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Prostate cancer screening with a PSA test[1]

Extract

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Key statement

Research question

The objective of this investigation is to assess the benefit of prostate cancer screening with the prostate-specific antigen (PSA) test in participants without suspected prostate cancer in respect of patient-relevant outcomes.

Conclusion

With regard to all-cause mortality, there was no hint of any benefit or harm of prostate cancer screening with the PSA test in comparison with no such screening. With regard to prostate cancer-specific mortality, the studies using a PSA cut-off value below 4 ng/mL revealed an indication of a benefit of prostate cancer screening with the PSA test. For the other subgroup, there was no hint of any benefit or harm. Since opportunistic prostate cancer screening with the PSA test was common in the control groups of the 2 largest studies using a PSA cut-off value of 4 ng/mL or higher (i.e. high contamination), it is doubtful whether the PSA cut-off value is the actual characteristic which convincingly explains the difference between subgroups. With regard to the outcome of diagnoses of metastatic prostate cancers, there was an indication of benefit. With regard to the outcomes of health-related quality of life and adverse events as well as the consequences of false-negative screening findings, there was no hint of benefit or harm, albeit based on insufficient available data (no data at all). Proof of harm was found for the consequences of overdiagnoses as well as for false-positive screening findings.

Prostate cancer screening by PSA test causes harm to overdiagnosed men (men with prostate cancer which does not require treatment) as well as to men with false-positive screening results (men without prostate cancer). Much of screening-related harm arises at an early time and, in many cases, persists lifelong.

Prostate cancer screening with the PSA test benefits some men with prostate cancer by sparing them the distress caused by metastatic cancer or delaying the same. However, this benefit arises only after several years. Even these men might experience early treatment-related complications which persist lifelong. It is unclear whether screening leads to any life extension at all in these men.

Considerably more men experience overdiagnosis-related harm rather than benefits from prostate cancer screening by PSA test. All things considered, the benefits of prostate cancer screening with the PSA test therefore do not outweigh the associated harms.

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
CI	Confidence interval
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin
DRE	Digital rectal examination
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HTA	Health technology assessment
IDR	Incidence density ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mpMRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
PSA	Prostate-specific antigen
RCT	Randomized controlled trial
TRUS	Transrectal ultrasound

1 Background

Prostate cancer is a malignant change in the prostate; as it progresses, it can infiltrate directly adjacent tissue (seminal vesicle, urinary bladder, large intestine) and can form distant metastases. As measured by the number of new cases, prostate cancer is the most common tumour disease in men in Germany, making up 23.0% of all cancer cases. For 2016, the Robert Koch Institute estimated that about 58 780 men received an initial diagnosis of prostate cancer [1]. Age is considered the most important risk factor for the development of prostate cancer [1, 2]. At a median age of onset of 72 years, prostate cancer occurs predominantly in advanced age; it is rarely found before the 45th to 50th year of life [1].

Every year, about 14 000 men in Germany die of the consequences of prostate cancer [1]. The prognosis of the disease decisively depends on the tumour stage as well as tumour typing with regard to cell type, grade of tumour cells, and changes in cell structure (often assessed using the Gleason score) [2]. While men with localized prostate cancer and a low Gleason score have a favourable prognosis even without immediate invasive treatment, men with metastatic prostate cancer are thought to have no curative treatment options available to them [2]. It is hoped that screening for prostate cancer will discover cases of prostate cancer with a high risk of progression at a curable stage in order to reduce the morbidity (e.g. pain due to bone metastases) and mortality associated with metastatic prostate cancer [2].

Currently, 2 screening tests are in use in Germany: the digital rectal exam (DRE) and the test for prostate-specific antigen (PSA). While the DRE is covered for male statutory health insurance members starting at age 45, the PSA test is available exclusively as an individual out-of-pocket health service (*Individuelle Gesundheitsleistung*, or IGeL).

Screening measures are potentially associated with considerable harm. For PSA screening, this potential harm particularly includes its high number of false-positive test results, which are associated with subsequent invasive biopsies, and the considerable proportion of overdiagnoses resulting in overtreatment [3–5]. Whether the benefit of PSA screening outweighs the associated harm is still being debated [3–8]. This is reflected by the fact that almost all competent national health authorities and professional societies worldwide are currently opposed to organized, population-based PSA screening [9], but simultaneously, they are often in favour of individual decision-making by the affected person following a shared decision-making process with a physician or using a decision-making aid [2, 10, 11]. Recently, the U.S. Preventive Services Task Force (USPSTF) changed its recommendation from a general rejection of screening to a recommendation of shared decision making in men 55 through 69 years of age [10].

1 Research question

The objective of this investigation is to

- assess the benefit of prostate cancer screening with the PSA test

in participants without suspected prostate cancer in respect of patient-relevant outcomes.

2 Methods

The target population of the benefit assessment is men without suspected prostate cancer. The experimental intervention is screening for prostate cancer with the PSA test. The comparator intervention is no screening with the PSA test.

The investigation examined the following patient-relevant outcomes:

- All-cause mortality
- Prostate-cancer-specific mortality
- Diagnosis of metastatic prostate cancer
- Morbidity (e.g. pain due to bone metastases)
- Health-related quality of life
- Adverse events
- Harm directly or indirectly resulting from the screening, including the consequences of false screening results and overdiagnoses (e.g. consequences of surgeries and other therapies)

Randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions regarding the study duration.

With the aim of retrieving results as efficiently as possible and using existing scientific evidence at the highest evidence level, the 1st step consisted of focused information retrieval for systematic reviews. The objective was to choose one or several systematic reviews, whose primary studies were to be extracted and selected. In a 2nd step, the information retrieval was updated for the time period not covered by the systematic reviews.

The search for systematic reviews as part of the focused information retrieval was conducted in MEDLINE, Cochrane Database of Systematic Reviews, and Health Technology Assessment (HTA) Database. In addition, the websites of HTA agencies, such as the National Institute for Clinical Excellence and Care (NICE) or the Agency for Healthcare Research and Quality (AHRQ), were searched for systematic reviews. The supplementary search for primary studies was done as part of the comprehensive information retrieval for the time period not covered by the systematic reviews in the databases of MEDLINE, Embase, and Cochrane Central Register of Controlled Trials.

