

Review Article

Number of screening rounds and risk of prostate cancer: a systematic review and meta-analysis

Tuo Deng^{1,2,3*}, Mengping Zhang^{4*}, Shijian Feng^{5*}, Xiaolu Duan^{1,2,3}, Tao Zhang^{1,2,3}, Chao Cai^{1,2,3}, Yu Lan^{1,2,3}, Wenqi Wu^{1,2,3}, Guohua Zeng^{1,2,3}

¹Department of Urology, Minimally Invasive Surgery Center, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; ²Guangzhou Institute of Urology, Guangzhou, China; ³Guangdong Key Laboratory of Urology, Guangzhou, China; ⁴Department of Oncology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; ⁵Department of Urology, Institute of Urology (Laboratory of Reconstructive Urology), West China Hospital, Sichuan University, Chengdu, China. *Equal contributors.

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Abstract: Purpose: To clarify the least number of prostate specific antigen (PSA) based screening rounds which is efficient in reducing the prostate cancer (PC) risk. Materials and methods: A systematic search was performed in Pubmed, Embase, Cochrane database of systematic review, web of science, CNKI and VIP databases to identify related articles (last search: August, 2016). The risk ratios (RRs) and 95% confidence intervals (CIs) of different numbers of screening rounds to reduce the prevalence of PC were calculated to assess the efficacy. Subgroup analysis was conducted according to different follow-up times. Results: A total of 9 randomized controlled trials were included in our analysis. Synthesized data showed that one or two rounds of PSA screening were not helpful in reducing the prevalence of PC (one round: RR = 1.11, 95% CI: 0.88-1.40, $P = 0.37$; two rounds: RR = 1.35, 95% CI: 0.90-2.02, $P = 0.14$). The PC prevalence was significantly reduced after three rounds of screening (RR = 0.63, 95% CI: 0.53-0.76, $P < 0.00001$), including advanced (RR = 0.18, 95% CI: 0.07-0.45, $P = 0.0003$) and high-grade PC (RR = 0.55, 95% CI = 0.45-0.66, $P < 0.00001$). Conclusions: At least three rounds of PSA screening are efficient and helpful in reducing PC risk. Thus, repeated screening cycles are necessary when PSA screening is applied on populations.

Keywords: Cancer risk, meta-analysis, number of screening rounds, prostate cancer, systematic review

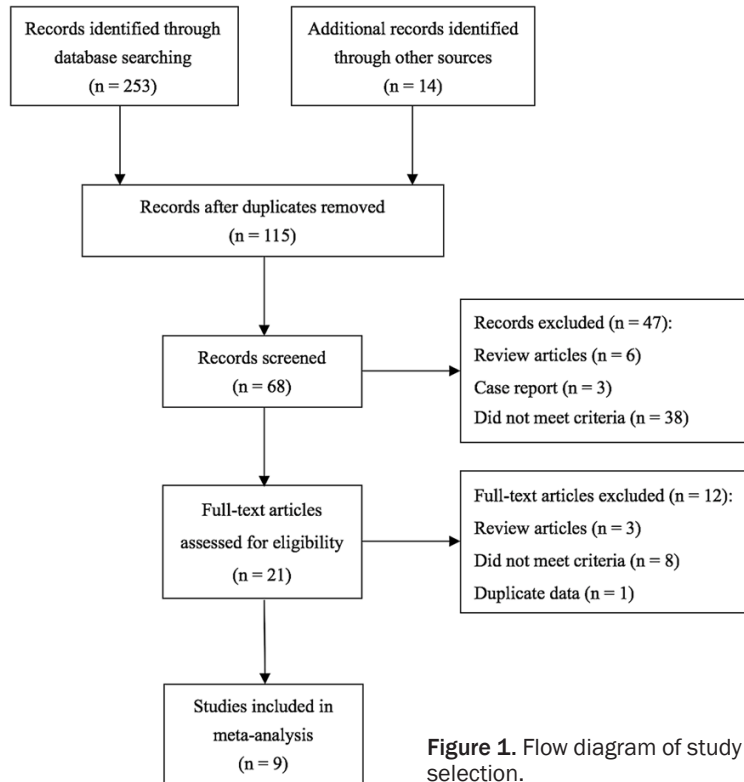
Introduction

Prostate cancer (PC) is the second most common cancer among men in developed countries, following the skin cancer [1, 2]. Its incidence and mortality has been reported to decline in black and white people since 1990s according to SEER cancer statistic review. Prostate-specific antigen (PSA) is considered to be a key biological marker to detect PC. If a blood test demonstrates a high level of PSA, prostate biopsy may be needed to determine whether cancer is actually presenting. Recent published studies showed different results related to PSA screen. The European Randomized Study of Screening for Prostate Cancer (ERSPC) conducted a study in 8 European countries to evaluate the efficacy of PSA screen on PC mortality, having illustrated a 21% reduc-

tion in screening population after 13-years follow-up [3]. However, the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) showed no significant reduction in the same follow-up period [4].

