measurements that are indicative of clonal evolution (e.g. the presence and abundance of different subclones in (pre)cancerous lesions) might yield markers for robust risk stratification.
OUTLINE OF THIS THESIS

This thesis attempts to increase the knowledge about cancer biomarkers in the gastrointestinal tract for the particular cases of Barrett’s esophagus and primary sclerosing cholangitis. Both are chronic inflammatory conditions that predispose to cancer development. We investigated markers that could be of value in predicting malignant progression (Part 1), predicting response to therapy (Part 2), and for diagnosing malignancy (Part 3). This thesis does not address epigenetic changes.

BARRETT’S ESOPHAGUS

Esophageal adenocarcinoma is one of the most rapidly increasing cancers in the Western world. It is a highly malignant cancer with a five-year survival rate of less than 15%. However, in the earliest stages of the disease curative treatment is possible in 80-95% of patients. Barrett’s esophagus is a condition in which the normal squamous mucosa of the lower esophagus is replaced by metaplastic columnar epithelium in response to gastroesophageal reflux of acid and bile. It is the only known precursor lesion for esophageal adenocarcinoma.

Part 1 - Biomarkers of progression in Barrett’s esophagus

The first part of this thesis focuses on the analysis as well as the identification of predictive biomarkers for progression of Barrett’s esophagus to esophageal adenocarcinoma. Surveillance programs involve repeated endoscopies with endoscopic biopsies with the aim to detect neoplastic progression in an early stage. However, only a small minority of patients with Barrett’s esophagus will develop this highly malignant cancer and, in general, Barrett’s esophagus is associated with a rather low rate of malignant transformation. Barrett’s esophagus without dysplasia has the lowest risk of malignant progression which is only 0.2-0.6% per year. Surveillance is controversial because the yield of cancer cases is low and high numbers of participants are required. In this part we investigated if we can identify effective tools for risk stratification that can be used to accurately detect high-risk Barrett patients to facilitate cost-effective surveillance.

In Chapter 2, we critically review the literature and present an overview of molecular markers with potential for clinical application in the prediction of progression in Barrett’s esophagus. In Chapter 3, we report on a prospective, multicenter cohort of 428 patients with non-dysplastic Barrett’s esophagus from six general hospitals and one academic center in the Netherlands that was prospectively followed from 2003. In this study we aimed to develop a multivariate model, based on clinical variables and genetic markers assessed by fluorescence in situ hybridization, to predict future progression. In Chapter 4, we report on a subset of patients (n=320) from the same surveillance cohort in which we aimed to quantify measures of clonal diversity at single cell resolution in endoscopic brushing specimens in order to relate these to the risk of progression. In addition, we performed repeated sampling in 195 patients (median 37 months) and studied clonal dynamics by comparing the different time points.
Part 2 - Biomarkers predicting response to endoscopic therapy in Barrett’s esophagus

The second part of this thesis investigates the development of biomarkers on prediction of treatment response for Barrett’s esophagus with high-grade dysplasia or intramucosal cancer. Over the past decade, endoscopic treatment techniques have advanced and lesions with high-grade dysplasia or early cancer confined to the mucosal layer can now be treated endoscopically without the need for esophagectomy. Although the overall treatment response is quite high, a subset of patients will not respond to endoscopic therapy. In Chapter 5, we report on a retrospective cohort of 181 patients with high-grade dysplasia or intramucosal cancer who underwent a variety of endoscopic treatment modalities and we investigated if the presence of genetic abnormalities in the Barrett’s mucosa was related to response to therapy. In Chapter 6, we continued our work on this topic and present the results of an interim-analysis of a multicenter prospective study that focused on patients treated with radiofrequency ablation.

PRIMARY SCLerosING Cholangitis

Part 3 - Biomarkers of cholangiocarcinoma in primary sclerosing cholangitis

The third part of this thesis examines another condition of the gastrointestinal tract that is associated with an increased risk of cancer development: primary sclerosing cholangitis. Primary sclerosing cholangitis is a rare disease characterized by chronic inflammation of the bile ducts. Patients with primary sclerosing cholangitis have a lifetime risk of 9-20% for the development of cholangiocarcinoma, a highly aggressive disease, which is associated with poor prognosis. Early diagnostic tools are lacking and the ultimate goal is finding biomarkers that can timely predict cancer development in order to perform curative treatment. In Chapter 7, we summarize the current literature on genetic abnormalities found in cholangiocarcinoma that could possibly serve as biomarkers. In Chapter 8, we evaluate the diagnostic value of a set of genetic markers in brush cytology specimens of patients with primary sclerosing cholangitis with benign biliary strictures and patients with cholangiocarcinoma.