Benefits and Risks of Prostate Cancer Screening

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Prostate Cancer Screening: Pro

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There are many reasons for writing a pro statement about prostate-specific antigen (PSA) screening for prostate cancer (PCa). The goal of this statement is to examine the efficiency of PSA as a screening tool.

Recent guideline statements and recommendations have led to further confusion and controversy about the use of PSA testing for the early detection of PCa. Much of this literature is not always unconvincing. Do we have evidence that something fundamental has changed in our knowledge about PCa screening? PCa is the second most frequently diagnosed type of cancer worldwide and the sixth leading cause of cancer deaths in men. In Germany, it is the most commonly diagnosed cancer and the third leading cause of cancer deaths [1]. The PSA test, like any early detection tool, has its limitations. However, it can be credited with saving lives by finding PCa at an early stage. In most cases, the disease is relatively slow growing and can be detected with high probability before it becomes incurable.

PSA is also known as human kallikrein 3 and belongs to the family of serine proteases. PSA is an androgen-regulated protease and abundantly produced and secreted from benign and malignant prostate epithelial cells. The PSA test was originally approved by the U.S. Food and Drug Administration (FDA) in 1986 to monitor the progression of PCa, due to the often elevated blood levels of PSA found in men who had been diagnosed with the disease. In 1994, the FDA approved the use of the PSA test in conjunction with a digital rectal exam (DRE) to test asymptomatic men for PCa. The PSA test can be done in the form of a simple blood test with insignificant side effects similar to a blood draw. In contrast, colon (colonoscopy) and breast cancer (mammography) screening involve more invasive

screening tools. The general use of PSA testing began in the early 1990s in the United States where a 40% decrease in PCa deaths has been found since as well as a 75% decrease in the incidence of advanced stages at the time of the initial diagnosis. This success has been largely attributed to PSA screening [2–4].

Over the past 25 years, the 5-year relative survival rate for all stages combined has increased from 68% to almost 100%. According to the most recent data, 10- and 15-year relative survival rates are 98 and 93%, respectively [5]. A benefit of PSA screening is also visible in Germany. A current publication by the Robert Koch Institute mentions a 20% reduction in age-specific mortality of PCa since 1980 [6]. Figure 1 represents the PCa incidence and mortality in Germany in the year 2000 compared to 2010.

It is well known that the harms of screening include false-positive results which can cause anxiety and lead to unnecessary biopsy which may result in overdiagnosis and overtreatment. However, it is also known that overdiagnosis does not automatically translate into overtreatment. Furthermore, overtreatment can be temporally avoided by offering active surveillance to men with low-risk PCa. The challenges of PSA screening are to maximize the benefit (reduction of PCa mortality) and minimize cost (overtreatment) (table 1).

Whether or not PSA testing is successful in the reduction of PCa mortality, remains to be seen as evidence is still lacking. That the harms of screening-induced overdiagnosis and overtreatment are justified by the benefits, in terms of reduced PCa mortality, is open to debate. Therefore, the topic of the degree of benefit and harm of such screening is continuously being discussed among the public and the medical community. Also, political healthcare discussions on PSA screening in Germany, in association with cost pressure on statutory health insurances, indicate a one-sided focus against routine PSA screening.

Fig. 1. Development of age-standardized incidence and mortality rates of PCa for men aged 45–85 years in Germany; data for 2000 and 2010. Data originated from surveys from the German Center for Cancer Registry Data at the Robert Koch Institute.

Another focus of this ongoing debate is the recommendation by the U.S. Preventive Services Task Force (USPSTF) against PSA-based screening for PCa (Grade D recommendation) [7]. There are several comments in the current literature, which disagree with the proposed recommendations [8, 9]. Carlsson et al. [10] stated that the USPSTF report contained a number of important errors of fact, interpretation, and statistics. Also, an important aspect was the publication of the results of the prospective randomized controlled clinical trials (RCTs) designed to analysis the theory that PSA screening would reduce mortality from PCa. The European Randomized Study of Screening for Prostate Cancer (ERSPC) [11] analyzed this topic in Europe like the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) [12] did in the United States. Important aspects of these two largest, highest-quality trials and current publications are succinctly summarized in the following.

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)

The PLCO trial was designed to determine the effect of annual PSA testing and DRE on mortality from PCa. The screening group was offered annual PSA testing for 6 years and DRE for 4 years. A sextant biopsy was recommended for PSA values ≥ 4.0 ng/ml and/or abnormal DRE. The initial power calculation included 37,000 men in each arm and documented a 27% mortality reduction in the screening group versus the control group, with 90% compliance and $<20\%$ contamination [13]. 38,350 men in the control group and 38,343 in the screening group between the ages of 60 and 74 years were enrolled [12].

Table 1. Expectations from PSA screening

Reduction in PCa mortality
Reduction in the development of symptomatic metastatic disease
Identifying men at highest risk for aggressive disease
Screening tools must be easy to apply in clinical practice
Minimizing overtreatment
PCa diagnosis must be uncoupled from PCa intervention
Improving future quality of life

The first reporting in the year 2009 on the PLCO trial after 7–10 years of follow-up screening demonstrated no reduction in PCa mortality, and similar results were shown at 10 years. The compliance rates with PSA and DRE were 85 and 86%, respectively. Crucially, at the time of reporting, for the 10-year follow-up only 67% of mortality data were available, with 89% complete follow-ups at 7 years. The authors of the PLCO trial attempted to explain the lack of reduction in mortality: One reason might have been the level of screening in the control group which was substantial enough to dilute any effect of annual screening in the screening group. The contamination from PSA testing was significant, increasing from 40% in year 1 to 52% in year 6 [12]. Therefore, an indirect indication of the dilution between screening and control group is the missing ‘stage shift’ of the screening group. Normally, screening results shift to a higher proportion of cases with an earlier stage of cancer at diagnosis. This shift might as a consequence result in a reduction in mortality. Another important flaw of the PLCO trial was noncompliance in the screening group. Only 40% of patients with an elevated PSA level were biopsied [14]. Also worth mentioning is the data on PCa mortality gathered with the screening arm of PLCO. Those men who were pre-screened and had undergone one or more PSA tests at baseline before being randomized to the screening arm, showed a 25% lower PCa mortality compared to those who were not pre-screened before randomization. This fact verifies a positive effect of screening and reveals a further limitation of this trial. Having a short follow-up of roughly 10 years is inadequate for a generally slowly growing and progressing cancer [8].

