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Evaluation of microRNAs for the detection of colorectal cancer

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With over 1.2 million new cases and 608,700 deaths per year, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, and the fourth most common cause of death from cancer worldwide. Due to its typically very slow development over many years, perspectives for early detection are much better than for many other forms of cancer. It has been estimated that over 95% of cases of CRC would benefit from curative surgery if diagnosis was made at an early or premalignant polyp stage. A number of early detection procedures have been developed and are increasingly applied, including endoscopic examinations, stool- and blood-based tests. Blood based tests would appear to be particularly attractive as they are minimally invasive and might receive high levels of adherence when applied as primary screening tests in population based screening. A large number of blood markers have been proposed and evaluated, including protein, cytological, mRNA, and DNA markers, but diagnostic performance has mostly been insufficient for application as a primary tool in population-based screening. Furthermore, most studies relied on small convenience samples from clinical settings, and rather promising results from small studies have often not been replicated in subsequent larger scale validations.

In this dissertation, a systematic review was first performed to summarize evidence for the use of miRNAs for CRC detection. The results of 36 studies were summarized which investigated more than 900 miRNAs in 2,354 cases of colorectal tumors/adenomas and 1,725 controls. Among them 236 miRNAs were found to be significantly dysregulated in at least one study, suggesting that aberrant expression of miRNAs might be indicative of presence of CRC. However, only 4 studies assessing miRNAs' expression in plasma of CRC patients have been reported, and only 96 miRNAs were investigated in these studies. In order to assess a panel of miRNAs which might be suitable for early CRC detection, 7 miRNAs (miR-18a, -20a, -21, -92a, -143, -145, -181b) which were most frequently reported to be dysregulated in CRC were considered to be further evaluated.

Second, 5 miRNAs (miR-29a, -106b, -133a, -342-3p, -532-3p) were found to be statistically significantly dysregulated in the plasma of CRC patients compared to neoplasm-free controls in microarray analyses.

Third, the 12 selected miRNAs (7 from the literature review, 5 identified by microarray analyses) were assessed among subsamples of the BliTz and DACHS+ study participants. The diagnostic performance of the panel of the 12 miRNAs was evaluated. The ROC analysis yielded an adjusted (optimism-corrected) AUC of 0.745 (95% CI: 0.708-0.846), which is compared favorably with the other blood-based tests for CRC detection. The results suggest that plasma miRNAs can be promising novel biomarkers for detecting CRC. However, further improvement of diagnostic performance, possibly by identification and inclusion of other miRNAs in a multi-marker panel or by combination of miRNA panels with other non-invasive tests, is desirable.

In conclusion, this study underscores the high potential of plasma miRNAs for the improvement of current offers of non-invasive CRC screening. However, larger diagnostic studies are needed to evaluate potential use of plasma miRNAs expression in early detection and diagnosis of CRC. Further development and evaluation of new techniques and markers are desired to improve population-based CRC screening.