Supplementary Online Content

Fenton J, Weyrich MS, Durbin S, Liu Y, Bang H, Melnikow J. Prostate-specific antigen–based screening for prostate cancer: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. doi:10.1001/jama.2018.3712

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Systematic Review Literature Search Strategies

Cochrane

#1 MeSH descriptor: [Mass Screening] explode all trees
#2 screening
#3 MeSH descriptor: [Prostatic Neoplasms] explode all trees
#4 prostate
#5 (#1 or #2) and #4
#6 MeSH descriptor: [Early Detection of Cancer] explode all trees
#7 MeSH descriptor: [Early Diagnosis] explode all trees
#8 early stage
#9 #6 or #7 or #8
#10 #5 and #9
#11 MeSH descriptor: [Prostate-Specific Antigen] explode all trees
#12 #10 and #11 Publication Year from 2011 to 2016

Ovid MEDLINE

1 exp "Prostatic Neoplasms"/ or prostate cancer.ti. or prostatic neoplasm*.ti. (115794)
2 "Risk Assessment"/ (209015)
3 "Survival Analysis"/ (113137)
4 "Treatment Outcome"/ (764101)
5 screening.mp. or Mass Screening/ (467821)
6 "Prostate-Specific Antigen"/ or PSA.mp. or prostate specific antigen.mp. (41541)
7 early diagnosis/ or early stage.mp. (89074)
8 "Watchful Waiting"/ or watchful waiting.ti,ab. (3945)
9 2 or 3 or 4 or 8 (1002677)
10 6 or 7 (129868)
11 1 and 9 and 10 (5667)
12 limit 11 to (yr="2007 -Current" and english) (3355)
13 exp "sensitivity and specificity"/ (489386)
14 (sensitivity or specificity).tw. (851972)
15 ((pre-test or pretest) adj probability).tw. (1699)
16 ((post-test or post test) adj probability).tw. (450)
17 likelihood ratio*.tw. (11693)
18 test performance.mp. (6762)
19 "predictive value of tests"/ or negative predictive value.mp. or positive predictive value.mp. (193939)
20 diagnostic accuracy.mp. (31481)
21 pca 3.mp. (86)
22 dd3.mp. (99)
23 4k score.mp. (1)
24 prostate health index.mp. (133)
25 four-kallikrein panel.mp. (9)
26 kallikreins/ (8482)
27 "early detection of cancer".mp. or "Early Detection of Cancer"/ (15663)
28 "Kallikreins"/ and ("Prostate-Specific Antigen"/ or ("Tumor Markers, Biological"/ and prostat*.mp.))
[mp=title,
abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary
concept word, rare disease supplementary concept word, unique identifier] (873)
29 or/13-20,27 (1227873)
30 prostate cancer gene 3.mp. (76)
31 or/21-26,28,30 (8848)
32 29 and 31 (902)
33 limit 32 to (yr="2007 -Current" and english) (468)
34 12 or 33 (3753)

35 Minority Groups/ (11981)
36 ethnology.fs. (141458)
37 exp Continental Population Groups/ (188428)
38 35 or 36 or 37 (279407)
39 risk.mp. or exp Risk/ (2010071)
40 1 and 38 and 39 (1447)
41 limit 40 to (english language and yr="2007 -Current") (888)
42 34 or 41 (4570)
43 treatment outcome.mp. or exp Treatment Outcome/ (801440)
44 prognosis/ or disease-free survival/ or prognos*.ti. or disease free.tw. (503696)
45 43 or 44 (1232919)
46 1 and 7 and 45 (351)
47 limit 46 to (english language and yr="2007 -Current") (156)
48 42 or 47 (4630)
49 (adverse adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (319580)
50 side effect$.ti,ab. (204402)
51 (unintended adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (1111)
52 (unintentional adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (175)
53 (unwanted adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (4963)
54 (unexpected adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (5142)
55 (undesirable adj2 (interaction$ or response$ or effect$ or event$ or reaction$ or outcome$)).ti,ab. (6613)
56 Harm Reduction/ (2016)
57 (ae or co).fs. (3083573)
58 or/48-57 (3392846)
59 1 and (5 or 6) and 58 (7541)
60 27 and 59 (411)
61 limit 60 to (english language and yr="2007 -Current") (397)
62 48 or 61 (4710)
63 remove duplicates from 62 (4459)
64 limit 63 to (english language and yr="2011 -Current") (2859)
65 from 64 keep 1-2492 (2492)
66 quality of life.mp. or "Quality of Life"/ (252030)
67 6 and 7 and 66 (60)
68 limit 67 to (english language and yr="2011 -Current") (22)
69 1 and 68 (15)
70 69 not 65 (9)
71 "Patient Acceptance of Health Care"/ (36136)
72 exp Attitude to Health/ (343442)
73 1 and (5 or 6) and (71 or 72) (996)
74 (7 or 27) and 73 (244)
75 limit 74 to (english language and yr="2011 -Current") (173)
76 75 not 65 (117)
77 remove duplicates from 76 (108)
78 limit 77 to (english language and yr="2011 -Current") (108)
79 70 or 78 (116)
80 remove duplicates from 79 (116)
81 limit 80 to ed=20160201-20161005 (22)