The results of the PLCO trial support the validity of the recent recommendation of the USPSTF, especially against screening all men over the age of 75 years [7]. The latest update of the PLCO trial with more person years of follow-up also failed to detect a reduction in mortality from PCa after 13 years. PSA screening was found to be associated with a statistically significant 12% increase in the incidence of PCa and a non-statistically significant decrease in the incidence of high-grade PCa in the screening arm. Correlations with age, baseline comorbidity, or pre-trial testing could not be demonstrated. However, it is important to note that only 57% of study participants were followed to 13 years and included in the update [15]. These results are difficult to interpret based on the flaws of this trial, such as the significantly increasing contamination from PSA testing in the control group.

Table 2. ERSPC trial

	Schröder et al., 2009 [11]	Schröder et al., 2012 [17]
Follow-up, years	9–11	11
Patients (core age group), n	162,234	162,388
Mortality reduction, %	20	21
Mortality reduction after adjustment for noncompliance, %	–	29

The European Randomized Study of Screening for Prostate Cancer (ERSPC)

A total of 182,000 men between the ages of 50 and 74 years were enrolled in the ERSPC trial in 7 European countries. The core age group included 162,234 men aged between 55–69 years. PCa mortality was the primary endpoint, similar to the PLCO trial. Men who were randomly assigned to the screening group were offered PSA screening for a period of 4 years and DRE once every year. Most centers recommended a sextant biopsy for PSA values ≥ 3.0 ng/ml and/or abnormal DRE.

In Italy, Finland, the Netherlands, and Belgium, biopsy was indicated in most centers at a PSA value of ≥ 4 ng/ml [11]. De Koning et al. [16] calculated the power of the core age group after final recruitment and found that the ERSPC trial had sufficient power to detect a significant difference in PCa mortality between the two arms if the true reduction in mortality by screening is 25%. After a median of 11 years of follow-up in the core age group, the cumulative incidence of PCa was 9.6% in the screened group and 6.0% in the control group. PCa death was reduced by 21% in the screened group compared with the control group and 29% after adjustment for non-compliance; no shift was displayed compared to the 9-year follow-up. Compliance with PSA testing was 82% and contamination 20% in the control group. The absolute reduction in mortality in the screening group was 1.07 deaths per 1,000 person years at a median follow-up of 11 years.

The benefit of screening was restricted to the core age group (55–69 years) at the time of randomization [11, 17] (table 2). The relative risk reduction was 38% during years 10 and 11, but screening had no effect on all-cause mortality [17]. An important item influencing PCa-specific mortality is where the patients were treated. Patients of the screening arm who were diagnosed with PCa were more likely to be treated in an academic center than men who were diagnosed in the control arm. The differences between the groups concerning the location of treatment are important because the outcomes of major surgery are better in large referral centers than in community hospitals, representing an advantage for the screening arm [18]. Furthermore, an accurate estimate from a screening trial requires longer follow-up. The Göteborg screening trial as part of ERSPC demonstrated after 14 years of follow-up a reduction in PCa mortality of 44 and 56% (unadjusted or adjusted for noncompliance), respectively. The authors explained the different reduction rates in PCa mortality compared to the PLCO trial by the absence of pre-screening in this trial, which

meant many aggressive cancers were still detectable. In addition, the rate ratio for death from PCa was 0.56 and thus can be compared with that of those practices of screening recommended for breast and colon cancer [19]. Another important finding of this study was that diagnosis of PCa did not automatically result in radical treatment. 40% of the men in the screening group were placed under active monitoring.

Results at 11 years of follow-up showed that in certain circumstances, PSA testing and early diagnosis reduce death from PCa. Furthermore, a 31% reduction in metastatic disease was documented [17]. Despite these findings, Schröder et al. [17] refrained from a general recommendation due to no current information on the balance of benefits and adverse effects of the screening being disclosed.

Conclusion

In conclusion, diverging results of these large clinical trials reflect the variable guidelines and recommendations for PSA screening for PCa. The primary goal of PCa screening is to reduce PCa-specific mortality. First, within the field of PCa screening, the issue of overdiagnosis and subsequent overtreatment is clearly acknowledged, and there is an ongoing discussion taking place worldwide. PCa remains a major health problem in an aging population. PSA screening saves lives and reduces the burden of metastatic disease [11, 19]. We also recognize and agree with Catalona and Loeb [20] who argue that PSA continues to be the best biomarker available for early PCa detection. At the 2013 DGU Congress in Dresden, William J. Catalona from Chicago gave an extremely critical appraisal of the USPSTF recommendation. He illustrated several methodological deficits and substantiated his disagreement with the USPSTF recommendation. Not involved in the decision-making were urologists or cancer specialists. Catalona highlighted that the PSA test remains an important tool for PCa screening, but emphasized the need to take into account patient-specific factors such as family history, comorbidities, and life expectancy. He demanded to sufficiently inform patients about the benefits and limitations of PSA testing [8].

