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Antibodies against tumor-associated antigens in early detection of colorectal cancer

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Colorectal cancer (CRC) is the third most cancer and the fourth most common cause of death from cancer worldwide. Screening could strongly reduce the burden of this disease. Blood-based screening tests might be an alternative approach to current established CRC screening modalities, such colonoscopy and fecal immunochemical tests (FITs). To date, many studies suggested blood autoantibodies may have a potential role for early detection of cancer. A major limitation of previous researches on cancer early detection markers was that many studies recruited participants in clinical settings rather than in screening settings. It is commonly seen that very promising biomarker findings for cancer early detection initially obtained in studies conducted in clinical settings are often not confirmed in later validations in screening settings. The main aim of this project was to identify autoantibody markers for early detection of CRC and to evaluate the diagnostic accuracy of identified autoantibody markers and their combinations with other tests in samples from a true screening setting. A second aim of this dissertation was to empirically evaluate the impact of study setting on identification of cancer early detection biomarkers.

In a first step, a comprehensive systematic literature review was performed summarizing current evidence on blood autoantibodies as biomarkers for early detection of colorectal cancer. 67 studies evaluating 106 different types of autoantibody markers were included in this review. Several autoantibody markers showing promising diagnostic potential were identified, which were further validated in the following analysis.

In a second step, in order to systematically assess differences in confirmation rates of early detection markers identified in clinical and screening settings, data from an empirical example using the search for plasma protein biomarkers for early detection of CRC were analyzed. In this analysis, the confirmation rates of single markers, 2- and 3- marker combinations identified initially in a clinical setting were only 42.9%, 18.6% and 25.7%, respectively, if subsequently validated in a screening setting. These confirmation rates were much lower than the confirmation rates of markers and marker combinations identified in a true screening setting. The results therefore underlined the necessity and importance of validating promising biomarker findings in prospective samples from screening settings to limit the numbers of false positive findings.

In a following step, 64 autoantibody markers comprising some promising candidates identified in the preceding review were measured in 380 clinically identified colorectal cancer patients and samples of participants with selected findings from a cohort of screening colonoscopy participants recruited in 2005-2013 (N=6826). A two-step approach with selection of biomarkers in a training set, and validation of biomarker combinations in a validation set, the latter exclusively including participants from the screening setting, was applied. In this analysis, anti-MAGEA4 exhibited the highest sensitivity for detecting early stage colorectal cancer and advanced adenoma as a single biomarker. Multi-marker combinations substantially increased sensitivity at the cost of a moderate loss of specificity. Four autoantibody markers (anti-TP53, anti-IMPDH2, anti-MDM2 and anti-MAGEA4) were consistently included in the best-performing 4-, 5-, and 6-marker combinations. Notably, the diagnostic performance of the multi-marker panels for detecting advanced adenomas was comparable to FITs, the current best-performing stool-based tests for CRC screening.

In a further step, the potential combination of the identified 4-autoantibody marker panel with FITs was explored. The results showed that the combination of 4-autoantibody panel and FITs conferred modest improvement for detecting advanced adenoma, the most import precursors of colorectal cancer, comparable to FITs alone, albeit at a decreased specificity. Potential combination of autoantibody markers with other blood-based markers was also explored. In a further analysis on the combination of 4-autoantibody panel with plasma protein markers, an 8-marker algorithm was developed using the Lasso logistic regression model. Validating this algorithm in an independent validation set from a true screening setting yielded promising diagnostic performance for detecting early stage CRC. Several novel protein markers, such as Amphiregulin, GDF-15 and IL-6, were identified in this analysis, which might also be promising candidates to be included in future multi-marker panels for CRC screening.

This dissertation demonstrated that serum autoantibodies might carry great diagnostic potential for detecting CRC and its precursors. It is important and necessary to validate biomarker findings in true screening settings to minimize the number of false positive findings. Combination of the most promising biomarkers identified in this dissertation with additional biomarkers or tests might contribute to the development of a powerful multi-marker blood-based test for early detection of CRC in the future.