To date, American cancer society (ACS) and American urological association (AUA) recommended an annual PSA screening for men over 50 years old because of its efficacy to detect early stage PC [5, 6]. Current ACS guideline pointed out that elder men should make a decision with their health care provider about screening PSA after achieving sufficient information of benefits, risks and uncertainties associated with it [5]. Although detecting PC at the early stage has a great influence on PC management, concerns about over-diagnosis of PC, which may lead to un-

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search. And no language restrict was applied in this search.

The inclusion criteria were: (1) randomized controlled trials (RCTs) concerning PSA screening rounds and PC incidence or prevalence; (2) report results of PSA screening which could be extracted or calculated; (3) study population received PSA screening for no less than two times. Accordingly, the exclusion criteria were studies as abstracts, case reports, conference proceedings, review articles, or repeat publications. Two reviewers screened all eligible studies, assessed study quality and extracted available data independently. If any disagreement appeared, a third reviewer was invited to help making proper decisions.

necessary treatments and health related costs, tend to reduce the number of PSA screening rounds and focus on detecting significant cancers. However, no guideline or protocol existed yet to address the least number of PSA screening that could significantly decrease the risk of PC, especially advanced and high-grade PC. Therefore, we conducted this systematic review to investigate the issue by collecting available published data and provide reasonable suggestions for patients and clinicians.

Methods and materials

Search strategy and study selection

We systematically searched Pubmed, Embase, Cochrane database of systematic review, web of science, CNKI and VIP databases to identify literature focused on numbers of PSA screening rounds and the risk of PC (last search: August, 2016). Search terms used were: “prostate cancer”, “prostate specific antigen based screening”, “screening rounds”, “incidence”, “morbidity”, and “prevalence”. Reference list of related studies and review articles were also searched to identify the missing articles by online

Study outcomes and data extraction

The main outcome of this analysis was PC risks of the study population after receiving different numbers of PSA screening rounds, which were presented by PC prevalence of the population. Additionally, we also extracted the numbers of advanced and high-grade PC patients detected by each PSA screening rounds. Advanced PC was defined as T3, T4, N1 or M1 cancers, while high-grade PC referred to Gleason 7 or higher cancers. Other data such as last name of the first author, publication year, country, populations, institution, age of participants, number of participants, positive test value, interval time between screen rounds were also collected.

Study quality assessment

The Cochrane Collaboration Risk of Bias Tool was applied to evaluate the quality of all included RCTs [7]. According to the Cochrane Collaboration Risk of Bias Tool, the risk of bias of each RCT was assessed through the following five aspects: selection bias, performance bias, detection bias, attrition bias and reporting bias.

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Table 1. The baseline characteristics of eligible studies

References	Country	Ethnicity	Age of participations (years, range)	Method of detection	Cut-off value for screening	Interval time between screen rounds	Number of screen rounds	No. participations
Grubb et al, 2008	USA	USA	55-74	The Tandem-R PSA and the Access Hybritech PSA assays	Serum PSA > 4.0 ng/mL	One year	Round 1	34262
							Round 2	32696
							Round 3	31697
							Round 4	30544
Hoedemaeker et al, 2001	Netherlands	European	55-75	NM	Serum PSA $\geq$ 4.0 ng/mL	Four years	Round 1	4133
Kilpelainen et al, 2010	Finland	European	55-71	The Hybritech Tandem-E and Wallac Delfia assays	Serum PSA $\geq$ 4.0 ng/mL	Four years	Round 2	2385
							Round 1	20789
							Round 2	18613
Laurila et al, 2010	Finland, Italy, Netherlands, Sweden and Switzerland	European	51-75	NM	Serum PSA $\geq$ 3.0 ng/mL or Serum PSA $\geq$ 4.0 ng/mL or PSA values 3-4 combined with percentage of free to total PSA 0.16 or higher	2-4 years	Round 3	12740
							Round 1	56653
							Round 2	41639
Otto et al, 2010	Belgium, Spain, Finland, Italy, Netherlands, Sweden, France, and Switzerland	European	50-74	NM	Serum PSA $\geq$ 3.0 ng/mL or Serum PSA $\geq$ 4.0 ng/mL or PSA values between 2.5 and 3.9 ng/ml underwent DRE and TRUS	2-7 years	Round 3	24957
							Round 1	66652
Roemeling et al, 2006	Netherlands	European	55-74	NM	Serum PSA $\geq$ 4.0 ng/mL in the first round and Serum PSA $\geq$ 3.0 ng/mL in the second round	Four years	Round 2	41678
							Round 1	19970
Schroder et al, 2008	Netherlands	European	55-74	NM	Serum PSA $\geq$ 4.0 ng/mL in the first round and Serum PSA $\geq$ 3.0 ng/mL in the next two rounds	Four years	Round 2	14217
							Round 1	15852
							Round 2	11001
van der Crujisen-Koeter et al, 2006	Netherlands	European	55-74	NM	Serum PSA $\geq$ 4.0 ng/mL in the first round and Serum PSA $\geq$ 3.0 ng/mL in the second round	Four years	Round 3	5180
							Round 1	19969
							Round 2	12483
Pakarainen et al, 2016						Four years	Round 1	4847
							Round 2	6958
							Round 3	9886

NM: not mentioned; PSA: prostate specific antigen.