A key point is that a targeted approach to PSA screening might help to reduce the harms of overtreatment and highlight the reduction in cancer-specific mortality. In 2014, Vickers et al. [21] published the ‘Five Golden Rules for Transforming Prostate-Specific Antigen Screening’ which describe responsible handling of PSA screening: i) Get consent; ii) Do

Table 3. RCTs investigating PCa screening

	ERSPC [17]	PLCO [15]	Norrköping [27]	Quebec [28]	Stockholm ^b [29]	Göteborg ^c [19]
n	162,387	76,685	9,026	40,486	27,204	20,000
Risk of bias ^a	low	low	high	high	high	low
rRR PCa mortality, %	20	–	–	62	–	44
rRI overdiagnosis, %	41	12	32	not reported	–	35

rRR = Relative risk reduction; rRI = relative risk increase.

^aAs assessed by Ilic et al. (Cochrane Review), 2013 [25].

^bOnly one single screening round.

^cSelective reporting of ERSPC results.

not screen men who will not benefit; iii) Do not biopsy without a compelling reason; iv) Do not treat low-risk disease; and v) If you have to treat, do so at a high-volume center. Based on these rules, it should be possible to avoid a step back into the pre-PSA era when a high proportion of PCa was diagnosed at an advanced stage.

The 2013 update of the EAU Guidelines on Prostate Cancer recommends screening on an individual basis which also implies a baseline measurement of PSA in all men aged 40–45 years to initiate a risk-adapted follow-up approach [22, 23]. The goal should therefore be to maximize the benefits of PSA testing for PCa screening and minimize its harms.

Prostate Cancer Screening: Contra

Corinna Schaefer (Berlin)

PSA testing has led to an ongoing controversy. It is estimated that more than half of all men over 50 years of age know their PSA level, and screening for PCa is wide-spread. However, meta-analyses and systematic reviews suggest that the benefit of PCa screening is to be doubted while its harms are serious [24, 25]. Richard Ablin, who discovered PSA in 1970, stated in 2010: ‘I never dreamed that my discovery four decades ago would lead to such a profit-driven public health disaster’ [26]. The PSA debate reveals a dilemma that inheres in all cancer screening tests but is hardly discussed for tests that seem to have undoubtedly proven to prevent cancer deaths: potential harms and benefits go hand in hand.

The Evidence: Benefits and Harms of PSA Testing

The description of the evidence for PCa screening is based on a systematic literature search performed in Medline in March 2013. Included were RCTs investigating PCa screening (PSA testing/DRE) and systematic reviews or meta-analyses that included RCTs.

Benefits

Compared to other screening tests, there is rather a high level of evidence for PSA testing. The Cochrane systematic re-

view [26] identified five RCTs [15, 17, 27–29] enrolling a total of 341,351 participants (table 3). After assessing for methodological quality items, three trials were considered low quality with a high risk of bias [27–29] while the remaining two provided contradictory results: ERSPC showed a 20% reduction in PCa mortality after 11 years of follow-up, PLCO showed a non-significant benefit in favor of the control. A meta-analysis of both trials suggested that screening does not significantly affect PCa mortality [25]. Hence, from a methodological perspective, the case seems obvious: No significant benefit means that the test is useless. However, it is to be questioned whether a meta-analysis, as conducted in this case, is appropriate. It was stated that both trials had a low risk of bias; however, the enormous contamination of the PLCO with 52% of men in the control group having had at least one PSA test was not considered. With a primary endpoint as rare as PCa mortality and the small possible effect size, the PLCO was underpowered to detect a screening effect [30]. Hence, pooling these data with ERSPC may be misleading, and the ERSPC results are likely to be more valid. It also has been argued that follow-up was not long enough to detect a screening effect, as PCa generally grows slowly. However, comparing the ERSPC findings after 9 and 11 years of follow-up showed no difference in effect size after longer follow-up: the relative risk reduction was 20% after 9 and remained so after 11 years. Observational data shows a considerable increase in (untreated) PCa mortality only 25 years after diagnosis [31], suggesting that a possible effect of screening would take a comparable time span to become apparent.

The 2010 publication of the Göteborg trial results, reporting a 44% relative risk reduction and a number needed to screen of 293 [19], has been criticized for selective reporting of the ERSPC results. Indeed, if the Swedish cohort had that enormous benefit, the screening effect in other ERSPC subgroups must have been much smaller. However, we can learn one thing from this trial which is of high internal validity: In a cohort at high risk of PCa mortality (which in that trial was 1.89-fold higher than in Germany) PSA testing may have a greater effect.

Summing up and weighing up these results, we concede – most astonishingly for a plead against PSA testing – that this screening test is likely to reduce PCa mortality.

Table 4. Harms per 1 PCa death prevented: the ERSPC results

	Results per 1,055 men screened, n
PCa death prevented	1
False-positive result	192
Overdiagnosis	37
Harms due to overtreatment ^a	
Erectile dysfunction	12
Urinary incontinence	4

^aData from Carlsson et al., 2011 [32].

Harms

While the evidence for benefit is conflicting, it is unambiguous with regard to the harms. Both trials report an increase in PCa incidence in the screening groups: The PLCO trial, even with its 52% contamination, shows a significant 12% relative increase, with the relative increase reported in the ERSPC being as high as 41%. Hence, evidence for overdiagnosis is robust. To be clear about the terminology, we do not talk about false-positive results (which, according to ERSPC data, were as high as 75%) but of cancer that would not have been detected without screening and would not have caused any symptoms. It is a paradox of any cancer screening test that it increases morbidity by inducing the condition it is supposed to detect.

Data on the natural history of PCa suggests that only a minority of these cancers is lethal even if left untreated: In a Swedish cohort of 223 men, only 17% of diagnosed PCa lead to death after the enormous follow-up of 32 years, and after all but 3 patients died [31]. Screening for non-lethal cancers leads to increased morbidity without reducing mortality.

