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Evaluation of new early detection markers for gastrointestinal tumors -perspectives for detection of colorectal cancer based on immunological fecal occult blood tests and blood-based markers

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Colorectal cancer is one of the most common cancers accounting for more than 1.2 new cases and 600.000 deaths per year globally. The slow development of CRC provides opportunities to reduce the burden of the disease, based on early detection of curable carcinomas or removable adenomas. From the public health point of view, CRC is a suitable disease for population-based screening according to the screening criteria from World Health Organization (WHO). Screening for CRC using FOBTs has been shown to reduce both mortality and incidence of CRC. However, the traditional gFOBT, which has been used for decades, is limited by its low sensitivity and the need for dietary restrictions. Further, more sensitive non-invasive methods for CRC screening are highly desirable. The aim of this thesis was to evaluate new early detection markers for CRC screening based on fecal occult blood tests and blood-based markers.

First, a systematic review was performed to summarize evidence for the use of various blood markers for detecting CRC and special attention was paid on the stage distribution of the cancer cases in the included analyses. In order to assess the impact of overrepresentation of advanced stage CRCs, estimates of sensitivity were adjusted based on the expected stage distribution of CRC in the screening setting. Most studies were conducted in clinical settings and they showed higher sensitivities than expected in the screening setting in most cases (90%). This over estimation is mainly due to substantially higher proportions of advanced stage cancers. Therefore adjustment of sensitivity to the stage distribution expected in the screening setting is crucial to obtain realistic and comparable estimates of sensitivities.

Second, based on the BliTz and DACHS+ study populations, six qualitative (office based) and two quantitative iFOBTs and one gFOBT were evaluated regarding their ability to detect CRC and their diagnostic performances were compared. Overall and stage specific

performance of iFOBTs were further compared with performance of previously reported DNA based stool tests through a systematic literature review. The qualitative iFOBTs showed promising performance for detection of CRC, even for early stages. At comparable levels of specificity, sensitivities were very similar for qualitative and quantitative iFOBTs. For both types of iFOBTs, sensitivities were substantially higher than sensitivity of gFOBTs and of stool DNA based tests reported in the vast majority of studies.

Third, selected blood based inflammatory markers were assessed among subsamples of the BliTz and DACHS+ study participants. The diagnostic performances of these tests were compared, alone and in combination with FOBTs, with respect to the detection of advanced adenoma and CRC. The blood levels of CRP, sCD26 and TIMP-1 showed statistically significant differences between CRC patients and neoplasm free participants, and levels of TIMP-1 were furthermore significantly elevated in advanced adenoma patients. However, at cut-off points yielding 97.7% specificity (the specificity observed for gFOBT), blood markers showed much lower sensitivities than FOBTs. Combining inflammatory markers with the quantitative iFOBT suggested only some very limited improvements in detection of advanced adenomas. The blood markers of inflammation assessed in this analysis do not seem to be alternatives or clinically relevant supplements for non-invasive CRC screening.

Finally, two office-based qualitative iFOBTs were evaluated for the detection of advanced adenoma and CRC at five different cut-offs among 229 participants of screening colonoscopy (45 patients with CRC, 65 with advanced adenoma, and 119 free of colorectal neoplasmas). For both qualitative tests, cut-offs from 75 to 125 ng/ml yielded sensitivities close to 30% for advanced adenoma and 80% for CRC at very high levels of specificity (98-99%). Comparison of results with the ROC curves for the quantitative test indicated the qualitative tests to yield similarly high levels of sensitivity at comparable levels of specificity. The results indicated that, with appropriate adjustment of cut-offs ensuring the levels of specificity needed in population-based screening, office-based iFOBTs can be a promising simple and inexpensive alternative to quantitative iFOBTs.

In conclusion, this study underlines the high potential of iFOBTs for the improvement of current offers of non-invasive CRC screening, which are so far restricted to gFOBT in many countries including Germany. However, careful adjustment of cut-off levels according to the screening target population has to be ensured for either quantitative or qualitative iFOBTs. Further development and evaluation of new techniques and markers are desired to improve

population-based CRC screening. In particular, possible combinations of multiple blood-based markers, alone or in combination with iFOBT might deserve further attention.