The following sources of information and search techniques were additionally used: trial registries, documents sent by the Federal Joint Committee (G-BA), documents made available from hearing procedures, and author queries.

The selection of relevant systematic reviews as part of the focused information retrieval was done by 1 reviewer. Relevant studies found in the comprehensive information retrieval were

selected by 2 reviewers independently from one another. Any discrepancies were resolved by discussion between them.

Data were extracted into standardized tables. To assess the qualitative certainty of results, study-level criteria of risk of bias were assessed and rated as high or low. Outcome-specific criteria of the risk of bias were not assessed because all studies already had a high risk of bias on the study level due to study-level criteria, and this directly affected the outcome-specific risk of bias of results. Nevertheless, the usability of the results of the outcomes was checked for these studies as well. The results of the individual studies were organized according to outcomes and described.

To the extent that the studies were comparable in terms of their research questions and relevant characteristics and no meaningful heterogeneity was observed, the results from individual studies were quantitatively combined in meta-analyses.

For each outcome, a conclusion was drawn on the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: Proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was the case if no data were available or the available data did not permit classification into one of the 3 other categories. In that case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn. Finally, the benefit and harm of prostate cancer screening with the PSA test was assessed across outcomes.

3 Results

3.1 Results of the comprehensive information retrieval

In a 1st step, a search was done for recent high-quality, systematic reviews on the basis of which primary studies were to be identified. The search was conducted on 29 January 2019. Among the 8 included systematic reviews (see Section A6.1 of the full report), 2 systematic reviews were rated as current and of high quality and were taken into consideration for the purpose of identifying primary studies (see Table 1).

Table 1: Systematic reviews considered

Systematic review	**Full publication**
Fenton 2018	Yes [3, 12]
Ilic 2018	Yes [5]

In a 2nd step, a supplementary search was conducted for primary studies for the time period not covered by the identified systematic reviews. The most recent search was conducted on 20 May 2019.

The search strategies for bibliographic databases and trial registries are found in the appendix.

The comprehensive information retrieval identified 11 randomized controlled studies as being relevant for the research question of this benefit assessment (see Table 2). Furthermore, 2 ongoing studies and 1 prematurely terminated study without reported results were identified.

Table 2: Study pool of the benefit assessment

Study	**Available documents**	
	Full publication (in professional journals)	**Registry entry / results report from the study registries**
ERSPC Belgium	Yes [6, 13–21]	Yes [22] / no
ERSPC Finland	Yes [6, 13–21, 23–33]	
ERSPC France[a]	Yes [6, 14, 15, 18, 20, 21, 33]	
ERSPC Italy	Yes [6, 13–21, 33]	
ERSPC Netherlands	Yes [6, 13–21, 23, 33–38]	
ERSPC Sweden	Yes [6, 13–21, 23, 39–41]	Yes [42] / no
ERSPC Switzerland	Yes [6, 13–15, 17–21, 23]	Yes [22] / no
ERSPC Spain	Yes [6, 13–15, 17–21, 33, 43]	
PLCO	Yes [44–56]	Yes [57] / yes [58]
Quebec[a]	Yes [59]	No/no
Stockholm	Yes [60, 61]	No/no
a: Not taken into account in the benefit assessment.		

Exclusion of studies

The largest screening study, CAP [62], with around 400 000 analysed men, was excluded due to its lack of allocation concealment for the intervention and control groups. Unlike the included screening studies, this study allocated to the screening and control groups not the men themselves, but the primary care practices. After randomization, a total of over 30% of these practices were no longer considered, in most cases because the practices failed to obtain informed consent for study participation. This post hoc exclusion of practices might conceivably have led to a selection of the men, e.g. due to the population structure found near the practices, which violates the randomization principle. Therefore, the CAP study is assessed as a study with inadequate randomization.

3.2 Characteristics of the studies included in the assessment

The study pool comprises the multicentric ERSPC study with a total of about 266 000 participants from 8 European countries [22]. Due to their different screening strategies, each of the studies from the 8 different countries was considered individually for the purposes of this assessment. Additionally, 3 further RCTs from Canada (Quebec [59]), Sweden (Stockholm [60]), and the USA (PLCO [51]) were included, with around 46 000, 27 000, and 77 000 participants, respectively. The follow-up was between 13 and 20 years. Nearly all studies included men between 55 and 70 years of age.

In all studies, screening for prostate cancer with the PSA test was compared to no screening, and prostate cancer-specific mortality was examined as the primary outcome. In the PLCO study, the intervention included prostate cancer screening as well as screening for colorectal and lung cancer.

The studies differed in terms of their sequence of randomization and consent as well as their screening strategies, particularly the PSA cut-off value, the use of additional screening tests (in addition to the PSA test), the number of screening rounds, and the period between screening rounds.

As a special characteristic of several ERSPC studies, different screening strategies were used for some members of the screening group: The number of screening rounds decreased with increasing participant age at inclusion since a maximum screening age was defined close to the highest inclusion age. Consequently, participants who had already reached the maximum screening age at the start of the study were screened only once, while the youngest participants at the start of the study were screened up to 3 times (e.g. ERSPC Belgium, ERSPC Finland, ERSPC Spain), 5 times (ERSPC Netherlands), or 10 times (ERSPC Sweden).

In several studies, the screening strategy changed over the course of the study. For instance, in the ERSPC Sweden study, the PSA cut-off value was lowered from initially 3.4 ng/mL to 2.9 ng/mL and then 2.5 ng/mL, and in the ERSPC Netherlands study, it was reduced from initially 5 ng/mL to 3 ng/mL. Further, several studies, such as ERSPC Netherlands, initially used DRE and transrectal ultrasound (TRUS) as screening tests in addition to the PSA test. In

the PLCO study, the men who were first included were offered 4 rounds of PSA screening, those included later, 5 rounds, and those included last, 6 rounds.

Finally, the studies differ in the percentage of men in the screening groups who participated in PSA screening at least once (adherence). While the PSA testing rate was 90% or higher in all studies where consent for participation was given before randomization, it was below 80% in all studies where consent for study participation was given after randomization.

