Submitted: 04 July, 2024 Accepted: 22 August, 2024 Published: 30 September, 2024 DOI:10.22514/jomh.2024.159

ORIGINAL RESEARCH

JOMH Journal of Men's Health

Research of the best screen interval for middle aged and elderly Chinese males with baseline prostate specific antigen levels <2.0 ng/mL in prostate cancer screening

Yu Chen[1], Gansheng Xie[2,*], Gang Li[2], Yu Li[2]

[1]Department of Geriatrics, The First Affiliated Hospital of Soochow University, 215006 Suzhou, Jiangsu, China
[2]Department of Urology, The First Affiliated Hospital of Soochow University, 215031 Suzhou, Jiangsu, China

***Correspondence**
liyufyy@suda.edu.cn
(Gansheng Xie)

Abstract

This study aimed to investigate the optimal screening interval of a prostate specific antigen (PSA) screening program for men aged 40–70 with a baseline PSA <2 ng/mL in China. 8-year period clinical data of Chinese males who underwent physical examination annually in our hospital were retrospectively collected. 397 healthy males were included.Total PSA (tPSA) and free PSA (fPSA) were collected, and the free/total PSA ratio (f/t PSA) was calculated. According to the baseline PSA value, study population was divided into 2 groups: 0–0.99 ng/mL and 1–1.99 ng/mL. Prostate biopsy indicates at tPSA >10 ng/mL, or 4–10 ng/mL (gray area) and f/t PSA <0.16. Kaplan-Meier survival analysis was used to calculate the relevant cumulative incidence rate. Over the eight-year screening period, 27 people (6.8%) had abnormal PSA that met prostate biopsy criteria. 7 cases of prostate cancer were detected (detection rate 25.9%) among the 27 patients who performed a biopsy. In the 0–0.99 ng/mL and 1–1.99 ng/mL group, 4.1% (13/317) and 17.5% (14/80) achieved biopsy criteria within 8 years, with a statistically significant difference ($p < 0.001$). In both groups, abnormal PSA began appearing in the sixth year. According to stratifying the cohort age and PSA, abnormal PSA levels began to appear in all subgroups by the sixth year, except for men aged <50 years plus baseline PSA <1 ng/mL, where they appeared by the seventh year. Furthermore, in the group of baseline 40–49 years and baseline PSA <2 ng/mL, the probability of meeting biopsy indications during eight years was very low (1.4%, 2/143). Chinese men aged 50–70 with baseline PSA <2 ng/mL should undergo for PSA retest in the sixth year, while aged 40–49 with a baseline PSA <2 ng/mL do not need PSA screening within eight years.

Keywords

Prostate specific antigen; Screening; Prostate cancer; Prostate biopsyProstate specific antigen; Screening; Prostate cancer; Prostate biopsy

1. Introduction

Prostate specific antigen (PSA) screening is proven to increase prostate cancer detection and decrease mortality [1]. PSA screening has become popular in China over the past 20 years among middle-aged and elderly men. Despite its advantages, PSA screening in China carries a huge social and economic burden due to its large elderly population. Majority of screening population has low baseline PSA. Studies show that individuals with baseline PSA <1.0 ng/mL have a very low incidence of prostate cancer within 4–7 years, less than 1% [2]. Screen intervals for men with baseline PSA ≤1.0 ng/mL were recommended as 8 years by the European Association of Urology and 3 years by the Japanese Urological Association [3, 4]. According to a recent study, men with baseline PSA <0.4 ng/mL with a Gleason score ≥7 are not recommended to undergo further examination because prostate cancer risk is low [5]. Therefore, it is necessary to develop a reasonable screening strategy that balances the advantages and disadvantages, such as over detection and unnecessary biopsy. Screening strategy involves baseline age, PSA, screening interval, and prostate biopsy indications.

This study retrospectively analyzed the 8-year screening data of middle-aged and elderly men with baseline PSA <2 ng/mL, to explore the optimal screening interval for Chinese men with low PSA.

2. Method

2.1 General information

We retrospectively collected clinical data from middle-aged and elderly men who underwent physical examinations in our hospital between January 2016 and December 2023 (an 8-year period). The inclusion criteria included: baseline age 40–70 years old; regular PSA checks; baseline PSA <2 ng/mL;

non-prostate cancer patients; without prostate cancer family history. Factors that may affect serum PSA were excluded: acute prostatitis, indwelling catheters, and administration of 5α-reductase inhibitors for more than six months. 397 males were included in the study. The interval between two PSA screenings was exactly one year since all subjects were examined every fixed month of the year. The endpoint is 31 December 2023 or being diagnosed with prostate cancer.