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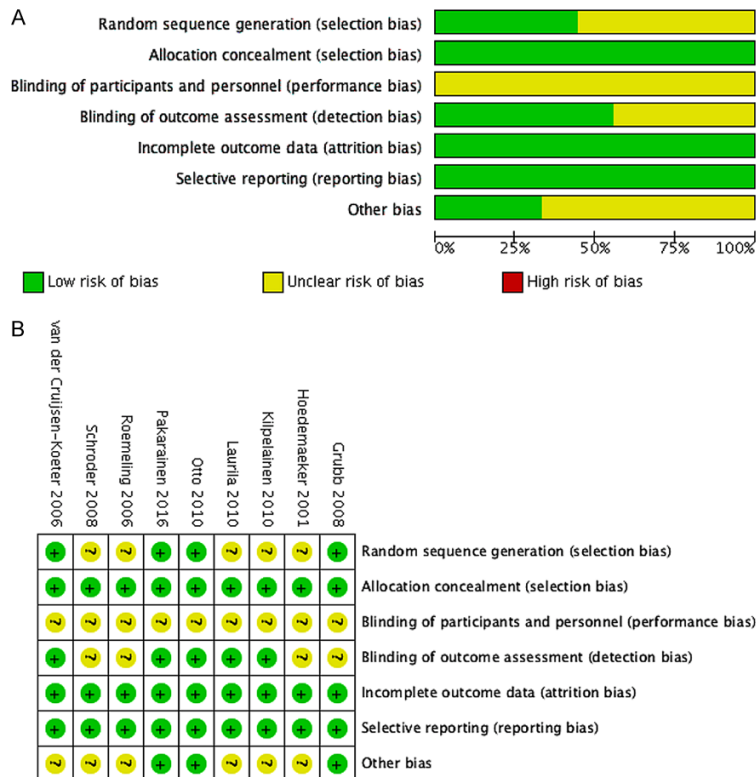


Figure 2. Assessment of bias risk for included RCTs (A: Methodological quality graph: authors' judgments about each methodological quality item presented as percentages across all included studies; B: Methodological quality summary: authors' judgments about each methodological quality item for each included study, "+" low risk of bias; "?" unclear risk of bias; "-" high risk of bias.).

Data synthesis and analysis

In this meta-analysis, we used the RevMan analytical software package (Version 5.3, Cochrane Collaboration, Oxford, UK) and STATA (Version 13.0, StataCorp, College Station, Texas, USA) to calculate, synthesis and analyze extracted data from eligible studies. Hazard ratios (HRs) or risk ratios (RRs) and 95% confidence intervals (CIs) of different numbers of PSA screening rounds in reducing the risk of PC were extracted and pooled. However, most of the included studies did not divide the screening populations into individual groups received different numbers of screening rounds, and all the screening populations received the same number of screening rounds, except for those PC patients detected in the screens. Thus, comparison of the incidences of PC after receiving different numbers of screening rounds in screening groups and control groups could not be achieved. Therefore, in our study, the PC

detection rates which could reflect the prevalence of PC in the screening population were chose to present the risk of PC in each screening time point. In other words, the basal PC prevalence of the screening population was verified in the first screening round, and every extra screening was an effective evaluation for the previous rounds. In addition, we regarded the interval time between each screening round as the follow-up time. In order to determine whether previous screening rounds are helpful in reducing PC risk, RRs and 95% CIs of PC detection rate in each screening round compared to the first round were calculated and combined. The heterogeneity was assessed using chi-square test based Q - and I^2 - statistic [8]. We used the fixed-effect model to calculate the combined RR when no heterogeneity existed among studies (P -value greater than 0.10 in heterogeneity test). Otherwise, randomized-

effect model was applied. All results in our meta-analysis considered as significant only if a two-tailed P -value was less than 0.05. Subgroup analysis was also performed according to different follow-up times. Inverted funnel plot visual inspection and Egger's test [9] were used to assess the publication bias of included studies.

Results

9 RCTs were included in our meta-analysis [10-18]. The flow diagram of online search was summarized in **Figure 1**. We performed this meta-analysis using the guidelines of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [19].