Non-consideration of studies

The testing rate was particularly low in the French ERSPC study (28%) and in the Quebec study (24%). In both studies, adherence was assessed as too low to permit an adequate comparison; consequently, the results of these two studies were disregarded. Data on the rate of PSA testing of study participants allocated to the control group (contamination) were reported for 4 of the 11 studies. In 3 of these studies – the PLCO study, ERSPC Finland study, and Quebec study – the difference between the two groups in terms of the PSA testing rate was less than 20 percentage points. In the 4th study, ERSPC Netherlands, however, the groups differed by more than 60 percentage points. Thus, the ERSPC Netherlands study exhibited a much greater difference between the screening group and the control group. Since data on contamination are missing from 7 studies, it is unclear which of these studies should be disregarded due to high contamination. Therefore, this criterion was not applied to decide whether study results can be included or not.

3.3 Overview of patient-relevant outcomes

Table 3 presents an overview of the available data on patient-relevant outcomes from the included studies. No studies reported (usable) data on the outcomes of adverse events or health-related quality of life.

Table 3: Matrix of patient-relevant outcomes

Study	Outcomes							
	Mortality		Morbidity					QoL
					Screening-related harm			
	All-cause mortality	Prostate cancer-specific mortality	Diagnoses of metastatic prostate cancer	AEs	Consequences of overdiagnoses	Consequences of false-positive diagnoses	Consequences of false-negative diagnoses	Health-related quality of life
ERSPC total[a]	●	●	-	-	●	-	-	-
ERSPC Belgium	-	●	-	-	●	●	-	-
ERSPC Finland	●	●	●[b]	-	●	●	-	○[c]
ERSPC France[d]	-	-	-	-	○	-	-	-
ERSPC Italy	-	●	-	-	●	●	-	-
ERSPC Netherlands	-	●	●	-	●	●	-	-
ERSPC Sweden	●	●	●	-	●	●	-	-
ERSPC Switzerland	-	●	●	-	●	-	-	-
ERSPC Spain	-	●	-	-	●	-	-	-
PLCO	○[e]	●	○[f]	-	●	●	-	-
Quebec[d]	-	○	-	-	-	-	-	-
Stockholm	●	●	-	-	●	-	-	-

● Data were reported and usable.

○ Data were reported but unusable for the benefit assessment.

- No data were reported (no further information). / Outcome not surveyed.

a: The pooled analysis of all 7 included ERSPC studies was used for the outcome of all-cause mortality (since separate results were available from only 2 out of 7 ERSPC studies) and for the outcome of prostate cancer-specific mortality with regard to the subgroup analysis by age.

b: Exclusively for the Finnish study centre of Tampere (25% of all Finnish men).

c: Results not usable since in both groups, no results on health-related quality of life are available for over 30% of the men in the random sample.

d: The result was disregarded since adherence to the screening intervention (operationalized as PSA testing rate) in the screening group was too low to adequately assess the comparison.

e: Result not usable since the PLCO study intervention consisted of not only prostate cancer screening, but also colorectal and lung cancer screening.

f: Result not usable since in both groups, results on the presence of metastases are missing for more than 30% of men with prostate cancer.

AE: adverse event; PSA: prostate-specific antigen; QoL: health-related quality of life

Non-consideration of results on patient-relevant outcomes

Two out of the 9 included studies reported data which were assessed as unusable: the PLCO study on the outcomes of all-cause mortality and diagnoses of metastatic prostate cancer, and the ERSPC Finland study on health-related quality of life.

The PLCO study's results on all-cause mortality were disregarded because in this study, the intervention consisted not solely of prostate cancer screening, but also of colorectal and lung cancer screening [52]. The most recent analysis of the PLCO study reveals a statistically significant effect in favour of the intervention [52]. It is unclear to what extent the intervention's statistically significant favourable effect on all-cause mortality is due to prostate cancer screening, particularly given the fact that colorectal cancer screening was the only one of the 3 cancer screening interventions to show a statistically significant favourable effect on cancer-specific mortality. The PLCO study's results on the outcome of diagnoses of metastatic prostate cancer were disregarded since data were missing from over 30% of men with prostate cancer. From the ERSPC Finland study, it was not possible to include the results on health-related quality of life because the data of over 30% of the men in the random sample were missing.

3.4 Assessment of the risk of bias of results

For all studies, the risk of bias of results was rated as high on the study level and, as a result, also on the outcome level. In all studies, it was unclear whether the allocation to the intervention and control groups was concealed. Consequently, the qualitative certainty of results was moderate for all outcomes of all included studies.

Some studies obtained consent for study participation only after randomization. Consent was provided exclusively by men in the screening group; men in the control group were not informed about the study. Therefore, the informed consent declaration presumably did not cover data analysis, but instead focused on the examinations associated with screening. In the analyses, all randomized men were included in accordance with their group allocation. Therefore, the sequence of randomization and informed consent procedure suggests that neither self-selections nor group switching relevant to the analysis had taken place.

3.5 Results on patient-relevant outcomes

3.5.1 Results on the outcome of all-cause mortality

For all-cause mortality, the qualitative evidence synthesis revealed no statistically significant result. For the outcome of all-cause mortality, there is consequently no hint of benefit or harm of prostate cancer screening with the PSA test.

3.5.2 Results on prostate cancer-specific mortality

With regard to prostate cancer-specific mortality, a statistically significant difference was found in favour of prostate cancer screening with the PSA test. For this outcome, it was possible to determine whether any effect modification was present. This was not the case for the

characteristics of age, number of screening rounds, or screening interval. Since no suitable data were available, no subgroup analysis was performed for the subgroup characteristic of duration of screening. For the potential effect modifier of PSA cut-off value (< 4 ng/mL versus ≥ 4 ng/mL), proof of interaction was found ($p < 0.001$). In the subgroup of the 4 studies using a PSA cut-off value below 4 ng/mL, a statistically significant difference was found in favour of prostate cancer screening with the PSA test. The incidence density ratio (IDR) is 0.68 (95% CI [0.51; 0.89]). In contrast, in the subgroup of the 4 studies using a PSA cut-off value of 4 ng/mL or higher, no statistically significant difference between groups was found (IDR 0.95; 95% CI [0.86; 1.05]).

