Thiosulfate in urine: new hope or new failure of a biomarker for prostate cancer?

Prostate cancer is the most frequent malignancy in men in the Western world. In Europe, last official data of 2010 report on an incidence of 379,097 new cases and a mortality of 94,080 cancer deaths per year while 238,590 new cases and 29,720 cancer deaths have been estimated in the USA for 2013 [1, 2]. This cancer is mainly detected by the determination of serum prostate-specific antigen (PSA) and/or the digital rectal examination, and subsequently confirmed by histological examination of bioptic samples. Although PSA was initially introduced as a monitoring biomarker to assess the treatment responses in prostate cancer patients, it is now one of the most widely used cancer screening tests. For example, in USA in 2008, 54.8% of all men aged 40 years or older were estimated to have a PSA test during the preceding 2 years [3]. However, several studies evidenced the limited ability of PSA in differentiating between benign and malignant prostate diseases and also between aggressive and insignificant tumors since a continuous risk of prostate cancer occurs at all PSA values [4]. Depending on the cut-off value (1.1, 2.1, 3.1, and 4.1 µg/L) applied for cancer detection with about 19,000 men in a 7-year follow-up study, sensitivities of 83%, 53%, 32%, and 21% with corresponding specificities of 39%, 73%, 87%, and 94% were found [5]. It was emphasized that overdiagnosis and overtreatment resulting from PSA testing would cause more harm than good [4]. This situation has led to intense controversial debates and partly contradictory recommendations concerning PSA testing by several US medical associations [6–9]. Therefore, one objective of the current biomarker research in urology is focused on the discovery of new markers and their translation into practice to improve both early prostate cancer detection and risk prediction for patients [10].

The new “omic” technologies such as genomics, transcriptomics, proteomics, and metabolomics make promise in this direction. Especially in this light, the study presented by Chwatko et al. [11] in this issue of Clinical Chemistry and Laboratory Medicine using thiosulfate in urine as a new metabolite for this purpose could be a promising approach. Biomarker research for prostate cancer using urine has recently been paid particular attention since urine offers a non-invasive approach to determine potentially indicative markers in a easily available sample [12]. The about six times higher urinary thiosulfate values of prostate cancer patients compared with data of patients suffering from benign prostatic hyperplasia and even 50 times higher values than in asymptomatic controls are remarkable. This discriminatory effect was confirmed by receiver-operating characteristics analysis with an area under the curve of 0.84 that was very good for a single marker. Urinary thiosulfate was correlated with prostate volume, but not with age, tumor stage, Gleason score, preoperative PSA, and PSA density. This unequivocal independence from other variables that generally characterize the status of prostate cancer was somewhat surprising, but it would imply an essential advantage for a future biomarker. Although not clearly pointed out by the authors, it might be an additional advantage for thiosulfate as potential biomarker for prostate cancer that no standardized digital rectal manipulation of the prostate is necessary before sampling the patients’ urine. Other urinary markers like transcripts of prostate cancer antigen 3 (PCA3) and of gene fusion of transmembrane protease, serine 2 (TMPRSS2) to v-ets erythroblastosis virus E26 oncogene homolog (avian) (ERG) (TMPRSS2:ERG), lose some of their power if not performing a digital rectal examination of the prostate. Furthermore, the molecular background of the higher thiosulfate concentration in prostate cancer patients as rationale of this test can be explained, as described in the article of Chwatko et al. [11], by an increased generation of hydrogen sulfide as so-called “third gasotransmitter” in prostate cancer and its following oxidation to thiosulfate [13, 14]. However, it should be stressed that all four recently known metabolomics studies of the prostate cancer tissue with their large number of several hundred metabolites did not identify thiosulfate as differentially expressed metabolite between malignant and benign prostate tissue or as noteworthy in the context of the aggressiveness or prognosis of the tumor [15–18]. However, it must be considered that sulfites occurring naturally or as additives in foods and beverages are also metabolized to thiosulfate and could...
be an interfering factor in this respect [19]. Other studies that aimed to validate differentially expressed metabolites in prostate cancer tissue [15] (sarcosine, proline, kynurenine, uracil, and glycerol-3-phosphate) as non-invasive biomarkers in urine proved a rather strong correlation of these metabolites with their renal excretion but not with the cancer status [20, 21].

In addition, two other limitations of this interesting pilot study should be mentioned. First, to assess the diagnostic power of a new biomarker for early prostate cancer detection the serum mean/median PSA concentrations in the study groups should be comparable and within the limits of the most important PSA “gray zone” until 10 µg/L. The best way is to match the patients according to their PSA values [22]. In this case, area under the receiver-operating characteristics curve would be near to 0.5 and significantly larger areas would indicate the higher diagnostic accuracy of the new marker. Despite some data for the subgroup of the 78 prostate cancer patients with PSA <10 µg/L and 10 patients with PSA <4 µg/L, the overall information given for this PSA “gray zone” was very limited.

Second, the diagnostic performance of every new marker should always be evaluated in comparison with the best markers currently available [23]. Chwatko et al. [11] did not incorporate the already mentioned new urinary biomarkers PCA3 and TMPRSS2:ERG in the study. In recent studies, especially PCA3 has been proven to be superior to PSA and percent free PSA [24, 25]. Thus, a comparison of the clinical validity of thiosulfate with PCA3 and TMPRSS2:ERG in a cohort with similar PSA concentrations below 10 µg/L or at least <20 µg/L would be necessary. It would also be of interest to further evaluate the utility of thiosulfate in comparison to the prostate health index (Phi) as derivative PSA test of combined determination of total PSA, free PSA, and [2] proPSA, which preferentially detects aggressive tumors [26]. In consequence, thiosulfate may become clinically important only if it shows better or at least equal clinical validity data compared with PCA3 and Phi. Both tests are already approved markers by the US Food and Drug Administration in well-selected groups.

In summary, the pilot study of Chwatko et al. [11] can be estimated as a hopeful novel approach that is worth validating without further delay. Our comments are in context with the numerous aspects that result in the frequent failure of new biomarkers [27]. However, reliable validation results can only be expected if these aspects are considered as essential conditions to enhance the translation process from research into clinical practice. And this task of the scientists in the biomarker translation process could be supported by the encouragement of scientific journals to publish also re-evaluation studies that fail to confirm original data as important information for the whole scientific community.

Conflict of interest statement

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References