Both trials also show that overdiagnosis leads to overtreatment with an increase in treatment-related harms, such as erectile dysfunction and urinary incontinence, in the screening group [32]. Hence, not only are otherwise healthy men confronted with an alarming diagnosis and undergo unnecessary treatment due to screening, but some of them even suffer long-term and irreversible complications that continuously affect their quality of life.

Uncertainty

Lastly, in the ERSPC and Göteborg trials, which showed a significant reduction in PCa mortality, overall mortality did not differ between the intervention and the control group. This does not mean that there is evidence that screening does not affect overall mortality: In fact, none of the trials were powered to detect such an effect. It would take a sample of 3,000,000 participants for an 80% power to detect a possible screening-related reduction in overall mortality [33]. Trials of such a size would not be manageable. Thus, we will never know if men who undergo PSA screening live longer. This uncertainty is the same for all other screening tests.

Drawing a Balance

Even if we concede that PSA screening reduces PCa mortality within a range as seen in the ERSPC, we must admit that the harms are considerable. To understand the correlation of harms and benefits, it is helpful to show the associated effects in absolute numbers rather than in terms of relative risk reduction. Based on the ERSPC findings, this balance is as follows (table 4): For one PCa death prevented, 192 men received a false-positive result and 37 an overdiagnosis [17], 12 men became impotent and 4 incontinent due to overtreatment [32].

Screening Decisions

There are two levels on which screening decisions are made: the collective or public health level (that is, making health policy decisions), and the individual level (every man making his personal decision whether or not to undergo a screening test). These two are clearly to be distinguished when weighing up the pros and cons of PSA testing.

Public Health Perspective

On a collective level, evidence clearly suggests that population-based PCa screening should not be installed: In Germany, the term ‘benefit’ of healthcare interventions is defined in the Code of Social Law, Book V as: ‘improvement of health status, reduction in disease duration, improvement of overall survival, reduction in complications or side effects, or improvement of quality of life’ [34]. The only proven benefit for cancer screening tests is a reduction in cancer-specific mortality; the effect on overall survival is unknown. On the other hand, the considerable number of overdiagnoses translates into an increase in disease burden and duration, harms and complications, and a reduction in health status and quality of life, which is 37-fold higher than the equivalent benefit for those whose PCa death is prevented. Hence, from the public health perspective, the harms clearly outweigh the benefit. With the evidence for a reduction in PCa mortality being weak and that for overdiagnosis being robust, it is likely that a population-based screening program would do more harm than good. Furthermore, the introduction of a population-based PCa screening program would at the least double treatment-related costs due to overtreatment [35].

Individual Screening Decisions

Individual screening decisions are ideally based on evidence and correct risk perception, individual risk factors, values, and preferences. The latter may differ as much as differ the men who make these decisions. When it comes to individual values and preferences, there are no objectively ‘right’ or ‘wrong’ decisions. It is possible and plausible that a man values the rare benefit of not dying of PCa much higher than the more common risk of being diagnosed with a cancer that would not have caused any symptoms or affected quality of

life without screening, and thus opts for screening. Only, it is essential that men who actively want to decide for or against screening are provided with the information that enables them to understand their individual risk factors, the benefits and harms of the screening test, and possible consequences. Informed decision has been formulated as a goal in the German National Cancer Plan [36], and criteria for high-quality screening information have been set [37, 38]. It is to be doubted that men will obtain appropriate information from their physician during consultation, as it has been shown that the majority of physicians have difficulties in understanding cancer statistics and conveying correct risk perceptions [39]. Men who want to make informed screening decisions will have to retrieve information from other reliable sources [40, 41]. However, even if provided with the best available information, having understood the balance of harms and benefits and the individual risk factors, it is helpful to further question some basic assumptions surrounding cancer screening before making a decision:

From Overdiagnosis to Overtreatment?

Overdiagnosis is the most severe side effect of PCa screening, and with 37 per one cancer death prevented it occurs alarmingly often. Overdiagnosis leads to overtreatment, and treatment-related long-term complications have shown to significantly affect quality of life [32]. In contrast to all other oncologic specialties, urologists have developed a strategy to avoid overtreatment: active surveillance is recommended for men with low-risk PCa [42–45] and aims at deferring active treatment as long as there is no sign of disease progression [46]. It has even been questioned whether Gleason 6 disease should still be labelled as cancer [47, 48]. Thus, active surveillance is a way of avoiding treatment-related harms and complications, and might serve as an argument for undergoing screening. On the other hand, men with an overdiagnosis on the active surveillance protocol are still chronic cancer patients with a threatening diagnosis as it is not possible to distinguish indolent from aggressive cancer at the time of diagnosis [49]. Without screening, they would not have known of their insignificant disease and would have considered themselves as ‘healthy’.

Risk-Adjusted Screening?

Evidence from the Göteborg trial suggests that men at high risk of dying from PCa may benefit substantially from PSA screening. The problem is that actual data and acknowledged risk factors before diagnosis (like age, family history, ethnics) only allow assessing the risk of developing PCa and not of dying from PCa. Screening for men at higher risk of developing PCa helps reduce false-positive results but not overdiagnosis. On the other hand, there is evidence from observational data and case control studies that PSA thresholds at a certain age are associated with a history of advanced or lethal PCa [50–52]. These findings allow to exclude some men at low risk – as defined by

the PSA threshold at a certain age – from further screening, and to reduce overdiagnosis to some extent. However, in these studies, even among the ‘high-risk’ group, only a minority developed fatal disease. The majority of men being labelled ‘high-risk’, who have to undergo further tests, will experience even more anxiety and impairment of quality of life without screening having any effect on morbidity and mortality.

What Is the Use of Not Dying from PCa?