Forearm venous blood samples were drawn from all subjects and sent for immediate testing. With a fully automatic chemiluminescence immunoassay analyzer (HealthDigit HD-2001A, Shukang Biotechnology Limited Company, Shanghai, China), tPSA and fPSA were measured by a protein chip chemiluminescence method. The free/total PSA ratio (f/t PSA) was calculated as fPSA/tPSA. According to the baseline PSA value, study population was divided into two groups: 0–0.99 ng/mL and 1–1.99 ng/mL.

According to the Chinese Urological Association guideline [6], indications for prostate biopsy include tPSA >10 ng/mL, or 4–10 ng/mL (gray area) with f/t PSA <0.16. Prostate biopsies were recommended to patients who met the criteria. We performed a systematic 12 needle puncture biopsy guided by transrectal ultrasound. In cases of suspicious nodules, 1 or 2 additional punctures were performed.

2.2 Statistical methods

Data analysis was performed using SPSS 17.0 (IBM SPSS, Chicago, IL, USA). According to frequency analysis, age and PSA did not follow a normal distribution, so median (range) was used for representation. Kaplan Meier survival analysis was used to calculate the cumulative incidence for each PSA group. Log rank test was used to compare cumulative incidence differences between groups. $p < 0.05$ (bilateral) indicates statistically significant differences.

3. Results

Table 1 lists the descriptive parameters of 397 study subjects. Over the eight-year screening period, 27 people (6.8%) had abnormal PSA that met prostate biopsy criteria. 7 cases of prostate cancer were detected (detection rate 25.9%) among the 27 patients who performed a biopsy. The descriptive parameters of the 27 biopsied males are shown in Table 2.

Kaplan Meier survival analysis evaluated the cumulative incidence of meeting prostate biopsy indications in different baseline PSA groups (Fig. 1). In the 0–0.99 ng/mL and 1–1.99 ng/mL group, 4.1% (13/317) and 17.5% (14/80) achieved biopsy criteria within 8 years. Both groups showed a statistically significant difference (χ^2= 18.093, $p < 0.001$). In both groups, abnormal PSA began appearing at the sixth year and increased in the following years (Fig. 1). Table 3 further stratifies the population by baseline PSA and age. All subgroups of subjects who needed prostate biopsy appeared in the sixth year. However, the subgroup with baseline age <50 years and baseline PSA <1 ng/mL had abnormal PSA in the seventh year. Furthermore, in subjects, only 2 males with baseline age 40–49 years and baseline PSA <2 ng/mL required prostate biopsy during eight years. Both were diagnosed with benign prostatic hyperplasia. Therefore, the probability of meeting biopsy indications within eight years in 40–49-year-old males was very low (1.4%, 2/143).

TABLE 1. Clinical characteristics of study subjects.

	Baseline PSA	
	0–0.99 ng/mL	1–1.99 ng/mL
n	317	80
Age (yr)		
Median	52	56
P25, P75	47, 59	51, 68
Range	40–69	45–70
Baseline PSA (ng/mL)		
Median	0.41	1.18
P25, P75	0.30, 0.59	1.06, 1.41
Range	0.04–0.98	1.00–1.98
PSA meeting biopsy indications (n (%))	13 (4.1%)	14 (17.5%)
Confirmed prostate cancer (n (%))	4 (1.3%)	3 (3.8%)

PSA: prostate specific antigen.

TABLE 2. Clinical characteristics of prostate biopsy subjects.

Parameters	
Age (yr)	
Median	57
P25, P75	52, 63
Range	45–69
Baseline PSA (ng/mL)	
Median	1.00
P25, P75	0.59, 1.38
Range	0.35–1.79
PSA at time of prostate biopsy (ng/mL)	
Median	6.41
P25, P75	5.23, 9.20
Range	4.39–22.11

PSA: prostate specific antigen.