Embase
#16 OR #19
#19
'prostate'/exp OR prostate AND ('cancer'/exp OR cancer) AND ('screening'/exp OR screening) AND ('prostate specific antigen'/exp/dd_ct AND [humans]/lim OR (prostate AND specific AND antigen:ti) OR psa:ti) AND ('risk benefit analysis'/exp OR 'risk' OR 'risk reduction'/exp OR 'attributable risk'/exp OR 'low risk patient'/exp OR 'risk management'/exp OR 'genetic risk'/exp) AND [english]/lim AND [1-2-2016]/sd

#16
'prostate specific antigen'/exp/dd_ct AND [humans]/lim OR (prostate AND specific AND antigen:ti) OR psa:ti AND ('sensitivity and specificity'/exp OR 'sensitivity and specificity') AND ('health care quality'/exp OR 'health care quality') NOT ('psoriatic arthritis'/exp OR 'psoriatic arthritis') OR ('prostate'/exp OR prostate AND ('cancer'/exp OR cancer) AND ('screening'/exp OR screening) AND ('sensitivity and specificity'/exp OR 'sensitivity and specificity')) AND [english]/lim AND ('early diagnosis'/exp OR 'cancer classification'/exp) AND [1-2-2016]/sd

Web of Science
14
469
For: A Comparative Effectiveness Trial of Alternate Formats for Presenting Benefits and Harms Information for Low-Value Screening Services A Randomized Clinical Trial
Refined by: TOPIC: (prostate) AND PUBLICATION YEARS: (2015 OR 2014 OR 2013 OR 2012 OR 2011) AND DOCUMENT TYPES: (ARTICLE OR REVIEW) AND LANGUAGES: (ENGLISH)
Indexes=BKCI-S, ESCI, SSCI, BKCI-SSH, SCI-EXPANDED, A&HCI, IC, CPCI-SSH, CPCI-S, CCR-EXPANDED Timespan=All years
# 13
483
For: A Comparative Effectiveness Trial of Alternate Formats for Presenting Benefits and Harms Information for Low-Value Screening Services A Randomized Clinical Trial
Refined by: TOPIC: (prostate) AND PUBLICATION YEARS: (2015 OR 2014 OR 2013 OR 2012 OR 2011) AND DOCUMENT TYPES: (ARTICLE OR REVIEW)
Indexes=BKCI-S, ESCI, SSCI, BKCI-SSH, SCI-EXPANDED, A&HCI, IC, CPCI-SSH, CPCI-S, CCR-EXPANDED Timespan=All years
# 12
580
For: A Comparative Effectiveness Trial of Alternate Formats for Presenting Benefits and Harms Information for Low-Value Screening Services A Randomized Clinical Trial
Refined by: TOPIC: (prostate) AND PUBLICATION YEARS: (2015 OR 2014 OR 2013 OR 2012 OR 2011)
Indexes=BKCI-S, ESCI, SSCI, BKCI-SSH, SCI-EXPANDED, A&HCI, IC, CPCI-SSH, CPCI-S, CCR-EXPANDED Timespan=All years
# 11
715
For: A Comparative Effectiveness Trial of Alternate Formats for Presenting Benefits and Harms Information for Low-Value Screening Services A Randomized Clinical Trial
Refined by: TOPIC: (prostate)
Indexes=BKCI-S, ESCI, SSCI, BKCI-SSH, SCI-EXPANDED, A&HCI, IC, CPCI-SSH, CPCI-S, CCR-EXPANDED Timespan=All years
# 10
7,537
For: A Comparative Effectiveness Trial of Alternate Formats for Presenting Benefits and Harms Information for Low-Value Screening Services A Randomized Clinical Trial
9
424
#8 AND #1
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 8
591,381
TOPIC: (effectiveness)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 7
22
#6 AND #5