PCa, in its final phase, is associated with pain and suffering. When hearing that PSA screening has the potential to prevent men from dying of the disease, we somehow assume that those men whose cancer death is prevented live a long and healthy life. However, we have learned from the existing trials that this is not necessarily the case: Overall mortality was not affected by screening, and we may never know if it has the potential to do so. Furthermore, living longer does not necessarily mean living healthier: Some conditions probably can be prevented and others cannot. We do not have valid data on the (co)morbidity and general health status of screened men; however, it is conceivable that some men whose PCa death is prevented, develop a history of stroke or dementia or other major conditions. We do not know if this will happen, or what the likelihood is for it to happen. Only, the benefit of not dying of PCa may be put into perspective. Preventing PCa death may be of high priority for men who fear being confronted with the certainty of pain and death. It may be less of a priority for men who accept any cause of death at a certain age as being natural.

Anxiety and Burden of Knowing

It seems obvious that preventing a history of advanced and lethal cancer improves quality of life, in the sense that ‘saved’ men do not have to suffer symptoms related to cancer progression and side effects of aggressive treatments like chemotherapy. Then again, quality of life is not only defined by disease-specific outcomes. Screening may adversely affect quality of life not only by inducing overdiagnosis and overtreatment. First, anxiety goes along with waiting for the results, and especially with interpreting them: In the ERSPC [17], three out of four elevated PSA levels were not caused by PCa. That does not only mean that three quarters of men undergoing biopsy are confronted with a false-positive result; in many cases, a negative biopsy will not necessarily give the all-clear but be the start of a long phase of uncertainty and fear of disease. Especially, when an elevated PSA level is not the result of a measuring error, but persists or even increases over time. With a 5- or 10-year history of slowly but continuously increasing PSA levels, uncertainty may grow to such an extent that a PCa diagnosis may come as a relief because at least there is an explanation for the phenomenon and active treatment provides a strategy to act and overcome uncertainty. Second, out of 1,055 screened men, one is saved from PCa death while 4 still die of their disease. Screening-induced lead time bias is esti-

mated to be 7–10 years for PSA testing [53]. For these 4 men diagnosed with incurable disease, screening means to be confronted up to 10 years earlier with a fatal diagnosis, without having any benefit from knowing earlier. Without screening, they would have had up to 10 more years in which they could have felt ‘healthy’ without worsening their prognosis.

Responsibility and Health as Obligation?

The German National Cancer Plan has set the goal that adherence to screening programs that have proven to reduce cancer-specific mortality is to be increased [36]. Many campaigns have been set up to motivate citizens to undergo screening tests like colonoscopy or mammography. Although PSA testing is not one of the population-based screening programs, the beliefs and rationales behind such campaigns are transferable to men who opt for it: The underlying principle is that we take responsibility and that we can actively influence our health status. This idea of ‘feasibility’ of health neglects that it is a complex phenomenon with many components, some of which man cannot influence at all, and it induces the concept of health as the product of active, careful, and responsible citizens [54]. Thus, far beyond any evidence for outcome-related harms and benefits, the idea of screening itself is highly valued, forcing people who decide against it – rather than those who opt for it – to justify their decision. The social consequences of this development, like the ideas of health as a social obligation and disease as an individual failure, are worth debating but ought to be discussed in another setting.

It May Be Reasonable Not to Undergo PSA Testing

A man carefully weighing up the pros and cons of PSA testing will have to consider the following facts: i) It may prevent death from PCa in 1 out of 1,055 screened men; ii) It has not proven to affect overall mortality; iii) It is not able to prevent fatal disease in 4 out of 1,055 screened men; iv) It causes overdiagnosis and overtreatment in 37 out of 1,055 men; v) It leads to false-positive results in 192 out of 1,055 men; vi) PSA thresholds help creating ‘risk groups’ that allow to exclude some men from further screening, but increase anxiety for the remaining men at high risk, of whom only a few will develop fatal disease; vii) It is unknown if screening restricted to men at high risk provides better outcomes as data is lacking; and viii) active surveillance offers a strategy to prevent the harms of overtreatment but not overdiagnosis.

This list comprises a few pros, some uncertainties, and considerable cons. The pro arguments can outweigh the cons and uncertainties, if preventing cancer death regardless of effect on overall mortality and morbidity is the primary goal. However, as opting for the test may entail considerable morbidity, and taking into account the uncertainty regarding its benefit, the process of decision making may result in a reasonable, responsible, and informed decision not to undergo PSA screening.

Prostate Cancer Screening: Comment

Jochen Heß (Essen); Herbert Rübben (Essen)

The debate on PSA-based PCa screening is mainly focusing on the evidence related to screening and the balance between expected benefits and potential associated harms. Solely based on statistical evidence, one must admit that there is no significant benefit. On this point, Mrs. Schaefer was right. However, statistics and meta-analyses are only as valid as the trials they refer to, and counseling a man on health issues is more than presenting survival estimates – despite the fact that those screening studies do not reflect daily urological routine.

First, Vickers and Lilja [55] have addressed two important facts: i) PSA does not qualify to predict detection of PCa in a core biopsy; and ii) the possibility to detect PCa is not a clinically relevant endpoint. Contrary to the statement by Fornara, it is not the aim of PSA testing to detect PCa but to discriminate at best significant from insignificant cancers. The rationale for screening asymptomatic men is the assumed reduction of mortality or symptomatic metastatic disease with early detection of the cancer.