However, it must be noted that the 2 largest studies in the subgroup using a PSA cut-off value of at least 4 ng/mL – PLCO and ERSPC Finland – showed high contamination in the control group. For the two other studies in this subgroup, the contamination rate remained unclear. Conceivably, a potential effect of prostate cancer screening using a PSA cut-off value of 4 ng/mL or higher might be masked by high contamination. Therefore, it is doubtful whether the PSA cut-off value is actually the characteristic which largely explains the difference between subgroups. Among the studies, PLCO and ERSPC Finland provide results with the largest numeric effects. The calculation of a pooled effect estimate for this subgroup, disregarding PLCO and ERSPC Finland, does not provide any different result.

In summary, for the outcome of prostate cancer-specific mortality, there is an indication of benefit of prostate cancer screening with the PSA test for the subgroup of studies using a PSA cut-off value below 4 ng/mL. Any benefit of prostate cancer screening with the PSA test using a PSA cut-off value of 4 ng/mL or higher remains unclear.

3.5.3 Results on the outcome of diagnoses of metastatic prostate cancer

A statistically significant difference was found in favour of prostate cancer screening with the PSA test. The incidence density ratio is 0.67 (95% CI [0.58; 0.78]). For the outcome of diagnoses of metastatic prostate cancer, this results in an indication of benefit of prostate cancer screening with the PSA test.

3.5.4 Results on health-related quality of life

None of the included studies reported any usable results on this outcome.

3.5.5 Results on adverse events

None of the included studies reported any usable results on this outcome.

3.5.6 Results on harm directly or indirectly resulting from the screening, including the consequences of false screening results and overdiagnoses (e.g. consequences of surgeries and other therapies)

Results on the consequences of overdiagnoses

In the studies using a PSA cut-off value below 4 ng/mL, the setting-dependent risk of overdiagnosis equalled 35 (95% CI [13; 56]) to 60 (95% CI [54; 66]) per 1000 invited men. In the studies using a PSA cut-off value of 4 ng/mL or higher, the setting-dependent risk of overdiagnosis risk equalled 7 (95% CI [3; 12]) to 16 (95% CI [11; 20]) per 1000 invited men.

Unlike in most publications on prostate cancer screening, it must be noted that the overdiagnosis rate in this assessment was calculated based on the number of men included in the screening group rather than the number of prostate cancer cases detected by screening test. In the studies using a PSA cut-off value < 4 ng/mL, about 100 prostate cancer cases were detected per 1000 invited men [18]. An overdiagnosis risk of 35 to 60 overdiagnoses per 1000 invited men (3.5% to 6%) therefore corresponds to a proportion of 35 to 60 overdiagnoses per 100 prostate cancer cases detected by screening test (35% to 60%) and therefore is at the same magnitude as the overdiagnosis rates reported in the studies [23, 63, 64].

It is safe to assume that all prostate cancer cases were diagnosed and treated by prostate biopsy. Hence, there was proof of harm of prostate cancer screening with the PSA test with regard to the consequences of overdiagnoses (i.e. complications of prostate biopsies and overtreatment). However, since different treatment concepts exist (e.g. radical prostatectomy, percutaneous radiotherapy, active surveillance, watchful waiting) and these concepts differ in their range of side effects as well as the timing of adverse events, it remains unclear in how many men overtreatment led to adverse events, which events they were, and how long they persisted. The included studies did not provide any data on this topic.

Results on the consequences of false-positive screening results

A false-positive screening result is an abnormal finding (e.g. elevated PSA value) for which the subsequently performed biopsy was negative for prostate cancer.

In the studies using a PSA cut-off value below 4 ng/mL, about 76% to 82% of positive screening results were found to be false (men with elevated PSA value in whom no prostate cancer was found), and about 8% to 19% of all screening participants had a false positive screening result. In these studies, after at least 3 screening rounds, 22.3% to 26.1% of all screening participants (men who took a PSA test) received at least 1 false-positive screening result.

In the studies using a PSA cut-off value of 4 ng/mL or higher, about 68% to 81% of positive screening results in each round were found to be false, and about 4% to 9% of all screening participants received a false-positive screening result. In these studies, after at least 3 screening rounds, 11% to 13% of all screening participants had at least 1 false positive screening result.

Complications after prostate biopsies were examined in 1 out of the 9 included studies. This study used a PSA cut-off value of 4 ng/mL. Usable data were reported exclusively for men in the screening group who had a false-positive screening result and in whom exactly 1 prostate biopsy was performed and no prostate cancer was confirmed within 1 year after prostate biopsy. In about 2% of these men, complications arose within 120 days after prostate biopsy. About one-third of these complications were due to infection. No information was available on the type and severity of infections. No deaths occurred as a result of biopsies.

Consequently, there is proof of harm of prostate cancer screening by PSA test with regard to the consequences of false-positive screening findings.

Results on the consequences of false-negative screening results

None of the included studies reported any usable results on false-negative screening results.

Consequently, there was no hint of any benefit or harm of prostate cancer screening by PSA test with regard to the consequences of false-negative screening results.

3.5.7 Subgroup characteristics and other effect modifiers

Subgroup analyses were performed only for the outcome of prostate cancer-specific mortality (see Section 4.5.2). The results reported on harm arising from the screening were stratified by the category of PSA cut-off value, thus permitting an assessment of the impact of this factor.

For all-cause mortality as well as the outcome of diagnoses of metastatic prostate cancer, no subgroup analyses were performed because either no data were available or no meaningful categorization of the studies was possible.