4. Discussion

Worldwide, PSA screenings are used to diagnose prostate cancer. Based on a randomized multicenter clinical study conducted in 2010, a 14-year systematic PSA screening can reduce the relative risk of prostate cancer (PC) mortality by 44% [7]. In the European Cancer Screening Randomized Study (ERSPC), the risk of prostate cancer mortality was reduced 21% over 11 and 13 years [8, 9]. However, controversy has persistently surrounded PSA screening. Despite increasing prostate cancer detection rates, PSA screening has also caused a huge socioeconomic burden. Several large multicenter stud-

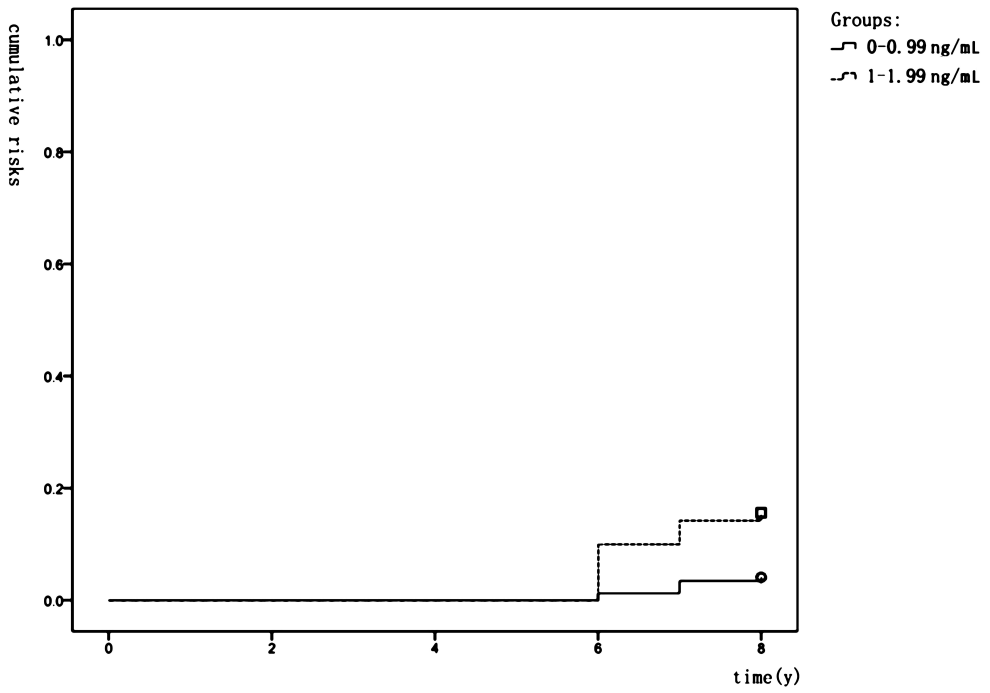

FIGURE 1. Cumulative incidence of meeting prostate biopsy criteria in different baseline PSA groups. y: year.

TABLE 3. Cumulative incidence of each subgroup meeting prostate biopsy criteria stratified by baseline PSA and baseline age.

Baseline PSA	n	Cumulative incidence of meeting prostate biopsy criteria (n (%))						
		2nd year	3rd year	4th year	5th year	6th year	7th year	8th year
0–0.99 ng/mL								
40–49 yr	129	0	0	0	0	0	1 (0.8)	1 (0.8)
50–59 yr	113	0	0	0	0	2 (1.8)	6 (5.3)	7 (6.2)
60–70 yr	75	0	0	0	0	2 (2.7)	4 (5.3)	5 (6.7)
1–1.99 ng/mL								
40–49 yr	14	0	0	0	0	1 (7.1)	1 (7.1)	1 (7.1)
50–59 yr	37	0	0	0	0	5 (13.5)	7 (18.9)	7 (18.9)
60–70 yr	29	0	0	0	0	4 (13.8)	5 (17.2)	6 (20.7)

PSA: prostate specific antigen.

ies indicate that PSA screening did not reduce prostate cancer specific mortality or improve survival [10–12]. Furthermore, the overdiagnosis caused by indiscriminate PSA screening was gradually emphasized, and a large number of early-stage tumors with Gleason score 6 were discovered [7], which had little impact on patient survival. Low-risk prostate cancer patients undergoing active surveillance have a 100% tumor specific survival rate at 10 years [13, 14]. Specific populations, however, still require PSA screening. For example, screening can increase survival rates for individuals with a family history of prostate cancer [15]. In addition, men with PSA >1 ng/mL at 40 and >2 ng/mL at 60 have an increased risk of dying from prostate cancer within 20 years. 1 death could be avoided for every 6 confirmed cases of prostate cancer [16].

