Sabrina Hundt
Dr. sc. hum.

Assessment of new avenues of screening for colorectal cancer based on novel molecular blood and stool tests.

Geboren am 03.02.1980 in Brandenburg an der Havel
Diplom der Fachrichtung Biologie am 01.12.2004 an der Universität Göttingen

Promotionsfach: DKFZ (Deutsches Krebsforschungszentrum)
Doktorvater: Prof. Dr. med. Hermann Brenner

Colorectal Cancer (CRC) is one of the most common malignancies in the world. Due to the underlying molecular mechanisms, development of sporadic CRC occurs slowly and over a long time from detectable and removable precancerous lesions in most cases, providing the opportunity to markedly reduce incidence and mortality through early detection. Currently, different screening modalities exist including screening colonoscopy, but costs, risk of complications and discomfort limits compliance with invasive methods. Non-invasive screening modalities might overcome this problem and stool- and blood-based testing offer particular advantages as regards practicability and acceptability. Fecal occult blood testing based on the chemical guaiac procedure has proven efficacy in reducing mortality in randomized controlled trials, but is limited by very low sensitivity for detection of precancerous lesions and by production of sizeable numbers of false-negative as well as false-positive results. Novel immunochemical fecal occult blood tests promise to overcome the limitations of guaiac-based testing through use of specific antibodies, but evidence on performance characteristics, in particular with respect to precancerous lesions, in a true screening setting is missing.

The aim of this project was to evaluate the potential use of novel blood and stool based tests to predict abnormal findings in the colon and rectum, especially as regards precancerous lesions and to assess the suitability of new screening modalities for early detection of colorectal cancer.

First, a systematic literature review using MEDLINE database for articles published until July 2008 was performed to summarize the current evidence on biomarkers in blood samples. Special attention was paid on the underlying study population and on performance

characteristics for early stage detection. One-hundred-eleven relevant articles evaluating 86 different biomarkers, including proteins, DNA and mRNA markers, met the inclusion criteria. Overall, performance characteristics varied widely between markers. Some recent approaches reported very promising results, with sensitivity for colorectal cancer and specificity above 90%. As a shortcoming, results were mostly reported by single studies and evidence on precancerous lesions is still limited, as study populations generally comprised colorectal cancer cases. In addition, as regards controls, study populations not necessarily representing the target population of screening were used in most studies. Nevertheless some biomarkers may have the potential to optimize current screening possibilities, but this potential has to be proven in larger, prospectively designed studies representing the target population for screening. In addition, practical issues have to be considered, as specimen handling procedures were very standardized in the majority of studies in a manner that might not be suitable for routine applications.

Second, stool samples from participants, recruited through a network of 20 gastroenterological practices in the context of the BliTz-study, a population-based study on participants of screening colonoscopy, were analyzed using a large panel of different stool tests, inlcuding the guaiac-based FOBT, 6 different qualitative immunochemical FOBTs, 2 quantitative FOBTs and a quantitative measurement of tumor M2-PK. Results of this analysis were very diverse, with widely varying estimates of performance indicators for the qualitative iFOBTs, yielding sensitivities for detecting any adenoma between 11% and 57% and specificities between 59% and 97%, while highest sensitivities were reported together with lowest specificities. Only two qualitative iFOBTs (*immoCARE-C* and *FOB advanced*) yielded specificities above 90%, typically required for routine testing of average-risk populations. Concerning the quantitative iFOBTs, results were superior to that of qualitative iFOBTs, yielding sensitivity for detection of any adenoma of around 20-25% at a specificity of around 90%. Fecal tumor M2-PK analyses yielded inferior results, as sensitivity for detection of adenoma was essentially equal to the false-positivity rate and even sensitivity for colorectal cancer was below 40%. As regards sub-analyses according to location, number and size of adenomas, higher sensitivities were revealed for distal, large and multiple adenomas for immunochemical FOBTs whereas no differences were observed for tumor M2-PK, except for number of adenomas.

Analyses conducted to control for a possible impact of sample handling and for possible effects of gender and age on performance characteristics, yielded no influence of the former and possible weak effects for the latter (more so for gender than for age). Further

simultaneous stratification by age and gender did not yield any significant trends, but the limited power due to lower sample size in the sub-groups has to be taken into account. Furthermore, co-variables such as medication or lifestyle factors, which could have an effect on colorectal bleeding, were not considered in this analysis.

All in all, a high potential of some immunochemical FOBTs to improve current CRC screening, using guaiac-based FOBT, could be shown, while the potential of tumor M2-PK is very limited. Given the large differences between immunochemical tests, careful evaluation of single test variants is needed, before recommendation are made. In addition, biomarkers in blood samples were shown to be an interesting option to improve CRC screening, but phased validation studies are needed