3.5.8 Weighing of benefits versus harm

Table 4: Weighing of benefits versus harm of prostate cancer screening with the PSA test per 1000 men who were offered screening, based on absolute effects

Outcomes	Baseline risk[a] per 1000 men	Absolute effect per 1000 invited men [95% CI]	Interpretation
Benefit[b]			
Prostate cancer-specific mortality	9	3[c] [1; 5]	Screening with the PSA test using a PSA cut-off value < 4 ng/mL would prevent the prostate cancer-related death of about 3 men within 16 years. Considering the high number of competing causes of death in the age group in question, it is questionable whether PSA screening leads to a notable extension of life for the affected men.
Diagnoses of metastatic prostate cancer	9	3[c] [2; 4]	Screening with the PSA test would prevent the occurrence of metastases in about 3 men within 12 years.
Harm[b]			
Consequences of overdiagnoses	-	35 [13; 56][d] to 60 [54; 66][e]	As a result of screening with the PSA test using a PSA cut-off value of < 4 ng/mL, about 35 to 60 men would receive an unnecessary prostate cancer diagnosis, which can lead to serious, long-term complications, particularly due to unnecessary therapy but also due to prostate biopsy.
Consequences of false-positive screening results	-	223[f] to 261[f]	As a result of screening with the PSA test using a PSA cut-off value of < 4 ng/mL, 223 to 261 screening participants would be upset at least once by the suspicion of prostate cancer, which is later rejected. The subsequent prostate biopsy can, in rare cases, lead to SAEs (e.g. sepsis).

a: Median risk of the control group.
b: For patient-relevant outcomes not listed in this table, there was no hint of benefit or harm.
c: It seems plausible that men who die of prostate cancer are a subgroup of the men with prostate cancer who (at an earlier time) had metastases.
d: ERSPC Spain.
e: ERSPC Netherlands.
f: Relative to the number of screening participants rather than the number of invited men.
CI: confidence interval; PSA: prostate-specific antigen; SAE: serious adverse event

3.6 Evidence map

Table 5 shows the evidence map regarding patient-relevant outcomes.

Table 5: Evidence map regarding patient-relevant outcomes

Mortality		Morbidity					Health-related quality of life
				Screening-related harm			
All-cause mortality	Prostate cancer-specific mortality	Diagnoses of metastatic prostate cancer	AEs	Consequences of overdiagnoses	Consequences of false-positive diagnoses	Consequences of false-negative diagnoses	
⇔	⇑[a] / ⇔[b]	⇑	-	⇓⇓[c]	⇓⇓[d]	-	-

⇓⇓: Proof of lesser benefit or proof of harm of PSA screening.

⇑: Indication of (greater) benefit or indication of lesser harm of PSA screening.

⇔: no hint, indication, or proof; homogeneous result.

-: no data reported.

a: Subgroup of studies using a PSA cut-off value below 4 ng/mL.

b: Subgroup of studies using a PSA cut-off value of 4 ng/mL or higher; due to high contamination in the 2 largest studies of this subgroup, it is doubtful whether the PSA cut-off value is actually the characteristic explaining the majority of the difference between the subgroups.

c: Particularly complications of prostate biopsies and overtreatment.

d: Particularly complications of prostate biopsies.

AE: adverse event; PSA: prostate-specific antigen

4 Classification of the assessment result

The objective of this investigation was to assess the benefit of prostate cancer screening with the PSA test. Included were only screening studies which compared prostate cancer screening with a PSA test versus no prostate cancer screening, but no study was found on the comparison of prostate cancer screening with the PSA test versus the standard procedure currently in use in Germany, prostate cancer screening with DRE. Consequently, the data are particularly suitable for determining whether prostate cancer screening with the PSA test is associated with any benefit or harm in comparison with no prostate cancer screening. Yet, there is nothing to suggest that DRE is superior to the PSA test or has any notable positive effects at all [65]. Therefore, the available evidence also permits drawing conclusions on the comparison of prostate cancer screening with the PSA test versus the procedure currently covered in Germany, prostate cancer screening with DRE (comparisons of PSA test plus DRE versus DRE as well as PSA test versus DRE).

The available information does not suggest publication bias.

Weighing of the benefits and harms of prostate cancer screening

Any screening causes harm as a result of false screening results and overdiagnoses. Screening is justified only if its associated benefits outweigh its harms.

Benefit of prostate cancer screening

Although PSA screening using a PSA cut-off value of < 4 ng/mL led to a statistically significant reduction in prostate cancer-specific mortality (see Table 4) in comparison with no screening, no statistically significant difference between the groups was found with regard to all-cause mortality. However, deaths due to prostate cancer made up only a small percentage of deaths of any cause, e.g. only 3% in the pooled analysis of all ERSPC studies. Therefore, the lack of statistical significance for all-cause mortality does not necessarily mean that PSA screening will not extend the lives of affected men. Simultaneously, in consideration of the median age of onset of 72 years [1], the relatively favourable prognosis of prostate cancer, and the numerous competing causes of death at that age, it is at least questionable whether PSA screening leads to a meaningful extension of the lives of affected men. Men who are spared death from prostate cancer might conceivably die at a similar time from another cause, or they might conceivably live longer.

PSA screening also led to a statistically significant reduction of the diagnoses of metastatic prostate cancer (see Table 4). In this regard, it appears plausible that men who die of prostate cancer are a subgroup of the men with prostate cancer in whom metastases occur (at an earlier time). Therefore, the effects in terms of prostate cancer-specific mortality and diagnoses of metastatic prostate cancer should be analysed together. Although it is unclear whether PSA screening led to any extension of lives of affected men, this outcome shows that the screening delayed or entirely spared patients the distress caused by metastatic cancer (e.g. due to chemotherapy, lymphadenectomy, palliative castration, and palliative radiotherapy).

A further conceivable benefit of screening for some men might arise from earlier treatment being associated with fewer adverse events than later treatment, and the adverse events of earlier treatment being of short duration. Unfortunately, however, no results are available on adverse events or health-related quality of life, and consequently, no conclusions can be drawn in this respect.

Harm of prostate cancer screening

Prostate cancer screening with the PSA test led to overdiagnoses and false-positive screening results (see Table 4).

Overdiagnosed men cannot benefit from screening. The diagnosis of a potentially fatal disease and its disclosure per se represent harm for overdiagnosed men. Furthermore, they suffer the distress of unnecessary prostate biopsy and unnecessary therapy as well as any related complications (e.g. impotence, incontinence), which are irreversible in many cases and, due to the early treatment time, affect the men for a long time. None of the included studies reported any results on adverse events. Modelling performed on the basis of a systematic review predicts about 3 additional men with permanent incontinence and 25 additional men with permanent impotence per 1000 screening participants [5]. It must be noted, however, that this model is based on a different study pool and therefore invariably rests on assumptions which do not necessarily apply to the study pool of this report. For instance, this model is based on the assumptions that (1) prostate cancer patients are treated exclusively by the 3 treatment modalities of radical prostatectomy, percutaneous radiotherapy, and active surveillance and (2) that radical prostatectomy is used in 40% of prostate cancer patients, while percutaneous radiotherapy and active surveillance are each administered to 30% of prostate cancer patients. In Germany, about 9% of prostate cancer patients are currently treated using an observational strategy (typically active surveillance) [66]. Modelling on the basis of the treatment methods used in Germany is therefore likely to show an even higher estimated number of additional men with permanent incontinence and/or impotence.