The total number of participants was 259971. Most studies were performed in European countries, only one study included American participants. 3 studies were based on single center, and the rest 6 studies were multicen-

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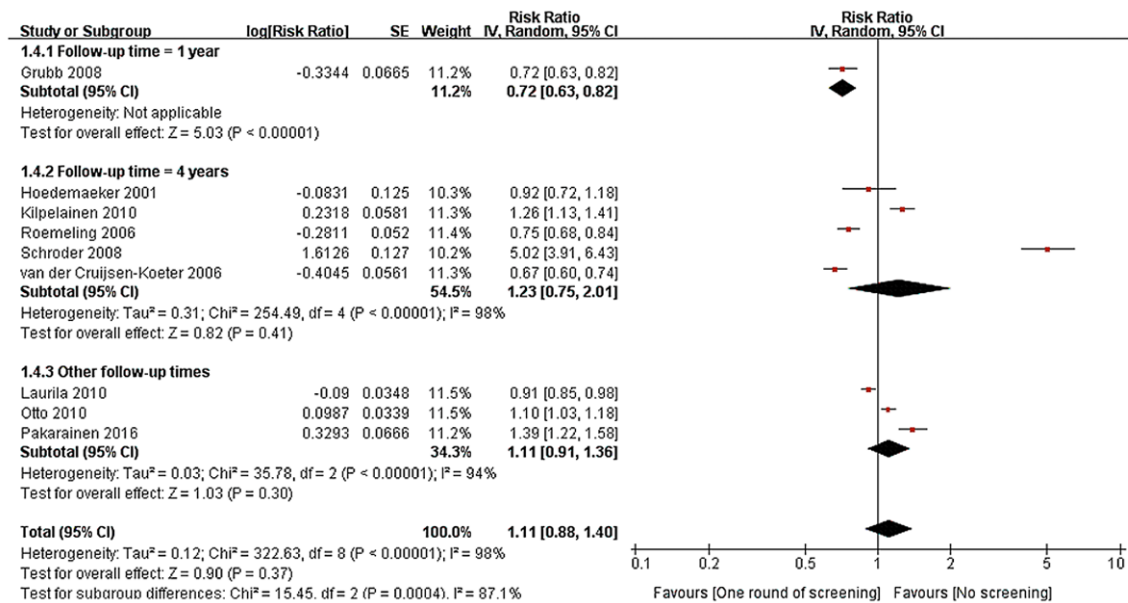


Figure 3. Forest plot of one round PSA screening for reducing PC risk.

tric. Age of participants ranging from 50 to 75. Most studies choose the threshold PSA value as 4.0 ng/ml, whereas others use 3.0 ng/ml. As to screening rounds, 4 studies screened 2 rounds, 4 studies screened 3, and 1 study screened 4. The main characteristics were summarized in Table 1.

The average basal PC prevalence of the screening population was 3.12% (range: 0.5% to 5.2%), which was assessed and calculated in Round 1 PSA screening. The remaining population without detection of PC in Round 1 were arranged to receive Round 2 to evaluate the efficacy of one round screening for reducing PC prevalence in this population. Our results showed that, after receiving one round of screening, the average PC prevalence of the population was decreased to 2.91% (range: 1.15% to 3.94%). Likewise, the average PC prevalence of the population after receiving two and three rounds of screening were 2.43% (range: 1.08% to 3.57%) and 1.11% (only 1 study), respectively.

Quality assessments of included studies

For all included RCTs, the risk of attrition and reporting biases were low in all of them. And among the 9 studies, 6 were in low risk of bias while other 3 were in moderate risk of bias (Figure 2). Additionally, 4 RCTs were in relative high quality.

Number of screening rounds for PC risk

In our analysis, effects of one to three rounds of PSA screening in reducing the risk of PC were assessed. 9 studies have explored the efficacy of one round screening, and the combined result showed no significant difference was found (RR = 1.11, 95% CI: 0.88-1.40, P = 0.37) (Figure 3). Effect of 2 rounds of screening was evaluated in 5 studies, and significant difference was also not found in the prevalence of PC between populations received no screening and two rounds of screening (RR = 1.35, 95% CI: 0.90-2.02, P = 0.14) (Figure 4). Only 2 studies available investigating the efficacy of 3 screening rounds, significantly lower PC prevalence in population received three screening rounds was observed compared to no screening population (RR = 0.63, 95% CI: 0.53-0.76, P < 0.00001) with slight heterogeneity (I² = 65%, P = 0.09) (Figure 5).

Among the 9 included RCTs, no significant publication bias was detected through both inverted funnel plot and Egger's test (t = 0.89, P = 0.403).

