Heiko Müller
Dr. sc. hum.

Evaluation of markers for the early detection of prostate cancer

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

Prostate cancer is the most common cancer in men globally. As prostate cancer develops more slowly than most other cancer, perspectives for the development of successful screening programs to reduce mortality and morbidity are in theory better than for many other forms of cancer. With PSA and DRE, two methods for early detection of prostate cancer are applied currently. While DRE detects prostate cancer rather late, PSA is supposed to miss clinically relevant cases and to be responsible for the overdiagnosis of prostate cancer as well. Furthermore, metabolic disorders such as diabetes or obesity were suggested to change PSA values and might warrant adaptation of currently employed cutpoints in these groups. The aim of this project was to evaluate the suitability of non-invasive promising markers in urine or blood for the early detection of prostate cancer in a population-based screening setting.

First, a systematic literature review was performed to summarize the current status of evidence regarding performance characteristics of urine-based tests and their practicality under screening conditions. Relevant articles published up to and including May 2005 were identified in the PubMed database. At least 10 cases and 10 controls had to be analyzed for a study to be included in the review. In all, 34 retrospective studies evaluating 21 different markers complied with the inclusion criteria. Most of the studies were rather small and included heterogeneous clinical study populations. Promising results regarding sensitivity and specificity were reported for a few markers, which were not replicated in subsequent larger studies yet or used specimen handling procedures that might be difficult to perform under mass screening conditions. Larger studies with a prospective design are required to confirm

the promising findings and should also pay particular attention to the practicality of the markers under screening conditions.

Furthermore, blood- (%fPSA, MRP-14) and urine-based markers (MRP-14) were evaluated within 33 incident prostate cancer cases (until the 2-year follow-up) and age-matched controls of the ESTHER study, a large population-based cohort study. The group of incident prostate cancer was further complemented by a sample of 25 prostate cancer cases from the clinical part of the ESTHER study. Additionaly, serum samples of these participants were analyzed with SELDI-TOF MS to identify potential markers for early detection of prostate cancer. %fPSA significantly differentiated between 759 controls and both goups of cases not only for PSA levels ranging 4-10 ng/ml, but also for PSA levels below 4 ng/ml. Some combinations of PSA and %fPSA yielded higher levels of both sensitivity and specificity compared to PSA alone. Serum and urine MRP-14 could not significantly discriminate between 74 controls and both case groups in contrast to PSA. The impressive results shown for analyses of serum samples with SELDI-TOF MS in two earlier studies were not replicated in the ESTHER study. In contrast to the identified peaks, PSA and %fPSA were able to discriminate cases and controls in both the prospective and clinical part of the study. Slightly – however unknown – different preanalytical sample handling between ESTHER 1 and ESTHER 2 might have influenced the results for the identified peaks, as in the prospective part of the ESTHER study the identified peaks were not able to discriminate controls (N=69) and case group 1, while the identified peaks were able to discriminate controls and case group 2 (clinical part of the study with case-control design). These results indicate the importance to evaluate promising results of diagnostic studies in population-based cohort studies, as diagnostic studies might tend to differ in preanalytical sample handling of cases and controls, and besides mostly use highly selected study populations, which might not necessarily reflect performance characteristics of a marker in the general population.

Finally, cross-sectional data of the ESTHER study were used to evaluate the influence of diabetes and obesity on PSA levels within 778 participants of the ESTHER study. PSA values were significantly reduced in men with insulin treatment and oral diabetic medication, and in men with elevated (6.1-6.9%) or highly (≥7%) elevated HbA1c values. Obesity was tentatively associated with a reduction of PSA levels. The observed PSA reduction parallels reported risk reduction of prostate cancer among diabetic men which suggests that PSA levels do not need to be adjusted in screening of diabetic men. However, further studies

investigating change in PSA and change in prostate cancer are necessary due to the limited data - especially for men with severe forms of diabetes, which showed the largest PSA reduction.

All in all, potential of %fPSA to improve prostate cancer screening was shown, while promising results for MRP-14 in urine and blood and for SELDI-TOF MS in serum were not confirmed. Nevertheless, the results for %fPSA warrant further evaluation in large-scale longitudinally designed studies. Despite the potential improvement of PSA by %fPSA in early detection of prostate cancer, recommendation of PSA as screening tool should await the evidence of mortality reduction in ongoing randomized controlled trials. Furthermore, the potential influence of metabolic disorders such as diabetes or obesity on PSA values should be regarded in further studies to clarify whether the cut-off values for PSA screening have to be changed in these men to avoid a potential detection bias. For the future, a key challenge in development and evaluation of markers for prostate cancer screening is the application of adequately designed studies to arrive at markers that are both effective and practical for screening.