Men whose screening test is false positive do not benefit from screening either. They experience exclusively harm in the form of worrisome screening test results leading to prostate biopsy which would have been unnecessary in the absence of screening. Complications following prostate biopsy arose in about 2% of men, who each underwent 1 prostate biopsy to confirm positive screening results. One-third of the complications were infections, which can manifest, inter alia, as sepsis [67–69]. In about 22% to 26% of screening participants, PSA screening using a PSA cut-off value of < 4 ng/mL was positive, but no prostate cancer was ultimately detected (ERSPC Sweden and ERSPC Netherlands). Hence, about 5 to 6 out of 1000 screening participants experienced prostate biopsy-related complications which would not have arisen in the absence of screening.

Further aspects in weighing the benefit and harm of prostate cancer screening

When weighing the benefit and harm of prostate cancer screening, it must also be noted that the results for the various outcomes differ in relevance from man to man.

For example, to some men, a benefit in prostate cancer-specific mortality might weigh more heavily than the harm of false-positive diagnoses. A systematic review concluded that men differ greatly with regard to their values and preferences concerning prostate cancer screening [70]. This result highlights the fact that in the individual decision in favour of or against PSA screening, the personal values and preferences of each man to be screened must be taken into account. This finding is in line with the recommendations of many of the competent national health authorities and professional societies [2, 10, 11, 71, 72].

Another aspect is that benefit and harm arise at different points in time. Many harms, such as the complications caused by overtreatment, occur at an early time and, in many cases, last for life (e.g. incontinence, impotence). In contrast, due to the long asymptomatic phase of prostate cancer, any benefit in terms of avoiding metastases or prostate cancer-specific mortality usually arises several years later.

In comparison with data collected for the mammography screening leaflet [73], it is striking that both the overdiagnosis risk and the number of false-positive screening results are estimated to be many times higher for prostate cancer screening than for mammography screening: 5 to 7 overdiagnoses within 20 years versus 35 to 60 overdiagnoses within 16 years as well as 24 false-positive screening results versus 80 to 187 false-positive screening results (each per screening round and 1000 participants). The estimated effect on cancer-specific mortality, in contrast, is at a similar magnitude for both screening procedures (3 avoided prostate cancer deaths per 1000 invited men within a time period of 16 years). These estimates demonstrate that the benefit-to-harm ratio is less favourable for prostate cancer screening than for mammography screening.

Implementation of prostate cancer screening

Regardless of whether the German statutory health insurance will cover prostate cancer screening with the PSA test, there will be a continued need for consultation on this topic. This consultation should be an unbiased discussion characterized by shared decision making. A suitable basis for this process is a patient information leaflet containing an unbiased description of the advantages and disadvantages of prostate cancer screening with the PSA test. According to a current investigation, however, half of the 14 reviewed German patient information leaflets did not describe the advantages and disadvantages of prostate cancer screening with the PSA test in a sufficiently neutral manner [74]. The recommendation in the S3 guideline on prostate cancer screening also fails to explicitly call for men to be informed about advantages and disadvantages in an unbiased manner [2][2]. This is all the more notable since the dissenting opinion from the German College of General Practitioners and Family

[2] Recommendation 3.1: “Men should be informed about the advantages and disadvantages of the early detection measures, particularly the informative value of positive and negative test results as well as about any further measures which might be necessary.”

Physicians (DEGAM) includes the term "unbiased" [2][3]. Hence, it is questionable how often men receive an unbiased consultation on the topic of prostate cancer screening with the PSA test as a basis for making a well-informed decision in favour or against it. In addition, men for whom no evidence is available from randomized studies on the screening chain, e.g. men over 75 years of age, are often (opportunistically) screened [75, 76]. This problem prompted the call for introducing an organized screening programme [75].

If a prostate cancer screening programme were to be introduced in Germany, the question is how exactly it should be designed. Unfortunately, the included studies do not provide any satisfactory information on this topic since they exhibit considerable heterogeneity in terms of their screening strategies, which were furthermore changed in the course of several of the studies. At the start of several of the studies (e.g. ERSPC Netherlands), for instance, the screening test comprised not only the PSA test, but also other tests, e.g. DRE and TRUS. The subgroup analyses did not permit answering this question either. This is reflected in the differing recommendations provided by different guidelines, which suggest various screening strategies which are not based on the study results alone, but include additional considerations [2, 71, 77]. It remains to be seen to what extent current efforts to establish a risk-based approach in prostate cancer screening change the assessment [78]. The following section discusses various measures for reducing screening-related harm.

Measures for reducing screening-related harm

Undeniably, the screening strategies used in the studies included on PSA screening were associated with a large number of false-positive screening results as well as overdiagnoses and the associated complications from unnecessary biopsies and/or treatment. Consequently, efforts are made to reduce this screening-related harm with the aid of supplementary measures. As part of the written and oral commenting procedure on the preliminary report, various measures intended to reduce screening-related harm were discussed:

- Before the screening test: Consideration of suitable criteria to limit the population to be screened, e.g. life expectancy under 10 years, prior illnesses, familial prostate cancer risk, genetic risk factors
- On the basis of the individual PSA test results:
  - Categorization of men into risk groups to be screened more or less intensively (e.g. as per a baseline PSA test at age 45 or 50)
  - Dynamic adjustment of the screening interval on the basis of the patient-specific development of the PSA value

[3] Dissenting opinion of DEGAM: "Men who ask for early detection should be informed about advantages and disadvantages in an unbiased manner. The potential benefit as well as risks (overdiagnosis and overtreatment) should be explained using natural numbers and graphics. Additionally, the informative value of positive and negative test results should be illustrated."