Number of screening rounds for advanced PC risk

4 studies focused on the influence of one round of screening on reducing the risk of advanced PC. Our meta-analysis indicated that the preva-

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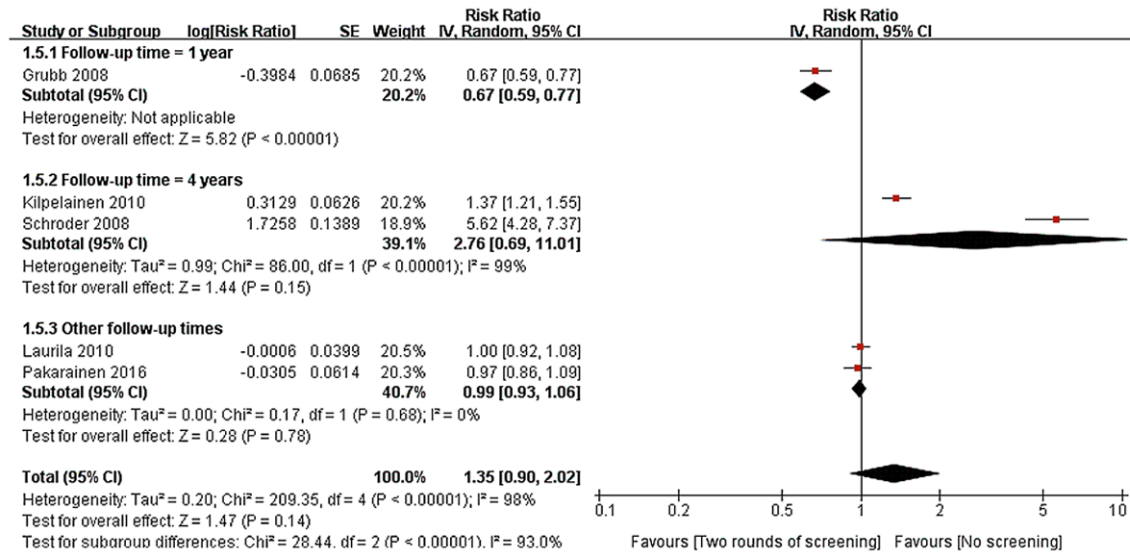


Figure 4. Forest plot of two rounds PSA screening for reducing PC risk.

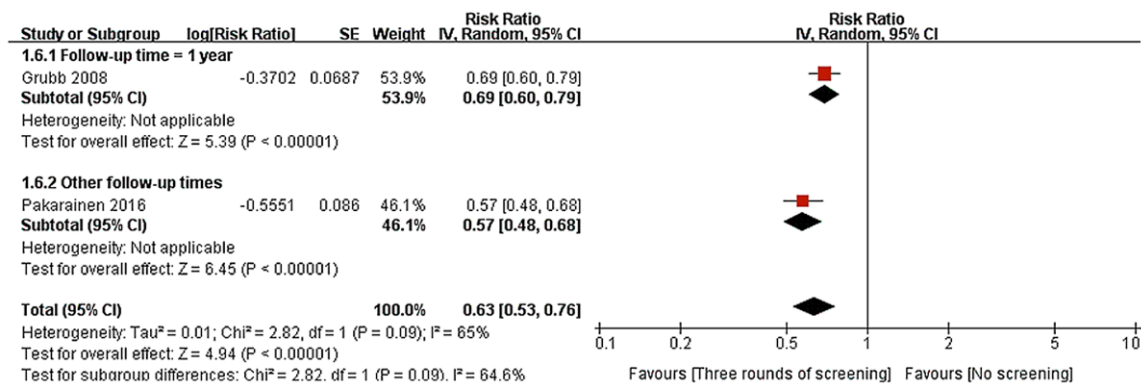


Figure 5. Forest plot of three rounds PSA screening for reducing PC risk.

lence of advanced PC did not decrease significantly after one round of screening ($RR = 0.43$, $95\% CI = 0.15-1.21$, $P = 0.11$). The pooled result of 3 studies concerning the effect of 2 screening rounds in reducing advanced PC prevalence also showed no significant difference ($RR = 1.05$, $95\% CI = 0.35-3.15$, $P = 0.93$). And only one study was available to assess the efficacy of 3 screening rounds, which showed a positive result ($RR = 0.18$, $95\% CI = 0.07-0.45$, $P = 0.0003$) (Figure 6). No obvious publication bias was detected through the inverted funnel plot for the 4 eligible studies.

Number of screening rounds for high-grade PC risk

Risk of high-grade PC after one round of PSA screening was assessed in 5 studies. Compar-

ed with no screening, only one round of screening could not reduce the high-grade PC prevalence of the population significantly ($RR = 0.83$, $95\% CI = 0.42-1.62$, $P = 0.58$). Two rounds of screening involved with high-grade PC risk was available in 3 studies, and still no significant difference was found ($RR = 1.01$, $95\% CI = 0.47-2.16$, $P = 0.98$). Only two studies were eligible for calculating the combined RR of three screening rounds in reducing high-grade PC risk. Our analysis indicated that at least three rounds of PSA screening were needed to achieve a significantly lower prevalence of high-grade PC in the population ($RR = 0.55$, $95\% CI = 0.45-0.66$, $P < 0.00001$) (Figure 7). The inverted funnel plot did not demonstrate any indication of publication bias among the five included studies.

