A case study in using spatial relative risk function for analysis of diagnostic studies of laboratory markers: total versus complexed prostate-specific antigen

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Introduction Spatial risk functions are commonly used within spatial epidemiology for geographical risk assessment. Because risk assessment is a very general approach, the application of spatial methods to other area of interest seems to be meaningful. In case of laboratory markers of clinical chemistry, the relationship of two markers is often graphically analysed by scatterplots showing test results of the two tests for patients and controls. The case study investigates whether spatial risk assessment could be helpful in order to find general patterns and relationship between the laboratory markers.

In this case study the relationship of several subforms of prostate-specific antigen (PSA) is analysed by spatial risk assessment methods. Total PSA (tPSA) is a widely used diagnostic test for prostate cancer. tPSA roughly corresponds to the sum of the free PSA (fPSA) and the PSA bound to complex ligands (cPSA). Within usual diagnostic pathway tPSA is used as a first line test. For patient in the so called "diagnostic grey zone" (tPSA = 4 µg/L [2,5 µg/L] … 10 µg/L), an additional measurement of fPSA is performed in terms of reflex testing: low ratios fPSA/tPSA (< 25%) indicate elevated risk for prostate cancer [1]. A similar diagnostic pathway is actually in discussion: usage of cPSA in terms of first line test with a cut off of about 3.4 µg/L [2], which might be followed by fPSA/cPSA or cPSA/tPSA ratios as reflex tests [3].

Using spatial relative risk function of populations of clinical diagnostic studies with values of laboratory markers as parameters, diagnostic pathways can be investigated in a new manner using visualised information about gradients of spatial relative risk function.

Material and Methods: *Spatial relative risk function:* 2-dimensional density functions $\Psi(p_1,p_2)$ of patients with prostate cancer (PCA) and $\Sigma(p_1,p_2)$ of all patients under investigation (with [PCA] and without prostate cancer [non PCA]) are determined, whereby p_1 and p_2 are concentrations of two laboratory markers. As a second step, spatial relative risk function $\Pi(p_1,p_2) = \Psi(p_1,p_2)/\Sigma(p_1,p_2)$ is calculated similar to [4, 5], however, those approaches include only controls into denominator function. Values of Π represent risk to have a tumour with a given combination of concentrations of laboratory markers. Connected with a positive test result, values of Π represent positive predictive values, too. Areas with $\Sigma(p_1,p_2)<0.05$ are excluded from the figures, because they do not contribute any information of clinical relevance.

Two-dimensional kernel density estimation with an axis-aligned bivariate normal kernel evaluated on a square grid was performed using software R [6]. Bandwidth was determined according to Silverman's "rule of thumb" [7].

Patients and laboratory method: For the case study, tPSA and cPSA data from a multicenter study are used [8]. Details concerning the study groups, blood sample collection and storage, and analytical methods were given in the original report [8]. Briefly, the study included 700 white men enrolled in screening studies and or case-finding studies with tPSA concentrations between 0 and 6 µg/L. All 700 men were untreated and underwent transrectal ultrasound-guided 6- to 10-sector needle biopsies of the prostate. A total of 283 patients were diagnosed as having prostate cancer (PCa), whereas in 417 men no evidence of prostate cancer (non-PCa) was found in prostate biopsies. PSA concentrations were measured by the Bayer Immuno 1 PSA and cPSA assays (Bayer Diagnostics) as described previously [8].

Cut off values: tPSA = 4 µg/L is used as cut off. Using criterion of same sensitivity, a cut off of 3.2 µg/L for cPSA was resulting.

Results: Figure 1 presents spatial relative risk function using parameters cPSA and tPSA. At tPSA levels > 2.5 µg/L, spatial relative risk function shows an asymmetric behaviour: Level curves of Π and lines cPSA = constant are roughly in parallel, whereas lines tPSA = constant are perpendicular to level curves. The dotted lines represent cut off values as described above : tPSA=4 µg/L, cPSA=3.2 µg/L, %fPSA = fPSA/tPSA = 1-cPSA/tPSA=25%. Figure 2 shows ROC curves of both tests including cut off values for tPSA and cPSA.

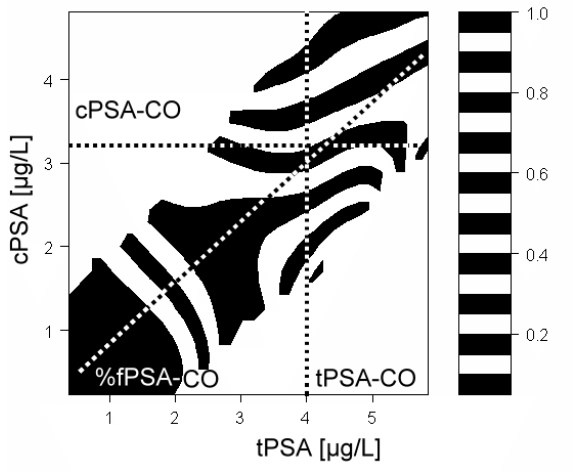

Fig. 1 2D-plot of spatial relative risk function. CO : cut off.
remark: Π increases from left bottom (0.1) to right top (0.6).

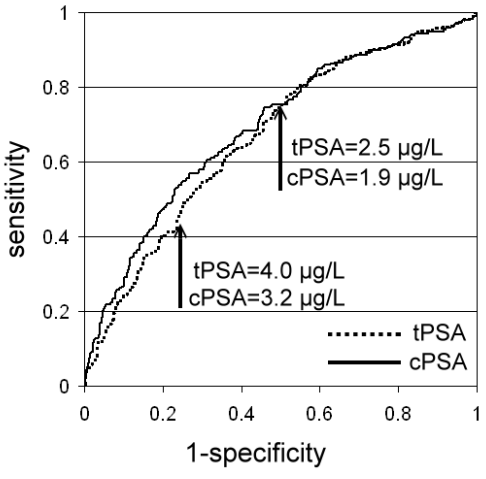

Fig. 2 ROC-curves for tPSA and cPSA, shown with two tPSA- and related cPSA cut off values

Discussion: The spatial relative risk function presented in figure 1 uses laboratory values of both laboratory markers being under discussion as first line tests for prostate cancer. Comparing angles between cut off lines and level curves, both markers show completely different behaviour. cPSA cut off values > ~2.5 µg/L are normals of gradients of Π indicating a better diagnostic discriminatory power than tPSA. tPSA cut offs are roughly parallel to gradients of Π. These qualitative results are in concordance with ROC analysis as well as results of DAC method [9] showing higher diagnostic accuracy of cPSA. Additionally, the effect of reflex-testing can be studied by figure 1. Regardless which test (cPSA or tPSA) is used as first line test, specificity is increased by preventing false positive results on the right hand side of the %fPSA-cut off line as well as related %cPSA cut off line. In terms of reflex-testing, high risk patients with cPSA > 3.2 µg/L and tPSA < 4 µg/L are detected in addition, when cPSA is used as first line test. These high risk patients would be overseen using a tPSA cut off of 4.0 µg/L.

Comparing spatial relative risk function with ROC curve, concordance of information can be concluded from similarity of regions with non-overlapping of ROC curves and asymmetric behaviour of Π. Visualisation using spatial relative risk function allows to investigate diagnostic pathways in a qualitative manner. However, one should take into account that absolute values of Π depend on prevalence of disease. Especially quantitative estimation of individual risk = $\Pi(p_1,p_2)$ on basis of laboratory marker values is influenced by prevalence of disease, population and setup of diagnostic study.

References

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