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 6
1,033
TOPIC: (risk) AND TOPIC: (calculator*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 5
1,384
#4 AND #3
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 4
368,489
TOPIC: (early stage) OR TOPIC: (screen detected)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 3
4,282
#2 AND #1
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 2
27,989
TOPIC: (prostate cancer antigen)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years
# 1
11,025
TOPIC: (prostate cancer) AND TOPIC: (screening)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

eTable 1. Quality Assessment Criteria

Study Design	Adapted Quality Criteria
Randomized controlled trials, adapted from the U.S. Preventive Services Task Force methods[1]	Was there valid random assignment? Was allocation concealed? Was eligibility criteria specified? Were groups similar at baseline? Was a difference in attrition between the groups after randomization not present? Were outcome assessors blinded? Were measurements equal, valid and reliable? Was the risk of contamination very low or not present? Was there adequate adherence to the intervention? Were statistical methods acceptable? Was the handling of missing data appropriate?
Observational studies (e.g., prospective cohort studies), adapted from the Newcastle-Ottowa Scale and the NICE methodology checklists [2,3]	Was there representativeness of the exposed cohort? Was the non-exposed cohort systematically selected? Was the ascertainment of exposure reported? Was eligibility criteria specified? Were groups similar at baseline? Was the outcome of interest not present at baseline? Were measurements equal, valid, and reliable? Were outcome assessors blinded? Was followup long enough for the outcome to occur? Was there acceptable followup? Was there adjustment for confounders?
Assessment of Multiple Systematic Reviews (AMSTAR)[4]	Was an 'a priori' design provided? Was there dual study selection? Was there dual data extraction? Was a comprehensive literature search performed? Was a list of studies included provided? Was a list of studies excluded provided? Were the characteristics of the included studies provided? Was the scientific quality of the included studies assessed and documented? Was the scientific quality of the included studies used appropriately in formulating conclusions? Were the methods used to combine the findings of the studies (i.e., pooled results) appropriate? Was the likelihood of publication bias assessed? Were potential conflicts of interest/source(s) of support of the systematic review stated? Were potential conflicts of interest/source(s) of support of the included studies stated?

eTable 2. Estimates of Overdiagnosis of Prostate Cancer Based on Excess Incidence in the Screening Groups of Randomized Controlled Trials (Key Question 2)[a]

Source	Patient Age Range, y	No. of Participants	Median Follow-up, y[b]	Numerator *(Excess Cases With Long-Term Followup)*	Denominator #1 *(PCa Diagnosed in Screening Arm During Screening Phase)*	Denominator #2 *(Screen-Detected PCa During Screening Phase)*	Overdiagnosis Estimate, Method #1 (%)[c]	Overdiagnosis Estimate, Method #2 (%)[d]
CAP, 2018[5]	50-69	Intervention: 189,386 Control: 219,439	10.0	1,276[g]	3,133	NR	40.7	NA
PLCO, 2016[6,7]	55-74	Intervention: 38,340 Control: 38,343	13.0[b]	425	2,577	2,049	16.4	20.7
ERSPC,[e,f] 2014[8,9]	55-69	Intervention: 72,891 Control: 89,352	13.0	2,461[g]	7,408	4,883	33.2	50.4
ERSPC-Goteborg, 2015[10]	50-64	Intervention: 10,000 Control: 10,000	14.0[b]	420	896	NR	46.8	NA
ERSPC – Spain, 2014[11]	45-70	Intervention: 2,415 Control: 1,861	15.2	58[g]	161	NR	36.0	NA
ERSPC – Rotterdam, 2014[12,13]	55-74	Intervention: 20,985 Control: 20,917	12.8	1,244	2,597	2,113	47.9	58.9
ERSPC – Finland, 2013[14,15]	55-67	Intervention: 31,866 Control: 48,278	12.0	680[g]	2,883	2,661	23.6	25.6

Abbreviations: CAP, Cluster randomized trial of PSA testing for Prostate cancer; ERSPC, European Randomized Study of Screening for Prostate Cancer; PCa, prostate cancer; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; y, year; NR, Not reported; NA, Not available due to non-report.