Both, the pros and the cons, mainly refer to a few screening studies published so far [17, 19, 27–29, 56]. After assessing for methodological quality items, Schaefer considered only two of them [17, 56] which had a low risk of bias. Noncompliance and contamination weakened the effect of screening in both trials, and follow-up was relatively short, particularly with regard to the mean lead time of PCa. If any effects of screening on survival are present in the trials, they are benefits in terms of cancer-specific survival. Overall mortality, however, is a more relevant endpoint because it takes into account possible adverse effects of screening and misattribution of the cause of death [57]. Dubben [33] pointed out that it would be nearly impossible to show an advantage for PCa screening regarding overall mortality because of the sheer number of participants needed. Besides, the effect of screening will not have an immediate impact on survival but will be evident only after many years. For statistical reasons, we will never be able to achieve valid data on impact on overall survival. Thus, it is not quite fair to state that there must be an ‘improvement in overall survival’ (Schaefer).

One criticism of the contra statement was that overdiagnosis would lead to overtreatment. This is a point that was addressed by the pro fraction with the concept of active surveillance as a welcome alternative to avoid an unnecessary immediate (over)treatment and thereby minimizing associated adverse effects. Additionally, prediagnostic PSA-based risk stratification helps to reduce the problem of overdiagnosis which precedes the problem of overtreatment. In the screening studies (PLCO/ERSPC), intervention was indicated when a predefined PSA threshold was exceeded, regardless of the patients’ individual clinical situation. In fact, a ‘risk-adopted approach’ (Fornara) or an individual ‘risk assessment’ (Schaefer) is mentioned in both statements, but neither go into detail.

To properly assess the PSA value later in life, it is useful to establish an individual baseline PSA value at a younger age (40–45 years). Some authors have shown that an elevated PSA value earlier in life indicates the existence and significance of PCa later on [52, 58, 59]. Approximately 99% of men <45 years of age had PSA values of <4 ng/ml [60]. Connolly et al. [61] demonstrated a direct correlation between PSA baseline value and risk of developing high-risk PCa and PCa-specific mortality. Consideration of early individual PSA baseline values could lead to risk stratification and a slim early detection program, and would spare many biopsies [62, 63]. This can be supplemented with an individual PSA velocity [64]. The combination of PSA-associated parameters can further improve the validity of a single PSA value. Roobol et al. [65] demonstrated a reduction in biopsy rates of about 37% with the use of a nomogram-based risk indicator.

Apart from the focus on mere survival estimates, the impact of screening on developing metastatic disease as a beneficial side effect was mentioned in the pro statement. The risk of being diagnosed with metastatic PCa was reduced by 48.9% in the Swedish part of ERSPEC [66]. Similar findings were reported elsewhere [67]. Reduction in metastatic disease leads to a reduction in PCa-related morbidity, and is of great importance especially for younger men.

Indeed, there are different perspectives – which was stated very well by Mrs. Schaefer. Public health aspects are rarely in line with individual perspectives. From the public point of view, common resources play an important role. Mrs. Schaefer stated that the introduction of a population-based PCa screening program would lead to an increase in treatment-related costs of at least 50%. Again (similar to the mentioned screen-

ing studies), this mathematical analysis refers to the exceedance of a single snapshot PSA threshold (and a hypothetical screening attendance of 100%), which leads to an unreflected biopsy independent of previous individual PSA values. The authors of this estimation clearly state: ‘Only a small part of this increase can be attributed to the cost of screening itself.’ [35]. In times of limited financial resources, a society has to decide what amount of money it is willing to dedicate to medical issues. Individual screening decisions are amongst others based on correct risk perception and preferences in situations where there are no objectively ‘right’ or ‘wrong’ decisions (Schaefer).

In summary, when advising a man on PSA screening it is necessary to inform him about the methodological pitfalls of the literature and evidence-focused debate. Taking into account the patient’s personal preferences, risk-adapted PSA-based screening is a good tool to determine whether a biopsy is needed. Along with the concept of active surveillance for men with a low-risk profile, overdiagnosis and overtreatment can be reduced substantially.

Disclosure Statement

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References

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D: Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
- Etzioni R, Tsodikov A, Mariotto A, Szabo A, Falcon S, Wegelin J, DiTommaso D, Karnofski K, Gulati R, Penson DF, Feuer E: Quantifying the role of PSA screening in the US prostate cancer mortality decline. *Cancer Causes Control* 2008;19:175–181.
- Loeb S, Catalona WJ: Prostate-specific antigen (PSA) should drive doing prostate biopsies. *Urol Oncol* 2012;30:1–2.
- Andriole GL Jr: PSA screening and prostate cancer risk reduction. *Urol Oncol* 2012;30:936–937.
- American Cancer Society: The American Cancer Society’s 2013 Cancer Facts & Figures. Atlanta, GA, ACS, 2013, p v.
- Robert Koch-Institut: Verbreitung von Krebserkrankungen in Deutschland. Berlin, RKI, 2010.
- Moyer VA, U.S. Preventive Services Task Force: Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2012;157:120–134.
- Catalona WJ, D’Amico AV, Fitzgibbons WF, Kosko-Lasaki O, Leslie SW, Lynch HT, Moul JW, Rendell MS, Walsh PC: What the U.S. Preventive Services Task Force missed in its prostate cancer screening recommendation. *Ann Intern Med* 2012;157:137–138.
- Kwiatkowski M, Klotz L, Hugosson J, Recker F: Comment on the US Preventive Services Task Force’s draft recommendation on screening for prostate cancer. *Eur Urol* 2012;61:851–854.
- Carlsson S, Vickers AJ, Roobol M, Eastham J, Scardino P, Lilja H, Hugosson J: Prostate cancer screening: facts, statistics, and interpretation in response to the US Preventive Services Task Force Review. *J Clin Oncol* 2012;30:2581–2584.
- Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis LJ, Recker F, Berenguer A, Maattanen L, Bangma CH, Aus G, Villers A, Rebillard X, van der Kwast T, Blijenberg BG, Moss SM, de Koning HJ, Auvinen A; ERSPEC Investigators: Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320–1328.
- Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, Fouad MN, Gelmann EP, Kvale PA, Reding DJ, Weissfeld JL, Yokochi LA, O’Brien B, Clapp JD, Rathmell JM, Riley TL, Hayes RB, Kramer BS, Izmirlian G, Miller AB, Pinsky PF, Prorok PC, Gohagan JK, Berg CD; PLCO Project Team: Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360:1310–1319.
- Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, Fogel R, Gelmann EP, Gilbert F, Hasson MA, Hayes RB, Johnson CC, Mandel JS, Oberman A, O’Brien B, Oken MM, Rafla S, Reding D, Rutt W, Weissfeld JL, Yokochi L, Gohagan JK; Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Project Team: Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials* 2000;21(suppl):273S–309S.
- Pinsky PF, Parnes HL, Andriole G: Mortality and complications after prostate biopsy in the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) trial. *BJU Int* 2014;113:254–259.