  - Adjustment of the PSA threshold for biopsy depending on PSA dynamics
- After the screening test and before biopsy: Use of suitable tests to limit the biopsy indication to men at high risk of clinically significant prostate cancer, e.g. risk calculators, multiparametric magnetic resonance imaging (mpMRI), or biomarkers
- For the biopsy itself: Use of new biopsy methods, e.g. mpMRI-targeted biopsy, which allows taking targeted biopsies from areas likely to harbour prostate cancer as per mpMRI

Many of these measures appear generally suitable for reducing screening-related harm. For instance, overdiagnoses might conceivably be avoided by not screening men with a life expectancy of less than 10 years (e.g. due to pre-existing conditions) in an effort to reduce the proportion of men who would die of other causes before the onset of symptomatic prostate cancer. It is also conceivable that overdiagnoses could be reduced by performing biopsy only on those men whose pre-biopsy test predicts clinically significant prostate cancer (e.g. with the aid of a risk calculator or mpMRI). These measures reduce the number of men who undergo biopsy and hence indirectly reduce overdiagnoses. In contrast, mpMRI-guided biopsy aims to identify more clinically significant prostate cancer cases among men with abnormal mpMRI findings than would be possible with systematic biopsy [79, 80]. This reflects the plausible assumption that overdiagnosis mainly occurs in clinically non-significant prostate cancer.

However, it must be noted that it is impossible to differentiate between the presence and absence of overdiagnosis on the individual case level. Even a man with (most likely) clinically significant prostate cancer might be overdiagnosed, and conversely, a man with (most likely) clinically non-significant prostate cancer might not be overdiagnosed. A further issue is that even some of the clinically significant prostate cancers will be left undetected by any of the suggested measures [81]. Furthermore, the large number of suggested measures shows that at this time, no risk-adapted screening strategy has gained general acceptance yet. The current guideline of the European Association of Urology (EAU) does not recommend a clear algorithm for a risk-adapted screening strategy either. For instance, it suggests various test candidates for limiting the biopsy indication: “In men at risk of significant prostate cancer according to PSA levels consider the following tests to select biopsy candidates: – Risk calculators – mpMRI – Tests based on biomarkers and genetic polymorphisms” [77]. All things considered, it is therefore unclear whether and how specifically the mentioned measures for reducing screening-related harm impact the benefit-to-harm ratio of prostate cancer screening. To answer the question whether screening strategies which include mpMRI can reduce overdiagnoses without associated mortality increases, 2 new screening RCTs [82, 83] recently started, but their results are expected no earlier than 2028. In addition, it must be noted that mpMRI is an expensive and time-consuming procedure whose availability throughout Germany cannot be guaranteed, at least not at this time.

Another strategy for reducing overdiagnosis-related harm is implemented after prostate cancer has been diagnosed; it involves reducing overtreatment by using an observational strategy instead of local treatment with curative intent in men with localized prostate cancer and a low

risk of progression. This strategy is based on the same assumption as foregoing biopsy in case of unremarkable mpMRI findings, namely that overdiagnosis applies particularly to men with localized prostate cancer and a low risk of progression[4]. With these men, it is therefore recommended to discuss not only local therapies with curative intent (e.g. radical prostatectomy and percutaneous radiotherapy), but also the concepts of watchful waiting (at a life expectancy of less than 10 years) and active surveillance (at a life expectancy of more than 10 years). However, these recommendations cannot contribute to reducing overdiagnosis-related harm unless they are both implemented by physicians and accepted by patients. On this topic, the current S3 guideline for early detection, diagnosis, and treatment of prostate cancer notes that active surveillance requires intensive consultation and care and is presumably often difficult for patients [2] In the ProtecT study, about 10% of the men from the active surveillance group decided to switch to local treatment within the first 9 months after randomization, thereby confirming that this treatment concept is not accepted by all patients [84]. In the USA, among prostate cancer patients eligible for active surveillance[5], the percentage of those treated using an observational strategy (active surveillance or watchful waiting) rose between 2010 and 2014, from about 30% to about 60% [85]. However, it is unclear for how long these men continued with the observational strategy and for which reasons they discontinued it. In the ProtecT study, about 50% of men in the active surveillance group who initially did receive active surveillance, switched to local treatment within a period of about 10 years. This is another study in which it remains unclear for what reasons active surveillance was discontinued. The data on the number of men with progression of prostate cancer in comparison with the number of treatment switchers suggest that a large percentage of patients switched to local treatment for non-clinical reasons [84]. In Germany, the percentage of prostate cancer patients eligible for active surveillance who have actually been treated using this strategy can be further increased. Between 2013 and 2017, it rose from about 16% to about 27% [66].

[4] PSA value ≤ 10 ng/mL, tumour stage ≤ T2a, Gleason score ≤ 6, tumour in ≤ 2 punch biopsies, with 10 to 12 punch biopsies taken in compliance with guidelines, ≤ 50% tumour per punch biopsy

[5] PSA < 10 ng/mL, tumour stage ≤ T2a, Gleason score ≤ 6 and positive punch biopsies < 33%

5 Conclusion

With regard to all-cause mortality, there was no hint of any benefit or harm of prostate cancer screening with the PSA test in comparison with no such screening. With regard to prostate cancer-specific mortality, the studies using a PSA cut-off value below 4 ng/mL revealed an indication of a benefit of prostate cancer screening with the PSA test. For the other subgroup, there was no hint of any benefit or harm. Since opportunistic prostate cancer screening with the PSA test was common in the control groups of the 2 largest studies using a PSA cut-off value of 4 ng/mL or higher (i.e. high contamination), it is doubtful whether the PSA cut-off value is the actual characteristic which convincingly explains the difference between subgroups. With regard to the outcome of diagnoses of metastatic prostate cancers, there was an indication of benefit. With regard to the outcomes of health-related quality of life and adverse events as well as the consequences of false-negative screening findings, there was no hint of benefit or harm, albeit based on insufficient available data (no data at all). Proof of harm was found for the consequences of overdiagnoses as well as for false-positive screening findings.

Prostate cancer screening by PSA test causes harm to overdiagnosed men (men with prostate cancer which does not require treatment) as well as to men with false-positive screening results (men without prostate cancer). Much of screening-related harm arises at an early time and, in many cases, persists lifelong.

