Editorial

The value of digital rectal examination in clinical practice

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The discussed study by Halpern *et al.* (1) evaluated the value of the digital rectal examination (DRE) in dependence of the prostate specific antigen (PSA) range. In men with a low PSA a suspicious DRE was associated with a higher increase in the relative risk of a clinically significant prostate cancer (CSPC) as compared to those men with higher PSA values. Because the increase in absolute risk was small (1.5% *vs.* 0.7% risk of CSPC at 10 years) and clinically irrelevant for normal PSA values (<2 ng/mL) the authors recommend a restriction of DRE only to men with higher PSA values >3 ng/mL where the risk of CSPC at 10 years increased from 13.7% to 23.0%. For the PSA interval 2–3 ng/mL the addition of DRE showed modest clinical relevance for CSPC detection within 10 years (6.5% *vs.* 3.5%). To evaluate these results, a step back in history is useful.

Both studies, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial (2) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) (3) were important trials with quite different results. These studies are most likely the last huge trials that really reflected a screening situation at least in the ERSPC. It is unlikely nor necessary to initiate further similar studies to evaluate the value of PSA and the role of DRE for prostate cancer (PCa) screening. It is also known since 1994 that PSA clearly outperforms DRE for early detection of PCa (4). However, in 2018, the questions are more specific. While PSA itself might serve as initial marker for PCa screening and early detection, other methods like the multiparametric MRI (mpMRI) (5) or PSA subforms like free PSA (fPSA) or the fPSA subform [-2]proPSA with the combined formula [-2]proPSA/fPSA × √PSA named Prostate Health Index (PHI) have been gained large attention and proven to be superior to PSA (6). Several years ago, a confirmed elevated PSA value of >2.5, >3 or >4 ng/mL has forced the urologist to offer a prostate biopsy. Now patients often request a MRI or want to avoid a regular biopsy. With a clearly suspicious DRE or a PSA >10 ng/mL all additional diagnostics should be abandoned and a biopsy should be offered. But in most cases the situation is not that clear and easy.

The current data regarding PSA screening are ambivalent when comparing the different recommendation of organizations. Some recommend PSA screening, like the AUA (7). On the other hand, some conclude that PSA testing has more negative (risk of infection at biopsy, overtreatment with incontinence with surgery) than positive (earlier detection, higher likelihood of curative treatment) aspects (8). Interestingly, the US Preventive Services Task Force with no urologists or oncologists in their panel, softened in 2017 their grade D recommendation against PSA screening with a draft recommendation that clinicians should now inform men aged 55 to 69 years about the potential benefits and harms of PSA screening [extensively discussed in (9)]. However, it is known that there is a clear correlation between a baseline PSA at age 40 to 55 and the risk of developing metastatic PCa (10). And the DRE has a much weaker role in screening because 11 of 12 PCa were detected with an elevated PSA value and only the remaining one with a suspicious DRE. Further, DRE itself is very subjective and it has been performed in the PLCO study by physicians, physician assistants or nurses (1). With known differences even between urologists in interpreting the DRE and a missing standardization the DRE itself remains a weak point when it comes to statistical

analysis. The reproducibility of DRE for detecting PCa was only fair among urologists in a study from 1995 (11). This should be considered when interpreting the data of this study by Halpern *et al.* (1). But in the hand of a urologist the usefulness of a DRE is without question. Despite clear epidemiological data with a small live time risk of only 3% to die of PCa, a patient who requests an individual check-up exactly wants to avoid this 3% risk because this is possible with a simple blood test. The study by Halpern *et al.* (1) can be also interpreted somewhat different. In rounded data and without considering the DRE status, the CSPC risk within 10 years is about 1%, 5% and 20% for men with PSA levels of <2, 2–3 and >3 ng/mL. With a suspicious DRE the respective risks are approximately doubled from 0.7% to 1.5%, from 3.5% to 6.5% and from 13.7% to 23%. Viewing this relative increase in each PSA interval, a DRE seems to be more useful than proposed by Halpern *et al.* (1). But the absolute numbers are truly low with developing CSPC in only one (DRE negative) or two men (suspicious DRE) out of 140 men within a 10 years' interval when the PSA is low and <2 ng/mL. But with PSA values >3 and again out of 140 men, already 19 (DRE negative) and 32 (suspicious DRE) men will develop CSPC within 10 years.

So, what can we learn from this study?

First, the risk to develop CSPC is low when the PSA is low and <2 ng/mL. This should not force a DRE if a screened man presents with these low PSA values at the office of his general practitioner.

Second, when requesting an individual check-up to exclude PCa, the patient should know that a suspicious DRE doubles his risk of a CSPC regardless the PSA value. Does the situation change from screening, which is defined as presumptive identification of unrecognized disease by means of tests or examinations that can be applied rapidly, to early detection, a DRE should be therefore offered from each physician.

The realistic situation in 2018 has no scenario for a screening anymore within or without studies. The data of the ERSPC show a significant 21% mortality reduction (3), which is likely to further increase to an unknown percentage. When considering influencing factors like compliance or detection of advanced PCa in the screening group simply due to their higher age or PSA contamination in the control group, the mortality reduction might reach numbers between 30% and 50% or even higher (80%) (12). With the known stage migration in screening patients to earlier PCa stages and especially lower metastatic cases (13) it is without any question that a PSA test in a man 40 to 55 years will reduce his risk to die of PCa (14,15). The clearly higher risk of dying from PCa with baseline PSA above the median has been summarized in detail (16).

If a man requests a possible early PCa detection, he should get all information of the consequences of a PSA test including a biopsy and infection or pain, a possible PCa detection and possible treatment disadvantages like incontinence or impotence (even if the likelihood is going lower with new treatment options). However, options of active surveillance or alternative treatments should be also mentioned. It would be advisable to present not only the relative PCa risk reduction but also the absolute risk reduction bearing in mind that the lifetime risk to die of PCa is only ~3% but the risk to get diagnosed with PCa is about 5- to 6-fold higher. The patient must also know that PCa is age related and that the risk of an occult PCa (which will never bother him) reaches extreme high number in older age groups (17). With a life expectancy of <10 years, a PSA screening should not be offered.

To summarize, if a man presents with a PSA <2 ng/mL a further distinction between <1 and 1–2 ng/mL should be used to recommend the next test interval in line with the EAU recommendation (18). If the PSA is <1 ng/mL, the next PSA test can be offered up to 8 years later (16) or 6–10 years later (15). A more conservative recommendation for early detection can be a 4-year interval for these very low PSA concentrations <1 ng/mL. For PSA values 1–2 and 2–3 ng/mL, the screening intervals should be 2–4 years (15,16). A DRE should be offered only if the patient requests an early detection. The much smaller group of men with PSA >2 should undergo a DRE and an increasing number will go for further diagnostic tests like a prostate mpMRI or PHI. If a man presents with a suspicious DRE and a PSA 2 to 10 ng/mL we recommend in 2018 a mpMRI.

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