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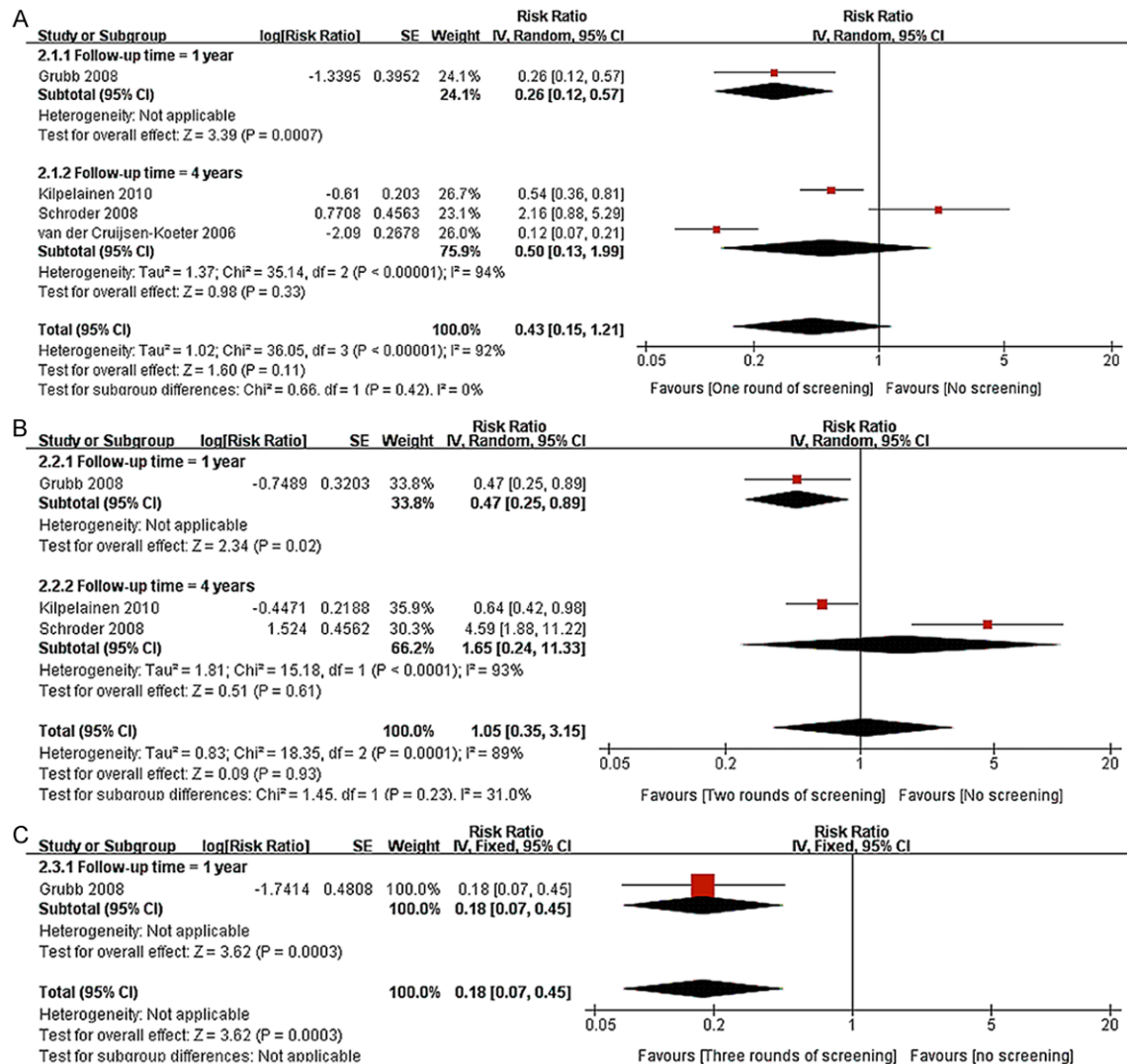


Figure 6. Forest plot of one (A), two (B) and three (C) rounds of PSA screening for reducing advanced PC risk.