Baseline PSA was associated with prostate cancer incidence and mortality. A European study showed that men with baseline PSA <0.4 ng/mL are significantly less likely to develop prostate cancer within 12 years than those with a baseline PSA of 0.4–1.0 ng/mL [5]. A Japanese study reported a prostate cancer risk of 0.35% within 14 years for men aged 55 to 69 with a baseline PSA <1 ng/mL [17]. Between 51 and 55, the cumulative risk of 20-year prostate cancer death with baseline PSA >2.4 ng/mL was 5.68%, whereas the cumulative risk of death with PSA <0.85 ng/mL in the same age was only 0.47% [18]. Therefore, different baseline PSA populations require different screening schemes. A multicenter clinical study recommended that PSA screening should be performed every two years in individuals with a family history or PSA >1 ng/mL at 40 years old, >2 ng/mL at 60 years, and reexamined 8–10 years later in low-risk populations [19]. The Japanese

Urology Association recommends screening every 3 years for men with baseline PSA <1.0 ng/mL, and screening annually for men with PSA >1.0 ng/mL [4].

Chinese populations, however, might not be suited to the above-mentioned screening programs. Among different races, PSA varies. As shown in our previous study, Chinese men in the same age have a lower normal PSA than Westerners [20, 21]. On the other hand, prostate cancer incidence varied. A multicenter study in Europe showed that the detection rate of prostate cancer with a PSA of 3.1–4 ng/mL and a negative rectal digital examination was 26.9% [22], whereas in a Chinese study of 365 patients [23], the prostate cancer incidence with a PSA of 4–10 ng/mL (grey area) was 23.84%, significantly lower than in Europe. It was therefore clinically necessary to establish PSA screening plans for the Chinese population.

This study retrospectively analyzed 8-year PSA data from 397 Chinese men aged 40–70 with a baseline PSA <2 ng/mL. The majority of the population undergoing a health examination falls within this range. It appears that baseline PSA and cumulative risk of prostate biopsy is positively correlated. An increased baseline PSA increases the risk of biopsy. Our findings demonstrate that the 1–1.99 ng/mL group had a statistically significant difference in cumulative incidence from the 0–0.99 ng/mL group. Further age stratification studies indicate that all subgroups developed abnormal PSA requiring prostate biopsy by the sixth year, except the 40–49 year with PSA 0.99 ng/mL subgroup, where biopsy occurred in the seventh year. Due to the very low probability of 40–49-year-old males with baseline PSA <2 ng/mL requiring prostate biopsy within eight years, this group may not require PSA screening within eight years. Our results are generally consistent with the American Urology Association's recommendation not to screen individuals 40–54 without risk factors [1].

This study had several limitations. Study subjects were from one single clinical center, which may not represent all Chinese males with the same baseline age and PSA. In addition, we lacked data of digital rectal examination. It was showed that the incidence rate of prostate cancer only with positive rectal digital examination (regardless of PSA value) is 18% [24]. During the baseline study, all subjects were not confirmed to be non-cancerous. In addition to the small sample size, there may have been selection bias in our study, which could weaken the reliability of our research conclusions. Besides, due to incomplete information on prostate cancer risk factors, such as metabolic syndrome, smoking and drinking habits, it was unable to exclude the impact of these risk factors on PSA screening. Last, because some prostate biopsy patients had incomplete Gleason scores, it was not possible to determine the correlation between baseline PSA, age and cumulative risk of clinically significant prostate cancer.

5. Conclusions

A baseline PSA <2 ng/mL should be retested at the sixth year for 50–70-year-old males. Men aged 40–49 with a baseline PSA <2 ng/mL do not need PSA screening within eight years. With a PSA screening schedule, annual testing can be avoided, reducing medical resources and household burdens.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

YC and GSX—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. YC, GSX, GL and YL—supervised the data collection; YC, GSX and GL—analyzed the data; interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital of Soochow University (No. 364 (2024)). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, *et al*. Early detection of prostate cancer: AUA guideline. The Journal of Urology. 2013; 190: 419–426.

[2] Sawada K, Kitagawa Y, Ito K, Takeda Y, Mizokami A, Namiki M. Cumulative risk of developing prostate cancer in men with low (≤2.0 ng/mL) prostate-specific antigen levels: a population-based screening cohort study in Japan. International Journal of Urology. 2014; 21: 560–565.

[3] Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, *et al.* EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent—update 2013. European Urology. 2014; 65: 124–137.

[4] Cancer CfEotGoSfP, Association JU. Updated Japanese urological association guidelines on prostate-specific antigen-based screening for prostate cancer in 2010. International Journal of Urology. 2010; 17: 830–838.

[5] Randazzo M, Beatrice J, Huber A, Grobholz R, Manka L, Chun FK, *et al*. Is further screening of men with baseline PSA <1 ng ml^{-1} worthwhile? The discussion continues—results of the Swiss ERSPC (Aarau). International Journal of Cancer. 2015; 137: 553–559.