[a]The comparator for each of these RCTs was a control group that was not offered any prostate cancer screening

[b]ERSPC-Goteborg reports longest follow-up. Follow-up times are for PCa incidence; in separate publications, the PLCO and ERSPC-Goteborg trials reported mortality outcomes at longer follow-up times.

[c]Overdiagnosis method 1: percentage of all cancer diagnosed during the screening phase that are overdiagnosed

[d]Overdiagnosis method 2: percentage of screen-detected cancers that are overdiagnosed

[e]Main ERPSC trial includes most patients that are included in site-specific ERSPC reports

[f]Results for core age group of 55-69 years only

[g]Prostate cancer cases in control arm were weighted according to the randomization ratio

eTable 3. Number of Patients With Surgical Complications and Perioperative Mortality After Radical Prostatectomy (KQ4)[*]

Source	Country	Patient Age Range, y	No. of Patients Receiving RP	Follow-Up (actual)	Thromboembolic/ Cardiovascular Events, n (%)	Re-intervention, n (%)	Perioperative Mortality, n (%)	Other serious events, n (%)	Quality
ProtecT, 2016[16]	United Kingdom	49-69	553	90-days	9 (1.6)	9 (1.6)	0 (0)	Blood transfusion: 14 (2.5)	Good
PIVOT, 2012[17]	United States	40-75	280	30-days	8 (2.9)	10 (3.6)	1 (0.36)	Wound infection: 12 (4.3) Urinary tract infection: 7 (2.5) Blood transfusion: 6 (2.1) Urinary catheter present >30 days after surgery: 6 (2.1) Sepsis: 3 (1.1) Pneumonia: 2 (0.7) Renal failure/dialysis: 1 (0.4)	Good
Bjorklund, 2016[18]	Sweden	NR	22,344	90-days	NR	NR	39 (0.17)	NR	Fair
Rabbani, 2010[19]	United States	55-64	4,592	37 months	Major: 48 (1.1)[a] All: 196 (4.3)	628 (13.7)	6 (0.13)	Pulmonary event: 10 (0.2) Gastrointestinal event: 7 (0.1) Acute renal insufficiency: 9 (0.2) Sepsis: 3 (0.06) *All were major events*[a]	Fair
Walz, 2008[20]	Canada	45-89	9,208	30-days	NR	NR	48 (0.52)	NR	Fair
Alibhai, 2005[21]	Canada	NR	11,010	30-days	524 (4.8)	NR	53 (0.48)	Genitourinary: 829 (7.53) Wound: 555 (5.04) Misc. surgical: 576 (5.23) Misc. medical: 427 (3.88) Respiratory: 293 (2.66)	Fair
Augustin, 2003[22]	Germany	40-76	1,243	30-days	9 (0.7)	NR	0 (0)	Any postoperative event: 51 (4.1) Sepsis: 3 (0.2) Postoperative bleeding: 3 (0.2) Acute renal insufficiency: 2 (0.2) Wound infection: 1 (0.1)	Fair
Yao, 1999[23]	United States	≥65	101,604	30-days	(5)[b]	(0.8)[b]	508 (0.5)	Serious respiratory: (6.1) Genitourinary: (5.72) Serious misc. medical: (0.48) Serious misc. surgical: (0.80) Serious wound/bleeding: (0.65)	Fair

Abbreviations: GI, gastrointestinal; NR, not reported; PIVOT, Prostate Cancer Intervention Versus Observation Trial; ProtecT, Prostate Testing for Cancer and Treatment trial; RP, radical prostatectomy; RR, relative risk.

[*]All studies report number of patients with events, except for Augustin (2003)[22] which report number of events.

[a]Major medical complications were classified as Grade III to V according to the modified Clavien classification.

[b]Absolute number of events not reported.

eReferences

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