- 15 Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, Fouad MN, Isaacs C, Kvale PA, Reding DJ, Weissfeld JL, Yokochi LA, O'Brien B, Ragard LR, Clapp JD, Rathmell JM, Riley TL, Hsing AW, Izmirlian G, Pinsky PF, Kramer BS, Miller AB, Gohagan JK, Prorok PC; PLCO Project Team: Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. *J Natl Cancer Inst* 2012;104:125–132.
- 16 De Koning HJ, Liem MK, Baan CA, Boer R, Schroder FH, Alexander FE; ERSPEC: Prostate cancer mortality reduction by screening: power and time frame with complete enrollment in the European Randomised Screening for Prostate Cancer (ERSPEC) trial. *Int J Cancer* 2002;98:268–273.
- 17 Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis LJ, Recker F, Páez A, Mänttinen L, Bangma CH, Aus G, Carlsson S, Villers A, Rebillard X, van der Kwast T, Kujala PM, Blijenberg BG, Stenman UH, Huber A, Taari K, Hakama M, Moss SM, de Koning HJ, Auvinen A; ERSPEC Investigators: Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med* 2012;366:981–990.
- 18 Wolters T, Roobol MJ, Steyerberg EW, van den Bergh RC, Bangma CH, Hugosson J, Ciatto S, Kwiatkowski M, Villers A, Lujan M, Nelen V, Tammela TL, Schroder FH: The effect of study arm on prostate cancer treatment in the large screening trial ERSPEC. *Int J Cancer* 2010;126:2387–2393.
- 19 Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, Pihl CG, Stranne J, Holmberg E, Lilja H: Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol* 2010;11:725–732.
- 20 Catalona WJ, Loeb S: The PSA era is not over for prostate cancer. *Eur Urol* 2005;48:541–545.
- 21 Vickers A, Carlsson S, Laudone V, Lilja H: It ain't what you do, it's the way you do it: five golden rules for transforming prostate-specific antigen screening. *Eur Urol* 2014;DOI: 10.1016/j.eururo.2013.12.049.
- 22 Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, Mottet N: EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent – update 2013. *Eur Urol* 2014;65:124–137.
- 23 Heidenreich A, Abrahamsson PA, Artibani W, Catto J, Montorsi F, van Poppel H, Wirth M, Mottet N: Early detection of prostate cancer: European Association of Urology recommendation. *Eur Urol* 2013;64:347–354.
- 24 Djulbegovic M, Beyth RJ, Neuberger MM, Stoffs TL, Vieweg J, Djulbegovic B, Dahm P: Screening for prostate cancer: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2010;341:c4543.
- 25 Ilic D, Neuberger MM, Djulbegovic M, Dahm P: Screening for prostate cancer. *Cochrane Database Syst Rev* 2013;1:CD004720.
- 26 Ablin R: The Great Prostate Mistake. *The New York Times*, March 9, 2010. www.nytimes.com/2010/03/10/opinion/10Ablin.html?_r=0.
- 27 Sandblom G, Varenhorst E, Rosell L, Löfman O, Carlsson P: Randomised PCa screening trial: 20 year follow-up. *BMJ* 2011;342:d1539.
- 28 Labrie F, Candas B, Cusan L, Gomez JL, Bélanger A, Brousseau G, et al.: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. *Prostate* 2004;59:311–318.
- 29 Kjellman A, Akre O, Norming U, Törnblom M, Gustafsson O: 15-year follow-up of a population based PCa screening study. *J Urol* 2009;181:1615–1621.
- 30 Gulati R, Tsodikov A, Wever EM, et al.: The impact of PLCO control arm contamination on perceived PSA screening efficacy. *Cancer Causes Control* 2012;23:827–835.
- 31 Popiolek M, Rider JR, Andrén O, et al.: Natural history of early, localized PCa: a final report. *Eur Urol* 2013;63:428–435.
- 32 Carlsson S, Aus G, Bergdahl S, et al.: The excess burden of side-effects from treatment in men allocated to screening for PCa. *Eur J Cancer* 2011;47:545–553.
- 33 Dubben HH: Trials of prostate-cancer screening are not worthwhile. *Lancet Oncol* 2009;10:294–298.
- 34 SGB V §35b. www.gesetze-im-internet.de/sbg_5/_35b.html.
- 35 Heijnsdijk EA, der Kinderen A, Wever EM, Draisma G, Roobol MJ, de Koning HJ: Overdetection, overtreatment and costs in PSA screening. *Br J Cancer* 2009;101:1833–1838.
- 36 Nationaler Krebsplan, Ziel 1. www.bmg.bund.de/praevention/nationaler-krebsplan/was-haben-wir-bisher-erreicht/ziel-1-inanspruchnahme-krebsfrueherkennung.html.
- 37 Klemperer D, Lang B, Koch K, et al.: Gute Praxis Gesundheitsinformation, Version 1.3 vom 10.03.2009. www.ebm-netzwerk.de/pdf/publikationen/gpgi.pdf.
- 38 Elwyn G, O'Connor A, Stacey D, et al.: Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. *BMJ* 2006;333:417.
- 39 Wegwarth O, Schwartz LM, Woloshin S, Gaismaier W, Gigerenzer G: Do physicians understand cancer screening statistics? *Ann Intern Med* 2012;156:340–349.