Prostate cancer screening with the PSA test benefits some men with prostate cancer by sparing them the distress caused by metastatic cancer or delaying the same. However, this benefit arises only after several years. Even these men might experience early treatment-related complications which persist lifelong. It is unclear whether screening leads to any life extension at all in these men.

Considerably more men experience overdiagnosis-related harm rather than benefits from prostate cancer screening by PSA test. All things considered, the benefits of prostate cancer screening with the PSA test therefore do not outweigh the associated harms.

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Please see full final report for full reference list.

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Appendix A – Search strategies

A.1 – Focused information retrieval for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to January Week 3 2019
- Ovid MEDLINE(R) Daily Update January 28, 2019
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to January 28, 2019
- Ovid MEDLINE(R) Epub Ahead of Print January 28, 2019

The following filter was adopted:

- Systematic review: Wong [86] – High specificity strategy

#	**Searches**
1	exp Prostatic Neoplasms/
2	(prostat* adj5 cancer*).ti,ab.
3	or/1-2
4	Mass Screening/
5	"Early Detection of Cancer"/
6	*Prostate-Specific Antigen/
7	prostate-specific antigen*.ti,ab.
8	(prostat* adj2 screening*).ti,ab.
9	or/4-8
10	3 and 9
11	cochrane database of systematic reviews.jn.
12	(search or MEDLINE or systematic review).tw.
13	meta analysis.pt.
14	or/11-13
15	14 not (exp animals/ not humans.sh.)
16	and/10,15
17	16 and (english or german).lg.
18	limit 17 to yr="2013 -Current"

2. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 1 of 12, January 2019

ID	Search
#1	[mh "Prostatic Neoplasms"]
#2	(prostat* NEAR/5 cancer*):ti,ab
#3	#1 or #2
#4	[mh ^"Mass Screening"]
#5	[mh ^"Early Detection of Cancer"]
#6	[mh ^"Prostate-Specific Antigen"[mj]]
#7	(prostate-specific* NEXT/1 antigen*):ti,ab
#8	(prostat* NEAR/2 screening*):ti,ab
#9	#4 or #5 or #6 or #7 or #8
#10	#3 and #9 with Cochrane Library publication date Between Jan 2013 and Jan 2019, in Cochrane Reviews, Cochrane Protocols

3. Health Technology Assessment Database

Search interface: Centre for Reviews and Dissemination

Line	Search
1	MeSH DESCRIPTOR prostatic neoplasms EXPLODE ALL TREES
2	(prostat* AND cancer*)
3	#1 OR #2
4	MeSH DESCRIPTOR mass screening
5	MeSH DESCRIPTOR early detection of cancer
6	MeSH DESCRIPTOR Prostate-Specific Antigen
7	(prostate-specific antigen*)
8	(prostat* AND screening*)
9	#4 OR #5 OR #6 OR #7 OR #8
10	#3 AND #9
11	(#10) IN HTA FROM 2013 TO 2019

A.2 – Bibliographic databases (primary studies)

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to May Week 2 2019
- Ovid MEDLINE(R) Daily Update May 17, 2019

The following filter was adopted:

- RCT: Lefebvre [87] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

#	**Searches**
1	exp Prostatic Neoplasms/
2	(prostat* adj5 cancer*).ti,ab.
3	or/1-2
4	Mass Screening/
5	"Early Detection of Cancer"/
6	*Prostate-Specific Antigen/
7	prostate-specific antigen*.ti,ab.
8	(prostat* adj2 screening*).ti,ab.
9	or/4-8
10	3 and 9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	(randomized or placebo or randomly or trial or groups).ab.
14	drug therapy.fs.
15	or/11-14
16	exp animals/ not humans.sh.
17	15 not 16
18	10 and 17
19	18 not (comment or editorial).pt.
20	19 and (english or german).lg.
21	limit 20 to yr="2018 -Current"

Search interface: Ovid

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to May 17, 2019
- Ovid MEDLINE(R) Epub Ahead of Print May 17, 2019

#	**Searches**
1	(prostat* adj5 cancer*).ti,ab.
2	prostate-specific antigen*.ti,ab.
3	(prostat* adj2 screening*).ti,ab.
4	or/2-3
5	(clinical trial* or random* or placebo).ti,ab.
6	trial.ti.
7	or/5-6
8	and/1,4,7
9	8 not (comment or editorial).pt.
10	9 and (english or german).lg.
11	limit 10 to yr="2018-Current"

2. Embase

Search interface: Ovid

- Embase 1974 to 2019 May 17

The following filter was adopted:

- RCT: Wong [86] – Strategy minimizing difference between sensitivity and specificity

#	**Searches**
1	exp prostate tumor/
2	(prostat* adj5 cancer*).ti,ab.
3	or/1-2
4	exp mass screening/
5	*cancer diagnosis/
6	*early diagnosis/
7	prostate specific antigen/
8	prostate-specific antigen*.ti,ab.
9	(prostat* adj2 screening*).ti,ab.
10	or/4-9
11	(random* or double-blind*).tw.

#	Searches
12	placebo*.mp.
13	or/11-12
14	and/3,10,13
15	14 not medline.cr.
16	15 not (exp animal/ not exp human/)
17	16 not (Conference Abstract or Conference Review or Editorial).pt.
18	17 and (english or german).lg.
19	limit 18 to yr="2018 -Current"

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 5 of 12, May 2019

ID	Search
#1	[mh "Prostatic Neoplasms"]
#2	(prostat* NEAR/5 cancer*):ti,ab
#3	#1 or #2
#4	[mh ^"Mass Screening"]
#5	[mh ^"Early Detection of Cancer"]
#6	[mh ^"Prostate-Specific Antigen"[mj]]
#7	(prostate-specific* NEXT/1 antigen*):ti,ab
#8	(prostat* NEAR/2 screening*):ti,ab
#9	#4 or #5 or #6 or #7 or #8
#10	#3 and #9 with Publication Year from 2018 to 2019, in Trials

A.3 – Study registries (primary studies)

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Basic Search

Search strategy
prostate cancer AND screening

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Search strategy
prostate cancer AND screening