Discussion

To the best of our knowledge, it is the first meta-analysis concerning the number of PSA screening rounds with PC risks. A total of 9 studies with 259971 participants were included in this study. We tried to search for the least number of PSA screening rounds which was most effective in reducing PC prevalence. Our results reached the conclusion that the average PC prevalence of the population decreased with the number of screening, which was 3.12%, 2.91% and 1.11% respectively after one, two and three rounds of screening. One or two rounds of PSA screening were not indicated to reduce PC prevalence, and the prevalence of both advanced and high-grade PC could only

significantly decrease after at least three rounds. However, as the PC risk keeps rising with the age, repeated and regular PSA screenings are still recommended to lower PC risk.

In epidemiology, incidence of a given medical condition is defined as the measurement of the probability of new occurrences in a population within a specified period of time. Some investigators usually express it as the number of new cases during a time period inaccurately. It is impossible for everyone in the population to participate in a disease examination, so some people bearing the disease might be ignored due. We considered that PC incidence in most studies cannot represent actual PC risk. In other words, the PC prevalence calculated by

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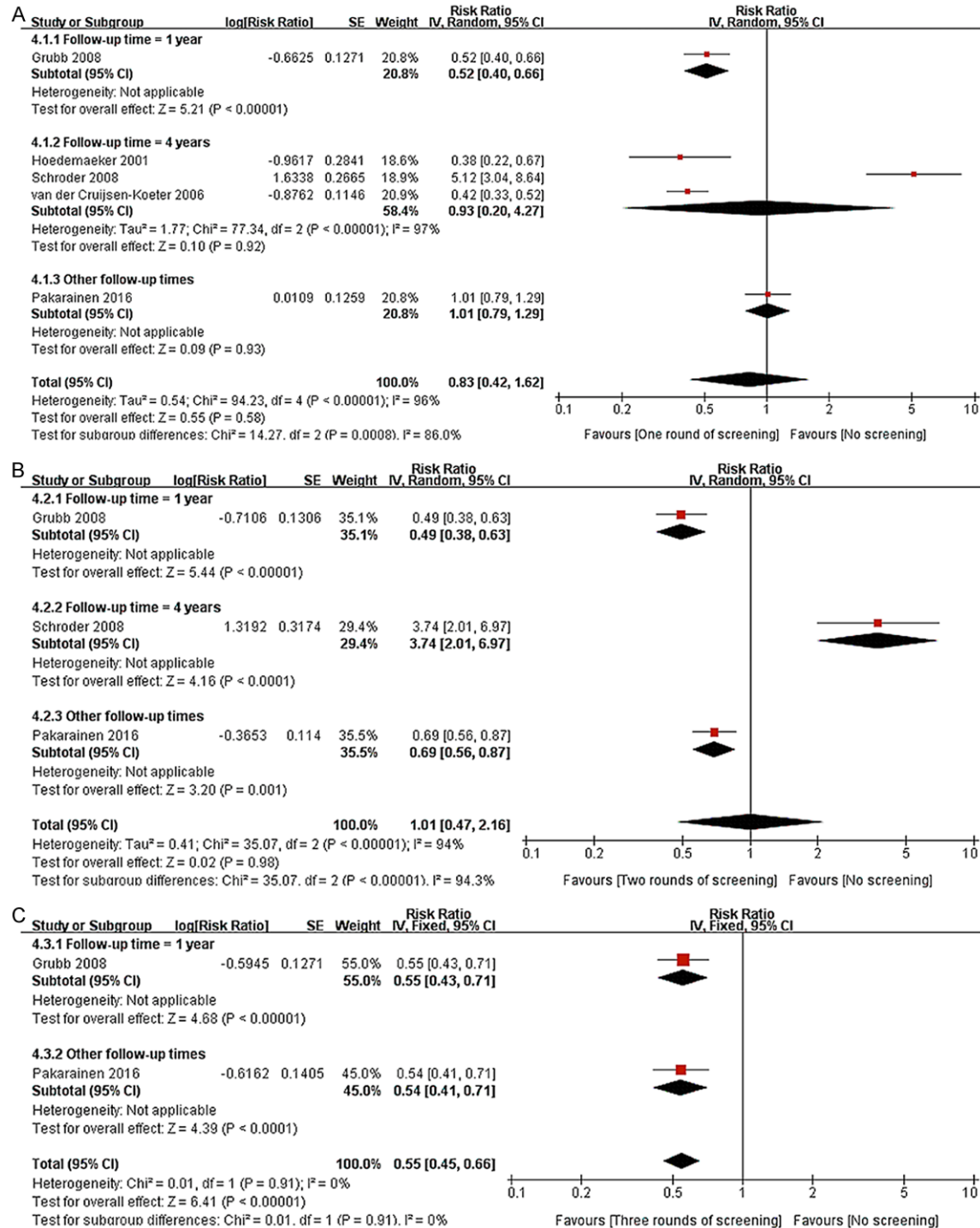


Figure 7. Forest plot of one (A), two (B) and three (C) rounds of PSA screening for reducing high-grade PC risk.

detecting PC in the PSA screening for the population could represent the risk of PC more precisely. Detected PC patients in the first screening round would be excluded from the population for next round, eliminating the contamination of assessing PC risk. In our meta-analysis, we considered the PC detection rate of the

first screening round in each study as the basal or initial risk of the population. The second screening round examined the PC prevalence of the remaining population who had received one round, indicating that every following screening was more effective based on the evaluation of previous rounds.