[6] Na R, Wu Y, Xu J, Jiang H, Ding Q. Age-specific prostate specific antigen cutoffs for guiding biopsy decision in Chinese population. PLOS ONE. 2013; 8: e67585.

[7] Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P,

et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. The Lancet Oncology. 2010; 11: 725–732.

[8] Frånlund M, Månsson M, Godtman RA, Aus G, Holmberg E, Kollberg KS, *et al*. Results from 22 years of Followup in the Göteborg randomized population-based prostate cancer screening trial. The Journal of Urology. 2022; 208: 292–300.

[9] Hugosson J, Roobol MJ, Månsson M, Tammela TLJ, Zappa M, Nelen V, *et al*. A 16-yr follow-up of the european randomized study of screening for prostate cancer. European Urology. 2019; 76: 43–51.

[10] Martin RM, Donovan JL, Turner EL, Metcalfe C, Young GJ, Walsh EI, *et al*. Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality: the CAP randomized clinical trial. JAMA. 2018; 319: 883–895.

[11] Pinsky PF, Prorok PC, Yu K, Kramer BS, Black A, Gohagan JK, *et al*. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer. 2017; 123: 592–599.

[12] Andriole GL, Crawford ED, Grubb III RL, Buys SS, Chia D, Church TR, *et al*. Mortality results from a randomized prostate-cancer screening trial. The New England Journal of Medicine. 2009; 360: 1310–1319.

[13] Obiora D, Orikogbo O, Davies BJ, Jacobs BL. Controversies in prostate cancer screening. To be published in Urologic Oncology. 2024. [Preprint].

[14] van As NJ, Norman AR, Thomas K, Khoo VS, Thompson A, Huddart RA, *et al*. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. European Urology. 2008; 54: 1297–1305.

[15] Jemal A, Culp MB, Ma J, Islami F, Fedewa SA. Prostate cancer incidence 5 years after US preventive services task force recommendations against screening. Journal of the National Cancer Institute. 2021; 113: 64–71.

[16] Carlsson S, Assel M, Sjoberg D, Ulmert D, Hugosson J, Lilja H, *et al*. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. The BMJ. 2014; 348: g2296.

[17] Urata S, Kitagawa Y, Matsuyama S, Naito R, Yasuda K, Mizokami A, *et al*. Optimal screening interval for men with low baseline prostate-specific antigen levels (≤1.0 ng/mL) in a prostate cancer screening program. World Journal of Urology. 2017; 35: 579–586.

[18] Vickers AJ, Ulmert D, Sjoberg DD, Bennette CJ, Björk T, Gerdtsson A, *et al*. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40–55 and long term risk of metastasis: case-control study. The BMJ. 2013; 346: f2023.

[19] Gelfond J, Choate K, Ankerst DP, Hernandez J, Leach RJ, Thompson IM. Intermediate-term risk of prostate cancer is directly related to baseline prostate specific antigen: implications for reducing the burden of prostate specific antigen screening. The Journal of Urology. 2015; 194: 46–51.

[20] Kalish LA, McKinlay JB. Serum prostate-specific antigen levels (PSA) in men without clinical evidence of prostate cancer: age-specific reference ranges for total PSA, free PSA, and percent free PSA. Urology. 1999; 54: 1022–1027.

[21] Xie G, Huang Y, Yan C, PU J, LI G, Ouyang J, *et al*. Analysis of age-specific prostate specific antigen and related parameters in 22 055 elderly men. Chinese Journal of Urology. 2013; 613–617. (In Chinese)

[22] Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, *et al*. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤4.0 ng per milliliter. The New England Journal of Medicine. 2004; 350: 2239–2246.

[23] Cao X, Gao J, Han G, Tang J, Hong B. Relationship between screening by stratifying cases into groups on prostate specific antigen level and the positive rate of transrectal ultrasound guided systematic sextant prostate biopsy. Chinese Journal of Surgery. 2006; 44: 372–375. (In Chinese)

[24] Krilaviciute A, Becker N, Lakes J, Radtke JP, Kuczyk M, Peters I, *et al.* Digital rectal examination is not a useful screening test for prostate cancer. European Urology Oncology. 2023; 6: 566–573.

How to cite this article: Yu Chen, Gansheng Xie, Gang Li, Yu Li. Research of the best screen interval for middle aged and elderly Chinese males with baseline prostate specific antigen levels <2.0 ng/mL in prostate cancer screening. Journal of Men's Health. 2024; 20(9): 146-150. doi: 10.22514/jomh.2024.159.