- 40 Leitlinienprogramm Onkologie: Früherkennung von Prostatakrebs. Eine Information für Männer. (2012). www.leitlinienprogramm-onkologie.de/uploads/tx_sbdownloader/Patientenleitlinie_Prostatakrebs_Frueherkennung.pdf.
- 41 Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG): Spezial Früherkennung von Prostatakrebs. www.gesundheitsinformation.de/psa-test.1056.56.de.html.
- 42 S3-Leitlinie Prostatakarzinom (2011). www.leitlinienprogramm-onkologie.de/uploads/tx_sbdownloader/S3-Prostatakarzinom-OL-Langversion.pdf.
- 43 National Institute for Health and Care Excellence: Prostate Cancer (CG 175), 2014. guidance.nice.org.uk/CG175.
- 44 European Association of Urology: Guidelines on Prostate Cancer (2013). www.uroweb.org/gls/pdf/09_Prostate_Cancer_LR.pdf.
- 45 National Institute of Health: Role of Active Surveillance in the Management of Men with Localized Prostate Cancer (2011). www.consensus.nih.gov/2011/prostate.htm.
- 46 Parker C: Active surveillance: towards a new paradigm in the management of early prostate cancer. *Lancet Oncol* 2004;5:101–106.
- 47 Carter HB, Partin AW, Walsh PC, et al.: Gleason score 6 adenocarcinoma: should it be labeled as cancer? *J Clin Oncol* 2012;30:4294–4296.
- 48 Klotz L: Cancer overdiagnosis and overtreatment. *Curr Opin Urol* 2012;22:203–209.
- 49 Harnden P, Naylor B, Shelley MD, Clements H, Coles B, Mason MD: The clinical management of patients with a small volume of prostatic cancer on biopsy. A systematic review and meta-analysis. *Cancer* 2008;112:971–981.
- 50 Vickers AJ, Ulmert D, Sjöberg DD, et al.: Strategy for detection of PCa based on relation between prostate specific antigen at age 40–55 and long term risk of metastasis. *BMJ* 2013;346:f2023.
- 51 Vickers AJ, Cronin AM, Björk T, et al.: Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer. *BMJ* 2010;341:c4521.
- 52 Lilja H, Cronin AM, Dahlin A, et al.: Prediction of significant PCa diagnosed 20 to 30 years later. *Cancer* 2011;117:1210–1219.
- 53 Draisma G, Etzioni R, Tsodikov A, et al.: Lead time and overdiagnosis in prostate-specific antigen screening. *J Natl Cancer Inst* 2009;101:374–383.
- 54 Maio G: *Mittelpunkt Mensch: Ethik in der Medizin*. Stuttgart, Schattauer, 2012, pp 376–383.
- 55 Vickers AJ, Lilja H: PSA is dead, long live PSA. *Eur Urol* 2012;61:467–468; discussion 469–470.
- 56 Andriole GL: Update of the prostate, lung, colorectal, and ovarian cancer screening trial. *Recent Results Cancer Res* 2014;202:53–57.
- 57 Black WC, Haggstrom DA, Welch HG: All-cause mortality in randomized trials of cancer screening. *J Natl Cancer Inst* 2002;94:167–173.
- 58 Loeb S, Carter HB, Catalona WJ, Moul JW, Schroder FH: Baseline prostate-specific antigen testing at a young age. *Eur Urol* 2012;61:1–7.
- 59 Orsted DD, Nordestgaard BG, Jensen GB, Schnohr P, Bojesen SE: Prostate-specific antigen and long-term prediction of prostate cancer incidence and mortality in the general population. *Eur Urol* 2012;61:865–874.
- 60 Borgermann C, vom Dorp F, Swoboda A, Ketteniss O, Becker M, Rubben H: PSA quo vadis? It is reasonable to start with prostate-specific antigen testing at the age of 40! *Cancer Epidemiol Biomarkers Prev* 2011;20:1190–1195.
- 61 Connolly D, Black A, Gavin A, Keane PF, Murray LJ: Baseline prostate-specific antigen level and risk of prostate cancer and prostate-specific mortality: diagnosis is dependent on the intensity of investigation. *Cancer Epidemiol Biomarkers Prev* 2008;17:271–278.
- 62 Loeb S, Kettermann A, Ferrucci L, Landis P, Mettler EJ, Carter HB: PSA doubling time versus PSA velocity to predict high-risk prostate cancer: data from the Baltimore Longitudinal Study of Aging. *Eur Urol* 2008;54:1073–1080.
- 63 Grubb RL 3rd, Andriole GL: Can preoperative PSA doubling time and PSA velocity predict outcomes following radical prostatectomy? *Nat Clin Pract Urol* 2006;3:306–307.
- 64 Orsted DD, Bojesen SE, Kamstrup PR, Nordestgaard BG: Long-term prostate-specific antigen velocity in improved classification of prostate cancer risk and mortality. *Eur Urol* 2013;64:384–393.
- 65 Roobol MJ, Steyerberg EW, Kranse E, et al.: A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. *Eur Urol* 2010;57:79–85.
- 66 Aus G, Bergdahl S, Lodding P, Lilja H, Hugosson J: Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer – results from a prospective, population-based randomized controlled trial. *Eur Urol* 2007;51:659–664.
- 67 Van Leeuwen PJ, Connolly D, Gavin A, et al.: Prostate cancer mortality in screen and clinically detected prostate cancer: estimating the screening benefit. *Eur J Cancer* 2010;46:377–383.