PC related health-care burden cannot be ignored. About 240890 US men have been diagnosed with PC, and approximate 33720 men died of it. According to Sakr's study, an estimate of one third of men aged from 40 to 60 years have histological evident PC, and this rate rose to three forth in men older than 85 [20, 21]. Besides treatment costs, the wide-spread of PSA screening, low biopsy threshold and increasing number of prostate biopsy also resulted in elevated PC detection rate and higher disease related cost. Therefore, PSA screening is not supposed to find as many cancers as possible but to find significant cancers preferentially nowadays.

Present recommendation of PC screening is measurement of serum PSA levels. Other methods including digital rectal examination and ultrasonography are also applied. Although PSA screening has been used as the most acceptable method to detect PC due to its low price and simple technique, still some controversies exist. For example, the USA Preventive Services Task Force and the American College of Physicians American Society of Internal Medicine do not recommend it owing to lack of clear benefits [22, 23]. PSA screening discovers early PCs guiding patients to receive timely treatment, but most cases share a relative reasonable prognosis even no treatment are given. A study in England reported that PC detected by PSA screening seemed to be less advanced than by clinical symptoms, but no significant difference was noticed in Gleason score between 8 and 10 [24]. Moreover, PSA screening detects asymptomatic PCs in which the tumor has not progressed or it will progress so slowly that might remain stable throughout their lifetime. In these cases, patients received unnecessary prostate biopsy and treatments. According to Schroder's clinical trials, over-diagnosis rate of PC was 17% to 50% from PC screening [25]. Patients who have been informed the state of disease would not only have extra unnecessary psychological concerns but also over-treatments and related side effects [26]. Prostate biopsy often leads to pain, fever, bleeding, infection and transient urinary difficulties [27]. It is still not clear how to achieve maximal reduction of PC mortality while minimal harm occurs to screened population.

The proper interval of screening time is also in debate. Smith et al recommended annual

screening, while ERSPC chose a 4-year interval with an exception of 2-year interval in Sweden. Some recent published studies showed no significant difference between longer and shorter interval time, with the evidence showed no major difference in the cumulative incidence of interval cancers were observed in Dutch and Sweden center [28, 29].

Tumor stage and grade could also evaluate the screening efficacy. According to ERSPC based on Swedish and Dutch center, Swedish results proved that the cumulative incidence of advanced PC in screening arm was lower than controlled arm in 8 years' follow-up with 4 screening rounds [30]. In Dutch study, PC characteristics were more favorable after the first screening with the detection rate of advanced PC decreased from 18.7% to 3.5% [31].

In spite of the concerns mentioned above, PSA screen tended to have desired results to reduce PC related risk in many studies. In our meta-analysis, we found that PSA screening was necessary and useful and 3 rounds of PSA screening were the least number of screening time, which balanced between reducing PC risk and controlling health related costs and unnecessary harm.

Some limitations should be stressed in our meta-analysis. All included studies were conducted in European or US populations, which may potentially influence the application of our results on other races. And many studies are multicenter designed with different detection technique and method, mode of recruitment, screening interval and PSA threshold for biopsy. In addition, the number of included studies in three screening rounds was too small. Thus, the findings from such meta estimation should be taken with caution. Last but not least, we regarded the interval time between each screening round as the follow-up time to evaluate the efficacy of different numbers of screening round, which might not be long enough. All of these mentioned above would possibly affect the strength of our conclusion.

Conclusion

PSA screening is still a promising method to detect advanced and high-grade PC to reduce PC risk. Our meta-analysis concluded that the PC prevalence of the screening population decreased with the number of screening,

and at least 3 times of PSA screening is necessary for the purpose to lower the PC risk (either advanced or high-grade PC). Therefore, repeated screening cycles are needed when PSA screening is applied on populations. Our result could provide reliable evidence to clinicians and patients for PSA screening assisting them to make proper management. Further detailed studies are anticipated to confirm our results.

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Disclosure of conflict of interest

None.

Address correspondence to: Guohua Zeng, Department of Urology, Minimally Invasive Surgery Center, The First Affiliated Hospital of Guangzhou Medical University, Kangda Road 1#, Haizhu District, Guangzhou, China; Guangzhou Institute of Urology, Kangda Road 1#, Haizhu District, Guangzhou, China; Guangdong Key Laboratory of Urology, Kangda Road 1#, Haizhu District, Guangzhou, China. Tel: +86-020-34294145; E-mail: gzgyzgh@vip.tom.com

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